MAJOR ARTICLE

Efficacy and Safety of Pegylated Interferon plus Ribavirin in HIV and Hepatitis C Virus–Coinfected Patients with Advanced Immunosuppression

José A. Mira,[1,2,14] Alicia Gutiérrez-Valencia,[3,14] Ignacio de los Santos Gil,[5] Dolores Merino,[6,14] Antonio Rivero,[7,14] María J. Ríos-Villegas,[4,14] Marcial Delgado,[8,14] Mercedes González-Serrano,[9,14] Antonio Collado,[10,14] Manuel Torres-Tortosa,[11,14] Mohamed Omar[12,14] Miguel Ángel López-Ruz,[13,14] Juan Macías,[1,2,14] Sari Arponen,[5] and Juan A. Pineda[1,14]

[1]Unidad de Enfermedades Infecciosas and [2]Servicio de Medicina Interna, Hospital Universitario de Valme, [3]Servicio de Enfermedades Infecciosas, Hospital Universitario Virgen del Rocío, and [4]Unidad de Enfermedades Infecciosas, Hospital Universitario Virgen Macarena, Sevilla, [5]Servicio de Medicina Interna-Infecciosas, Hospital Universitario de la Princesa, Madrid, [6]Servicio de Medicina Interna, Hospital Juan Ramón Jiménez, Huelva, [7]Sección de Enfermedades Infecciosas, Hospital Universitario Reina Sofía, Córdoba, [8]Servicio de Enfermedades Infecciosas, Hospital Universitario Carlos Haya, [9]Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Hospital Universitario Virgen de la Victoria, Málaga, [10]Servicio de Medicina Interna, Hospital Torrecárdenas, Almería, [11]Sección de Enfermedades Infecciosas, Hospital Punta Europa, Algeciras, [12]Unidad de Enfermedades Infecciosas, Complejo Hospitalario de Jaén, Jaén, [13]Unidad de Enfermedades Infecciosas, Hospital Universitario Virgen de las Nieves, Granada, and [14]Grupo HEPAVIR de la Sociedad Andaluza de Enfermedades Infecciosas (SAEI), Spain

Background. The aim of this study was to assess the efficacy and safety of pegylated interferon (IFN) plus ribavirin (RBV) in human immunodeficiency virus (HIV) and hepatitis C virus (HCV)–coinfected patients with severe immunodeficiency in a clinical cohort.

Methods. A total of 542 HIV-infected patients receiving treatment with pegylated IFN plus RBV from June 2001 through April 2007 were included in this study. The outcome variables were sustained virologic response (SVR) rate and the emergence of AIDS-defining events during HCV infection therapy. SVR rates among patients with a CD4 cell count ⩽250 cells/mm^3 at baseline were compared with those among patients with CD4 cell counts >250 cells/mm^3. The association between SVR and potential predictors was analyzed.

Results. Ten (26%) of 39 individuals with a baseline CD4 cell count ⩽250 cells/mm^3 and 198 (39%) of 503 with baseline CD4 cell counts >250 CD4 cells/mm^3 achieved SVR ($P = .09$). In a nested case-control study with populations matched at a 1:2 ratio, the SVR rate was 26% in the CD4 cell count ⩽250 cells/mm^3 group and 32% in the CD4 cell count >250 cells/mm^3 group ($P = .5$). Baseline CD4 cell count (⩽250 cells/mm^3 vs >250 cells/mm^3) was not associated with SVR in the multivariate analysis. Two (5%) individuals in the CD4 cell count ⩽250 cells/mm^3 group experienced opportunistic events during follow-up. In the CD4 cell count ⩽250 cells/mm^3 group, severe hematological toxicity and pegylated IFN or RBV dosage reductions occurred in 16 (41%) and 12 (31%) patients, respectively. In the CD4 cell count >250 cells/mm^3 group, severe hematological toxicity and pegylated IFN or RBV dosage reductions occurred in 29% ($P = .1$) and 20% ($P = .1$) of patients, respectively.

Conclusions. The efficacy of pegylated IFN plus RBV in HIV-HCV–coinfected patients with advanced immunosuppression is substantial and not significantly different to that observed in the overall coinfected population. HCV therapy is generally safe in the population of coinfected patients with advanced immunosuppression.

Hepatitis C virus (HCV)–related chronic liver disease follows an accelerated evolution to liver failure and death in human immunodeficiency virus (HIV)–infected patients [1, 2]. HCV treatment is likely the best tool to control the progression of liver disease in the HIV-HCV–coinfected population, because this therapy seems to reduce the risk of hepatocellular carcinoma, end-stage liver disease, and mortality due to liver failure [3]. Because of this, the combination of pegylated interferon (IFN) plus ribavirin (RBV) is currently recommended for HIV-infected patients who fulfill certain selection criteria [4–6].

Received 18 January 2009; accepted 25 May 2009; electronically published 22 September 2009.

Reprints or correspondence: Dr Juan A. Pineda, Unidad Clínica de Enfermedades Infecciosas, Hospital Universitario de Valme, Avenida de Bellavista s/n. 41014 Sevilla (japineda@telefonica.net.).

Clinical Infectious Diseases 2009; 49:e84–91

1058-4838/2009/4908-00E1$15.00
DOI: 10.1086/605677

According to commonly used recommendations for chronic hepatitis C treatment in HIV-HCV–coinfected patients [4–6], pegylated IFN plus RBV should not be given to subjects with low CD4 cell counts. A low probability of reaching sustained virologic response (SVR) and the possible emergence of AIDS-defining events during HCV therapy are the reasons for this recommendation, which is based on studies assessing the efficacy and safety of standard interferon alone [7–10]. However, in a pivotal clinical trial with pegylated IFN plus RBV, there was no relationship between CD4 cell count at baseline and SVR [11]. In addition, in this study, there were no AIDS-defining events observed during pegylated IFN plus RBV treatment among coinfected individuals with a baseline CD4 cell count <200 cells/mm^3 [11]. Nevertheless, the number of HIV-infected patients with severe immunodeficiency who received this antiviral combination was very low [11]. Therefore, available information about this issue among patients treated with pegylated IFN plus RBV is insufficient. Larger studies are needed to clarify whether HCV therapy is effective and safe in HIV-infected individuals with advanced immunosuppression, to determine whether it is a suitable treatment option in these patients. Advanced immunosuppression in this population is a factor that promotes a rapid liver fibrosis progression [12]. Because of this, these individuals would probably obtain a maximum benefit from HCV eradication.

The objective of the present study was to determine the efficacy and safety of pegylated IFN plus RBV in HIV-HCV–coinfected patients with severe immunodeficiency in a clinical cohort.

PATIENTS AND METHODS

Study population and follow-up. From June 2001 through April 2007, 4392 HIV-HCV–coinfected patients were prospectively followed in 13 hospitals in Spain. The patients from this cohort who fulfilled the following criteria were included in the study: (1) aged >16 years; (2) received a diagnosis of chronic hepatitis C, with persistently detectable HCV RNA in plasma; (3) HCV-therapy naive; and (4) started treatment against HCV infection with pegylated IFN plus RBV. All individuals included were followed up at least every 4 weeks during the first 24 weeks of treatment and every 8 weeks during the remaining treatment period. Clinical, biochemical, and hematological assessments were performed at every visit. Plasma HCV RNA level was assessed at least at weeks 12, 24, and 48 during treatment and at week 24 after treatment completion. Plasma HCV RNA load was measured using a quantitative polymerase chain reaction assay that varied according to the available technique at each participating center (Cobas Amplicor HCV Monitor [detection limit, 600 IU/mL], Cobas AmpliPrep-Cobas TaqMan [detection limit, 50 IU/mL], or Cobas TaqMan [detection limit, 10 IU/mL]; Roche Diagnostic Systems).

Treatment modality. All individuals received pegylated IFN alfa-2a at a dose of 180 μg per week or pegylated IFN alfa-2b at a dose of 1.5 μg/kg per week, along with oral RBV at a dose of 600–1500 mg per day. Treatment duration was 48 weeks for patients infected with HCV genotype 1 or 4, whereas those infected with genotype 2 or 3 received therapy for 24 or 48 weeks, according to the decision of the treating physician. At weeks 12 and 24, pegylated IFN and RBV treatment was discontinued in nonresponders; patients were considered to be nonresponders if they did not achieve a decrease in HCV RNA levels of at least 2 $\log_{10}$ at week 12 of therapy or undetectable serum HCV RNA at 24 weeks after starting therapy. Dosage adjustments for pegylated IFN and RBV were made according to the criteria of the physician who was treating the patient.

All patients with CD4 cell counts ⩽250 cells/mm^3 at baseline received secondary prophylaxis for previous AIDS-defining events during anti-HCV therapy, when applicable. Patients who had CD4 cell counts <200 cells/mm^3 during HCV therapy were treated with primary prophylaxis against opportunistic infections according to Centers for Disease Control and Prevention recommendations [13].

Assessment of efficacy and safety. The main efficacy end point was SVR, defined as undetectable HCV RNA in serum samples at 6 months after the end of pegylated IFN plus RBV treatment. The efficacy analysis of HCV therapy was performed according to the principle of intention to treat, and missing values were considered to be failures. The main safety end point was the emergence of AIDS-defining events during HCV therapy (according to 1993 Centers for Disease Control and Prevention definitions). Severe hematological toxicity, use of growth factors, and dosage reductions of pegylated IFN and RBV were assessed. Severe hematological toxicity was defined as the appearance of at least 1 of the following laboratory abnormalities during HCV therapy: (1) hemoglobin level <10 g/dL; (2) neutrophil counts <750 cells/mm^3; or (3) platelet counts <50000 cells/mm^3.

Statistical analysis. Comparative analyses of efficacy were performed using 2 approaches. First, SVR rates in patients with a CD4 cell count ⩽250 cells/mm^3 at baseline (the CD4⩽250 group) were compared with those observed among patients with CD4 cell counts >250 cells/mm^3 (the CD4>250 group). Second, a nested case-control substudy was performed to examine patients with similar baseline characteristics in both groups. In this substudy, case patients were all patients with CD4 cell counts ⩽250 cells/mm^3. Control patients, matched at a 1:2 ratio with case patients according to HCV genotype (1 or 4 vs 2 or 3), cirrhosis, and baseline plasma HCV RNA load (⩽600,000 IU/mL vs >600,000 IU/mL) [14], were selected from the remaining population. The diagnosis of cirrhosis was made by liver biopsy according to the Scheuer's scoring system [15].

Additionally, we assessed the relationship between SVR and

Table 1. Main Characteristics of Study Population

Parameter	CD4 cell count at the beginning of therapy		
	⩽250 cells/mm^3 (n = 39)	>250 cells/mm^3 (n = 503)	P
Age, median years (IQR)	39 (36–43)	40 (37–43)	.6
Male sex	34 (87)	403 (80)	.3
Baseline body weight, median kg (IQR)[a]	63 (59–74)	69 (61–77)	.06
Former IDU	31 (80)	431 (86)	.3
AIDS-defining events before HCV therapy	21 (53)	149 (30)	.002
Baseline serum ALT, median IU/mL (IQR)	60 (46–111)	85 (57–128)	.1
Baseline HCV RNA load >600,000 IU/mL	27 (69)	289 (57)	.1
Advanced liver fibrosis (F3–F4)[b]	20 (66)	152 (46)	.02
Cirrhosis (F4)[b]	10 (33)	64 (19)	.05
HCV genotype			
1	28 (72)	267 (53)	.1
2	1 (3)	7 (1)	
3	7 (18)	175 (35)	
4	3 (8)	54 (11)	
Baseline CD4 cell count <125 cells/mm^3	7 (18)	…	
Receipt of pegylated IFN alfa-2a no. (%)	34 (87)	383 (76)	.1
RBV dosage, median mg/kg/day (IQR)[a]	15.4 (13.3–16.8)	13.8 (12.5–15.6)	.01
Baseline undetectable HIV load	31 (80)	361 (72)	.3
Baseline LDL cholesterol level, median mg/dL (IQR)	83 (50–110)	90 (66–114)	.1
Baseline hemoglobin level, median g/dL (IQR)	14.4 (12.7–15.8)	15.1 (14–16.2)	.02
Baseline neutrophil count, median cells/mm^3 (IQR)	2270 (1885–2682)	3026 (2310–3940)	.002
Baseline platelet count, median cells/mm^3 (IQR)	146,000 (117,000–190,000)	172,500 (127,750–223,000)	.04
Compliance with HCV therapy⩾80%	32 (82)	447 (89)	.2
Concomitant antiretroviral therapy	37 (95)	411 (82)	.03
TDF plus 3TC or FTC as NRTI backbone	12 (31)	130 (26)	.5
Receipt of zidovudine	8 (20)	92 (18)	.7
Receipt of abacavir	13 (33)	105 (21)	.07
Receipt of growth factors	10 (26)	39 (8)	.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. 3TC, lamivudine; ALT, alanine aminotransferase; FTC, emtricitabine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug user; IFN, interferon; IQR, interquartile range; LDL, low-density lipoprotein; NRTI, nucleoside or nucleotide reverse-transcriptase inhibitor; RBV, ribavirin; TDF, tenofovir.

[a] Available for 36 patients with CD4 cell counts ⩽250 cells/mm^3 and 459 patients with CD4 cell counts >250 cells/mm^3.

[b] Liver biopsy was available for 30 patients with CD4 cell counts ⩽250 cells/mm^3 and 332 patients with CD4 cell counts >250 cells/mm^3.

the following potential predictors in the entire cohort: sex, age, risk factor for HCV transmission, previous AIDS-defining events, baseline serum level of alanine aminotransferase, liver fibrosis stage according to the Scheuer's scoring system [15], HCV genotype, baseline plasma HCV RNA load, baseline level of low-density lipoprotein cholesterol, CD4 cell count at baseline, type of pegylated IFN received, daily dose of RBV by weight, self-reported compliance with HCV therapy, use of concomitant antiretroviral therapy, and type of nucleoside or nucleotide reverse-transcriptase inhibitor (NRTI) backbone.

Continuous variables are expressed as median values (interquartile range [IQR]), and categorical variables are expressed as number (percentage; 95% confidence interval [CI]). The Student's t test was used for comparisons between continuous variables if a normal distribution was followed, and the Mann-Whitney U test was used otherwise. The frequencies were compared using the χ^2 test or the Fisher's exact test if the expected frequency for any cell was ⩽5. In the case-control study, continuous variables and frequencies were compared using the Wilcoxon test and the McNemar test, respectively. The variables that showed a relationship with SVR in the univariate analysis with a $P < .2$ were entered in a multivariate step-wise logistic regression model. The adjusted odds ratio and the respective 95% CI were calculated. Associations with $P < .05$ were considered to be significant. Data were analyzed using the SPSS statistical software package, release 14.0 (SPSS).

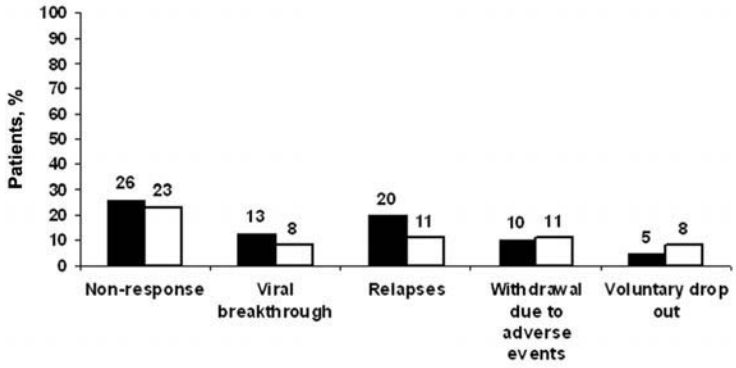

Figure 1. Rates of lack of response to pegylated interferon plus ribavirin according to CD4 cell count at the beginning of hepatitis C virus (HCV) infection therapy. *Black bars* represent patients with CD4 cell counts ≤250 cells/mm^3 at baseline, and *white bars* represent patients with CD4 cell counts >250 cells/mm^3 at baseline. Numbers above bars represent the percentage of patients in each category. Nonresponse to treatment, $P = .7$; viral breakthrough, $P = .3$; relapse, $P = .07$; withdrawal from the study because of adverse events, $P = .9$; voluntary drop out, $P = .7$.

Ethical aspects. The study was designed and performed according to the Helsinki declaration and was approved by the Ethics Committee of the Hospital Universitario de Valme.

RESULTS

Characteristics of the study population. Five hundred forty-two individuals who were treated with pegylated IFN plus RBV fulfilled the inclusion criteria. Thirty-nine (7%) of them had ≤250 CD4 cells/mm^3 at baseline (the CD4≤250 group). At beginning HCV therapy, the median CD4 cell count in the CD4≤250 group was 200 cells/mm^3 (IQR, 136–230 cells/mm^3), whereas among patients with CD4 cell counts >250 cells/mm^3 (the CD4>250 group), the median CD4 cell count was 526 cells/mm^3 (IQR, 396–720 cells/mm^3). Thirty-one (80%) individuals in the CD4≤250 group were infected HCV genotype 1 or 4, compared with 321 (64%) of the 503 patients in the CD4>250 group ($P = .04$). The remaining baseline characteristics of both groups are shown in Table 1.

Virologic response according to baseline CD4 cell count. A total of 208 (38%; 95% CI, 34%–42%) patients achieved SVR in the entire cohort; 10 (26%; 95% CI, 13%–42%) in the CD4≤250 group and 198 (39%; 95% CI, 35%–43%) in the CD4>250 group ($P = .09$). In the subpopulation of patients infected with HCV genotype 1 or 4, 5 (16%; 95% CI, 5%–33%) with CD4 counts ≤250 CD4 cells/mm^3 at baseline achieved SVR, compared with 83 (26%; 95% CI, 21%–31%) of the patients in the CD4>250 group ($P = .2$). Among patients infected with HCV genotype 2 or 3, 5 (62%; 95% CI, 24%–91%) patients in the CD4≤250 group and 115 (63%; 95% CI, 55%–70%) in the CD4>250 group achieved SVR ($P = .9$). The differences in the frequencies of other types of response to HCV therapy between both groups were not significant in the sta-

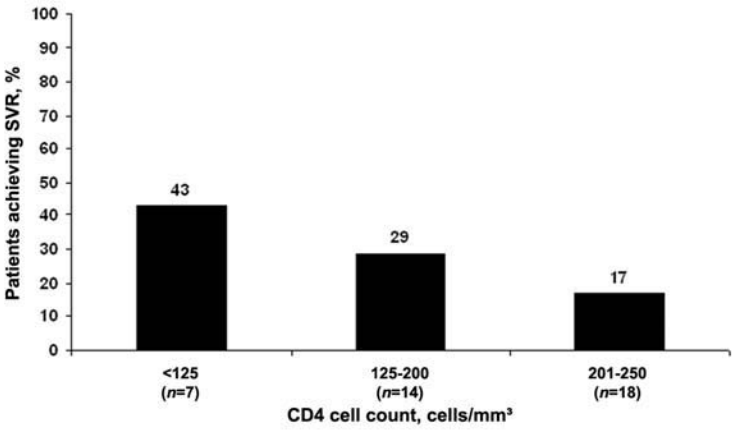

Figure 2. Rate of sustained virologic response (SVR) among patients with CD4 cell counts ≤250 cells/mm^3 at the beginning of hepatitis C virus (HCV) infection therapy. $P = .385$, for the comparison of SVR among the 3 patient groups.

Table 2. Main Features of Patients Included in the Case-Control Study

Parameter	CD4 cell count at the beginning of therapy		
	⩽250 cells/mm^3 (n = 39)	>250 cells/mm^3 (n = 78)	P
HCV genotype 1 or 4	31 (79)	62 (79)	>.99
Baseline HCV RNA level >600,000 IU/mL	27 (69)	54 (69)	>.99
Cirrhosis (F4)[a]	10 (33)	10 (33)	>.99
Liver fibrosis (F3)[a]	9 (30)	12 (20)	.3
Baseline CD4 cell count, median cells/mm^3 (IQR)	200 (136–230)	523 (397–685)	<.001
Male sex	34 (87)	60 (77)	.2
Baseline undetectable HIV load	31 (80)	60 (77)	.8
Baseline LDL cholesterol level >100 mg/dL	11 (34)	22 (35)	.9
Daily dose of RBV >13.9 mg/kg	25 (64)	37 (52)	.1
Concomitant antiretroviral therapy	37 (95)	71 (91)	.9
Nonresponse	10 (26)	23 (29)	.6
Viral breakthrough	5 (13)	8 (10)	.7
Relapse	8 (20)	11 (14)	.4
Withdrawal because of adverse events	4 (10)	8 (10)	>.99
Voluntary drop out	2 (5)	3 (4)	.9

NOTE. Data are no. (%) of patients, unless otherwise indicated. HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; LDL, low-density lipoprotein.

[a] Liver biopsy was available in 30 subjects in the CD4⩽250 group and in 60 subjects in the CD4>250 group.

tistical analysis, although relapses tended to be more common in the CD4⩽250 group (Figure 1). In the CD4⩽250 group, there were no statistically significant differences in SVR rates according to baseline CD4 cell count when patients were categorized as having CD4 cell counts <125 cells/mm^3, 125–200 cells/mm^3, or 201–250 cells/mm^3 (Figure 2).

In the substudy with case and control patients matched at a 1:2 ratio according to HCV genotype, baseline plasma HCV RNA load, and cirrhosis (Table 2), 10 (26%; 95% CI, 13%–42%) individuals in the CD4⩽250 group and 25 (32%; 95% CI, 21%–43%) in the CD4>250 group achieved SVR (P = .5). Among the subpopulation of patients infected with HCV genotype 1 or 4, the rates of SVR in the CD4⩽250 group and CD4>250 group were 16% (95% CI, 5%–33%) and 21% (95% CI, 11%–33%), respectively (P = .6). Among patients infected with HCV genotypes 2 or 3, the rates of SVR were 62% (95% CI, 24%–91%) in the CD4⩽250 group and 75% (95% CI, 47%–92%) in the CD4>250 group (P = .7). In this substudy, the frequencies of other responses to HCV therapy were comparable in the 2 groups (Table 2).

Predictors of SVR. In the entire cohort, subjects who achieved and who did not achieve SVR had median baseline CD4 cell counts of 538 cells/mm^3 (IQR, 392–746 cells/mm^3) and 475 cells/mm^3 (IQR, 348–659 cells/mm^3), respectively (P = .02). In the multivariate analysis, HCV genotype 2 or 3, baseline plasma HCV RNA load <600,000 IU/mL, lack of concomitant antiretroviral therapy, use of NRTI backbone containing tenofovir plus lamivudine or emtricitabine during HCV therapy, baseline low-density lipoprotein cholesterol levels ⩾100 mg/dL, and exposure to the planned HCV therapy ⩾80% were associated with SVR (Table 3). In the same analysis, CD4 cell count (⩽250 cells/mm^3 vs >250 cells/mm^3) was not associated with SVR (Table 3).

Safety. Two (5%; 95% CI, 0.6%–17%) individuals with a CD4 cell count ⩽250 cells/mm^3 at baseline experienced a major opportunistic event during the follow-up period. One of them with advanced liver fibrosis and a CD4 cell count of 239 cells/mm^3 at baseline presented a first episode of *Pneumocystis jiroveci* pneumonia at the end of HCV therapy. At that moment, this patient had an undetectable HIV viral load and a CD4 cell count of 108 cells/mm^3. She self-reported that she was completely compliant with the chemoprophylaxis prescribed during HCV therapy, specifically oral cotrimoxazole. The second patient discontinued pegylated IFN plus RBV at week 19 because of an episode of symptomatic visceral leishmaniasis relapse. This individual had advanced liver fibrosis and a CD4 cell count of 129 cells/mm^3 at baseline. He was receiving oral miltefosine as secondary prophylaxis against leishmaniasis during anti-HCV therapy. When this individual experienced this event, he had an undetectable HIV viral load and his CD4 cell count had decreased to 28 cells/mm^3. Both patients showed resolution of their opportunistic infections after treatment with cotrimoxazole and liposomal amphotericin B, respectively. No patient died during the study period in the CD4⩽250 group. In

Table 3. Sustained Virologic Response (SVR) According to Different Variables in the Entire Cohort of Patients Coinfected with Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) Treated with Pegylated Interferon plus Ribavirin

Parameter	SVR, no. (%) of patients	*P*, univariate	Adjusted OR (95% CI)	*P*, multivariate
Age, years				
<40	102 (42)		…	
⩾40	89 (36)	.2	…	
Sex				
Male	156 (36)		…	
Female	52 (50)	.009	…	
Baseline ALT level, IU/L)				
⩽89	94 (35)		…	
>89	88 (40)	.3	…	
Injection drug user				
Yes	174 (37)		…	
No	34 (42)	.4	…	
Previous AIDS-defining events				
Yes	66 (39)	.8	…	
No	137 (38)		…	
Cirrhosis				
Yes	16 (22)		…	
No	115 (40)	.003	…	
HCV genotype				
1 or 4	88 (25)		…	
2 or 3	120 (63)	<.001	6.6 (3.6–9.9)	<.001
Baseline HCV RNA load, IU/mL				
<600,000	107 (43)	<.001	2.5 (1.4–3.8)	<.001
⩾600,000	101 (32)		…	
Daily dose of RBV, mg/kg				
<13.9	100 (41)	.06	…	
⩾13.9	84 (33)		…	
Type of pegylated IFN				
Alfa-2a	168 (40)	.09	…	
Alfa-2b	40 (32)		…	
Exposure to HCV therapy				
<80%	10 (16)		…	
⩾80%	198 (41)	<.001	3 (1.3–7.1)	.008
Undetectable plasma HIV RNA				
Yes	149 (38)		…	
No	59 (39)	.7	…	
Baseline CD4 cell count, cells/mm^3				
>250	198 (39)	.09	…	
⩽250	10 (26)		…	
Baseline CD4 cell count, cells/mm^3				
>200	201 (39)	.6	…	
⩽200	7 (33)		…	
Baseline LDL cholesterol level, mg/dL				
⩾100	70 (45)		…	
<100	88 (35)	.03	2.2 (1.3–3.7)	.002
Lack of ART or TDF plus 3TC or FTC as NRTI backbone				
Yes	108 (45)		…	
No	100 (33)	.005	1.75 (1.07–2.8)	.024

NOTE. 3TC, lamivudine; ALT, alanine aminotransferase; ART, antiretroviral therapy; CI, confidence interval; FTC, emtricitabine; IFN, interferon; LDL, low-density lipoprotein; NRTI, nucleoside or nucleotide reverse-transcriptase inhibitor; OR, odds ratio; RBV, ribavirin; TDF, tenofovir.

the CD4>250 group, 1 (0.2%) patient experienced an AIDS-defining event during HCV therapy, specifically an episode of pulmonary tuberculosis.

The rate of discontinuation of pegylated IFN plus RBV attributable to adverse events was similar in patients with CD4 cell counts ⩽250 cells/mm^3 or >250 cells/mm^3 at the beginning of HCV therapy (Figure 1). In the CD4⩽250 group, 16 (41%; 95% CI, 25%–57%) patients demonstrated an episode of severe hematological toxicity, compared with 146 (29%; 95% CI, 25%–33%) of the patients in the CD4>250 group ($P = .1$). In the CD4⩽250 group, severe anemia, neutropenia, and thrombocytopenia occurred in 5 (13%), 11 (28%), and 6 (15%) patients, respectively. In the CD4>250 group, severe anemia, neutropenia, and thrombocytopenia occurred in 12% ($P = .8$), 15% ($P = .02$), and 10% ($P = .2$) of patients, respectively. Pegylated IFN or RBV dosages had to be reduced in 12 (31%) patients in the CD4⩽250 group and in 102 (20%) patients in the CD4>250 group ($P = .1$). The use of growth factors was more frequent among patients with a baseline CD4 cell count ⩽250 cells/mm^3 (Table 1).

DISCUSSION

We found that the efficacy of pegylated IFN plus RBV in HIV-HCV–coinfected patients with advanced immunosuppression is substantial and not significantly different from that observed in the overall coinfected population. Therapy against HCV infection is generally safe in coinfected individuals who start this treatment with a low CD4 cell count. Appropriate strategies to accurately prevent opportunistic events should be implemented in this population, although this option might not be entirely effective.

The results of this study provide relevant information on the efficacy of pegylated IFN plus RBV treatment among HIV-HCV–coinfected individuals with advanced immunosuppression. In fact, this study analyzed the largest population of patients with low CD4 cell counts yet examined, to our knowledge, including clinical trials and cohort studies [11,16]. In this study, the rate of SVR was higher among patients with a CD4 cell count >250 cells/mm^3, compared with those with CD4 cell counts ⩽250 cells/mm^3 at baseline, especially among patients infected with genotypes 1 and 4, although these differences did not reach statistical significance. However, predictors of poor response to HCV therapy were not equally frequent among patients belonging to both treatment groups. The percentages of HCV genotype 1 or 4 infection and cirrhosis were greater among patients with lower CD4 cell counts at baseline, which might have been accounted for the differences in the rate of SVR. For this reason, we performed a nested, matched case-control study according to these variables, to increase the comparability of both arms. In this case-control study, we did not find significant differences in SVR between the populations. Finally, multivariate analysis did not show an association between SVR and baseline CD4 cell count categorized as ⩽250 cells/mm^3 versus >250 cells/mm^3. Therefore, according to our results, the efficacy of pegylated IFN plus RBV among HIV-infected individuals with severe immunodeficiency is considerable and similar to that found in subjects without severe immunodeficiency.

Our findings are in agreement with those reported in 2 other studies that have assessed the relationship between CD4 cell count at baseline and SVR in HIV-infected individuals [11, 16]. In these studies, CD4 cell count at baseline was not associated with SVR. Nevertheless, firm conclusions cannot be drawn from these studies because of their limitations. In a substudy of the APRICOT trial [11], only 17 patients with a baseline CD4 cell count <200 cells/mm^3 received pegylated IFN plus RBV. Moreover, a considerable proportion of these individuals were infected with HCV genotypes 2 or 3, which probably contributed to the higher rate of SVR achieved in this group. In addition, one study did not find a relationship between SVR and baseline CD4 cell count categorized as ⩽350 cells/mm^3 versus >350 cells/mm^3 [16]. However, this level of CD4 cell count is too elevated to make definitive conclusions regarding the efficacy of HCV therapy in patients with lower CD4 cell counts at baseline. Our study included a population of 39 patients with CD4 cell counts ⩽250 cells/mm^3, 79% of whom were infected with HCV genotypes 1 or 4. Thus, our study strongly supports data from other studies demonstrating that advanced immunosuppression may not be a major factor in predicting SVR. Nevertheless, larger studies are needed to confirm this finding.

We found that the frequency of AIDS-defining events during anti-HCV therapy was not high among HIV-infected patients with advanced immunosuppression. This finding agrees with the results of the APRICOT trial [11]. In our study, secondary chemoprophylaxis of visceral leishmaniasis, 1 of the opportunistic events observed during HCV therapy, did not prevent a relapse. Nevertheless, secondary prophylaxis of visceral leishmaniasis is not entirely effective [17]. Consequently, although data on this topic are very limited, HIV-infected individuals with severe immunodeficiency should receive effective primary prophylaxis against preventable opportunistic infections and secondary prophylaxis against prior opportunistic disease during anti-HCV therapy. When this option is not possible, pegylated IFN plus RBV should be deferred in these patients to avoid the development of AIDS-defining events. On the other hand, both patients with severe immunosuppression who experienced an opportunistic event in our study had advanced liver fibrosis, whereas a subject without severe immunodeficiency experienced an episode of pulmonary tuberculosis. Although additional studies are needed to assess these issues, these findings suggest that it is necessary to determine the severity of liver fibrosis and screen for tuberculosis before starting HCV

therapy. Finally, in this study, severe neutropenia has been found to be associated with CD4 cell counts ≤250 cells/mm^3 at baseline. This finding could be secondary to the elevated proportion of subjects with low pretreatment neutrophil counts included in this subgroup of patients, which is a known risk factor for severe neutropenia in HIV-infected patients treated with anti-HCV therapy [18]. In addition, the frequency of overall severe hematological events and dosage reductions of HCV therapy was higher in individuals with CD4 cell counts ≤250 cells/mm^3 at baseline, although differences between both populations did not reach statistical significance, probably because of a lack of statistical power. For these reasons, patients with severe immunodeficiency who are receiving treatment with pegylated IFN plus RBV should be more carefully monitored for hematological laboratory abnormalities during HCV therapy.

The main limitation of this study is the limited sample size. In spite of the fact that the present study included a sample size larger, to our knowledge, than any clinical trial or cohort study published so far [11, 16], we cannot exclude that it was too small to detect some differences that otherwise could have been observed, such as the possible relationship between overall severe hematological toxicity and lower CD4 cell counts at baseline.

In summary, on the basis of the results of this study, pegylated IFN plus RBV is a feasible therapy option in HIV-HCV–coinfected patients with advanced immunosuppression. Effective chemoprophylaxis against opportunistic infections should be received by these patients during HCV therapy.

Acknowledgments

Financial support. Consejería de Salud of the Junta de Andalucía (Reference 0133/08); and the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Red de SIDA (ISCIII-RETIC RD06/006).

Potential conflicts of interest. J.A.M. has received a research grant from GlaxoSmithKline. D.M. has participated as an investigator in a clinical trial supported by GlaxoSmithKline and has received consulting fees from Roche, Abbott, and Bristol-Myers Squibb. A.R. has received consulting fees from Bristol-Myers Squibb, Abbott, Gilead, Roche Pharma, and Boehringer Ingelheim Pharmaceuticals. M.G.-S. has participated as an investigator in clinical trials supported by Roche and GlaxoSmith-Kline and has received lecture fees from Boehringer Ingelheim. J.M. has been an investigator in clinical trials supported by Roche, Bristol-Myers Squibb, and Abbott Pharmaceuticals and has received lectures fees from Roche and consulting fees from Boehringer Ingelheim. J.A.P. has received consulting fees from GlaxoSmithKline, Bristol-Myers Squibb, Abbott, Gilead, and Boehringer Ingelheim Pharmaceuticals; has received research support from GlaxoSmithKline, Roche, Bristol-Myers Squibb, Schering-Plough, Abbott, and Boehringer Ingelheim Pharmaceuticals; and has received lecture fees from GlaxoSmithKline, Roche, Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, and Schering-Plough Pharmaceuticals. All other authors: no conflicts.

References

1. Graham CS, Baden LR, Yu E, Mrus JM, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis **2001**; 33: 562–9.
2. Pineda JA, Romero-Gómez M, Díaz-García F, et al. HIV coinfection shortens the survival of patients with hepatitis C virus–related decompensated cirrhosis. Hepatology **2005**; 41:779–89.
3. Berenguer J, Álvarez-Pellicer J, López-Aldeguer J, et al. Sustained virologic response to interferon plus ribavirin reduces liver-related complications and mortality in HIV/HCV-co-infected patients [abstract 60]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.
4. Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from HCV-HIV International Panel. AIDS **2007**; 21:1073–89.
5. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV co-infection. AIDS **2004**; 18:1–12.
6. Rockstroh JK, Bhagani S, Benhamou Y, et al. European AIDS clinical society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. HIV Med **2008**; 9:82–8.
7. Soriano V, García-Samaniego J, Bravo R, et al. Interferon alpha for treatment of chronic hepatitis C in patients infected with HIV: Hepatitis-HIV Spanish study group. Clin Infect Dis **1996**; 23:585–91.
8. Mauss S, Klinker H, Ulmer A, et al. Response to treatment of chronic hepatitis C with interferon alpha in patients infected with HIV-1 is associated with higher CD4$^+$ cell count. Infection **1998**; 26:16–9.
9. Vento S, Di Perri G, Cruciani M, Garofano T, Concia E, Bassetti D. Rapid decline of CD4$^+$ cells after interferon treatment in HIV-1 infection. Lancet **1993**; 341:958–9.
10. Pesce A, Taillan B, Rosenthal E. Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. Lancet **1993**; 341:1597.
11. Opravil M, Sasadeusz J, Cooper DA, et al. Effect of baseline CD4 cell count on the efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in patients with HIV/hepatitis C virus coinfection. J Acquir Immune Defic Syndr **2008**; 47:36–49.
12. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol **2006**; 44:47–55.
13. Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the U.S Public Health Service and the Infectious Diseases Society of America. Ann Intern Med **2002**; 137:435–78.
14. Zeuzem S, Buti M, Ferenci P, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. J Hepatol **2006**; 44:97–103.
15. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol **1991**; 13:372–4.
16. Valerio L, Yazdanpanah Y, Poizot-Martin I, et al. Baseline CD4 cell count and outcome of pegylated interferon plus ribavirin therapy in HIV/hepatitis C virus–coinfected patients. J Acquir Immune Defic Syndr **2008**; 47:50–5.
17. Mira JA, Corzo JE, Rivero A, et al. Frequency of visceral leishmaniasis relapses in HIV-infected patients undergoing highly active antiretroviral therapy. Am J Trop Med Hyg **2004**; 70:298–301.
18. Mira JA, López-Cortés LF, Merino D, et al. Predictors of severe hematological toxicity secondary to pegylated interferon plus ribavirin in HIV/HCV-coinfected patients. Antivir Ther **2007**; 12:1225–35.