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Comparison of high ribavirin induction versus standard ribavirin dosing, plus peginterferon-α for the treatment of chronic hepatitis C in HIV-infected patients: the PERICO trial

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Abstract

Background. Ribavirin (RBV) exposure seems to be critical to maximize treatment response in human immunodeficiency virus (HIV)–positive patients with chronic hepatitis C virus (HCV) infection.

Methods. HIV/HCV-coinfected individuals naive to interferon were prospectively randomized to receive peginterferon-α-2a (180 μg/d) plus either RBV standard dosing (1000 or 1200 mg/d if <75 or ≥75 kg, respectively) or RBV induction (2000 mg/d) along with subcutaneous erythropoietin β (450 IU/kg/wk), both during the first 4 weeks, followed by standard RBV dosing until completion of therapy. Early stopping rules at weeks 12 and 24 were applied in patients with suboptimal virological response.

Results. A total of 357 patients received ≥1 dose of the study medication. No differences in main baseline characteristics were found when comparing treatment arms. Sustained virological response (SVR) was attained by 160 (45%) patients, with no significant differences between RBV induction and standard treatment arms (SVR in 72 of 169 patients [43%] vs 88 of 188 [47%], respectively). At week 4, undetectable HCV RNA (29% vs 25%) and mean RBV trough concentration (2.48 vs 2.14 μg/mL) were comparable in both arms, whereas mean hemoglobin decay was less pronounced in the RBV induction plus erythropoietin arm than in the RBV standard dosing arm (−1.7 vs −2.3 mg/dL; $P < .005$). Treatment discontinuation occurred in 91 (25%) patients owing to nonresponse and in 29 (8%) owing to adverse events. HCV relapse occurred in 34 patients (10%). Univariate and multivariate analyses identified HCV genotype 2 or 3 (odds ratio [OR], 10.3; 95% confidence interval [CI], 2.08–50.2; $P = .004$), *IL28B* CC variants (OR, 2.92; 95% CI, 1.33–6.41; $P = .007$), nonadvanced liver fibrosis (OR, 2.27; 95% CI, 1.06–5.01; $P = .03$), and rapid virological response (OR, 40.3; 95% CI, 5.1–314.1; $P < .001$) as predictors of SVR.

Conclusions. A 4-week course of induction therapy with high RBV dosing along with erythropoietin does not improve SVR rates in HIV/HCV-coinfected patients. Preemptive erythropoietin might blunt the benefit of RBV overdosing by enhancing erythrocyte uptake of plasma RBV.

Chronic hepatitis C virus (HCV) infection is a major cause of complications and death in human immunodeficiency virus (HIV)–positive patients in the era of highly active antiretroviral therapy [1, 2]. The combination of peginterferon-α (pegIFNα) and ribavirin (RBV) has been the only treatment for chronic hepatitis C during the last decade, providing rates of cure ranging from 20% to 50% in the HIV/HCV-coinfected population [3–7], lower than in HCV-monoinfected patients [8, 9]. Whereas the use of higher dosing of pegIFNα has not shown any benefit in terms of treatment success [10, 11], the use of higher RBV exposure has led to improvements in the rate of HCV clearance, although development of anemia is a major limitation of this approach [12, 13]. A direct correlation exists between the trough concentration of RBV within the first 12 weeks of treatment and the rate of rapid and early virological response, which finally impacts on sustained virological response (SVR) [14–16]. Although the exact mechanism of RBV action has not been fully elucidated, its effect seems to be more critical in HIV-positive patients in whom the interferon effect is compromised [17].

The deleterious drug-drug interactions between DAA and antiretroviral agents, and the fact that DAA will be initially given along with pegIFNα/RBV may preclude a broader use of these drugs within the short term [18]. For this reason, strategies exploring ways to increase RBV exposure, whereas protecting from severe anemia remain attractive. Herein, we report the results of a trial that examined whether the preemptive administration of erythropoietin for the first 4 weeks of therapy along with double doses of RBV might increase antiviral activity with a reduced risk of anemia.

MATERIAL AND METHODS

Study Design

PERICO (Peginterferon Ribavirin in Coinfection) is a multicenter, randomized, prospective trial that examined the efficacy and safety of subcutaneous pegIFNα-2a (Pegasys; Roche) (180 μg/wk) plus 2 different oral doses of RBV (Copegus; Roche) in HIV/HCV-coinfected patients (ClinicalTrials.gov identifier: NCT00526448). The 2 treatment arms received either standard weight-based RBV dosing (1000 or 1200 mg/d if <75 or ≥75 kg) or a high fixed dosing (2000 mg/d) during the first 4 weeks of therapy. Patients in the latest group also received subcutaneous erythropoietin β (Neorecormon; Roche) (450 IU/kg) on the first day and every week for the first 4 weeks of therapy. Thereafter, RBV was given adjusted to weight in both treatment arms until completion of therapy.

Following guidelines at the time the trial begun [1, 19], the length of therapy was decided based on the achievement of rapid virological response, meaning HCV RNA undetectability at week 4. Patients infected with HCV genotype 1 or 4 were treated for 48 or 72 weeks, whereas those infected with HCV genotype 2 or 3 were treated for 24 or 48 weeks. Early stopping rules at weeks 12 and 24 were applied in patients with unsatisfactory virological responses. Dose adjustments for pegIFNα and/or RBV owing to neutropenia, thrombocytopenia, or anemia were made according to standard recommendations.

The primary objectives of the study were to explore whether an RBV dosing induction supplemented with erythropoietin could increase the SVR rate compared with standard RBV dosing in HIV/HCV-coinfected patients. Secondary objectives were focused on the incidence of anemia, RBV trough concentrations, and the impact of *IL28B* polymorphisms in both treatment arms.

The main inclusion criteria were as follows: age ≥18 years; confirmed HIV (positive results of enzyme-linked immunosorbent assay and Western blot analysis) and HCV (serum HCV RNA level >1000 IU/mL) infections for >6 months; stable highly active antiretroviral therapy for >6 months without didanosine, zidovudine, or stavudine; CD4 cell counts >200 cells/μL; plasma HIV RNA levels <50 copies/mL. In patients who were not receiving antiretroviral therapy, CD4 cell counts had to be >500 cells/μL, and plasma HIV RNA levels <10 000 copies/mL. In addition to those with HCV genotype 1 or 4, patients infected with HCV genotype 2 or 3 were also included in the study, because according to

European guidelines [19] all might benefit from enhanced RBV exposure. Patients with any stage of liver fibrosis were allowed in the study.

The main exclusion criteria were as follows: prior exposure to interferon-based therapies, decompensated cirrhosis, serious neuropsychiatric conditions, markers of autoimmunity (antinuclear antibodies >1/160), positive hepatitis B surface antigen results, alcohol abuse, illicit drug consumption, hemoglobin levels <10 mg/dL, and neutrophil counts <1000 cells/μL or platelet counts <75 000 cells/per μL.

Study variables were recorded at baseline, at weeks 4 and 12, and every 3 months thereafter until completion of therapy. Further assessments were made 12 and 24 weeks after drug discontinuation. Main demographics and anthropometric parameters, *IL28B* polymorphisms, and liver fibrosis stage, determined using transient elastometry, were obtained at baseline. Main blood cell and biochemistry analyses, CD4 cell and plasma HIV RNA and HCV RNA levels were recorded at every visit. Trough concentrations of RBV were measured at week 4 for each patient. All patients signed informed consent and the study was approved by the ethics committees of all participating clinics.

Study Variables

Plasma HCV RNA was measured using a real-time polymerase chain reaction (PCR) assay (COBAS TaqMan; Roche), which has a lower limit of detection of 10 IU/mL. HCV genotyping was performed using a commercial reverse-transcription PCR hybridization assay (Versant HCV Genotype v2.0 LiPA; Siemens), which maximally reduces the chances of HCV genotype misclassification [20]. Plasma HIV RNA was measured using Versant HIV-1 RNA v3.0 (Siemens), which has a lower limit of detection of 50 copies/mL. Plasma RBV trough concentrations were measured at week 4 using high-performance liquid chromatography, as described elsewhere [21] testing blood obtained before the morning drug dose.

The extent of liver fibrosis was measured within the 6 months before initiation of HCV therapy using transient elastography by FibroScan (Echosens). Details about this noninvasive method, the examination procedure, and correlation of liver fibrosis estimates with liver biopsy findings have been reported elsewhere [22, 23]. The median value of all tests per patient is expressed in kilopascals. Based on previous studies conducted in HIV/HCV-coinfected patients [24–26], the best cutoff values, by METAVIR stages, were as follows: <7.2 kPa for null or minimal liver fibrosis (METAVIR F0-F1), 7.2–9.5 kPa for moderate liver fibrosis (METAVIR F2), 9.6–14.5 kPa for advanced liver fibrosis (METAVIR F3), and >14.5 kPa for cirrhosis (METAVIR F4).

The *IL28* gene polymorphisms at rs12979860 were examined testing DNA specimens collected from peripheral blood mononuclear cells, using the 5′ nuclease assay with allele-specific TaqMan probes (ABI TaqMan allelic discrimination kit) and the ABI7900HT Sequence Detection System (Applied Biosystems) [27].

Statistical Analyses

The main characteristics of the study population and the different parameters evaluated are expressed as means (and SD) or proportions. Comparisons of continuous variables were performed using parametric or nonparametric tests, as required. Associations between different qualitative parameters were explored using χ^2 or Fisher's exact tests, as appropriate. Logistic regression analysis with backward selection was performed to identify variables associated with SVR; all variables with *P* values <.5 in the univariate analysis were included in the model. All statistical analyses were performed using SPSS software, version 15.0 (SPSS). All *P* values were 2-tailed, and differences were considered significant only at $P < .05$.

RESULTS

A total of 377 patients were screened, of whom 357 were finally randomized and received ≥1 dose of the study medication; 169 (47%) in the induction arm and 188 (53%) in the control arm.

Baseline Characteristics

The main features of the study population are depicted in Table 1. Most patients were males (73%), with a mean age of 43 years and a mean body mass index of 24 kg/m^2. Serum HCV RNA levels were >500 000 IU/mL in 72% of patients, and 80% were infected with HCV genotype 1 or 4. The favorable *IL28B* CC alleles were present in 43% of patients. Advanced liver fibrosis was recognized in 49% of cases. Most patients (92%) were receiving antiretroviral therapy, 85% had undetectable plasma HIV RNA, and the mean CD4 cell count was 553 ± 254 cells/μL. As shown in Table 1 there were no significant differences in baseline characteristics between the 2 study arms.

Table 1. Baseline Characteristics of the Study Population

Characteristic	All (n = 357)	RBV Induction (n = 169 [47%])	RBV Standard (n = 188 [53%])	*P*
Age, mean, y	43.0 ± 5.5	42.9 ± 5.5	43.0 ± 5.5	.8
Male sex	261 (73)	120 (71)	141 (75)	.3
BMI, mean, kg/m^2	24.1 ± 3.9	24.0 ± 3.5	24.1 ± 4.2	.6
HCV RNA level, mean, log IU/mL	6.12 ± 0.81	6.13 ± 0.77	6.11 ± 0.85	.7
HCV RNA level >500 000 IU/mL	255 (72)	122 (72)	133 (71)	.8
HCV genotype				.1
1	224 (63)	109 (65)	115 (61)	
2	6 (2)	5 (3)	1 (1)	
3	68 (19)	26 (15)	42 (22)	
4	59 (17)	29 (17)	30 (16)	
IL28B CC alleles	100 (43)	49 (46)	51 (40)	.3
Advanced liver fibrosis	146 (49)	76 (51)	70 (47)	.4
On HAART	322 (92)	149 (90)	173 (93)	.3
HIV RNA level <50 copies/mL	267 (85)	127 (85)	140 (85)	.8
CD4 cell count, mean, cells/μL	553 ± 254	549 ± 239	557 ± 269	.7

Abbreviations: BMI, body mass index; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RBV, ribavirin.
Unless otherwise specified, data represent no. (%) of patients.

Treatment Outcome

A total of 251 (70%) patients completed the planned length of therapy. Of them, 160 patients attained SVR, which represented 45% of the whole treated population in the intention-to-treat analysis (55% on treatment). There were no significant differences when comparing both treatment arms, with SVR attained in 43% in the RBV induction arm and 47% in the control arm (P = .4) (Figure 1).

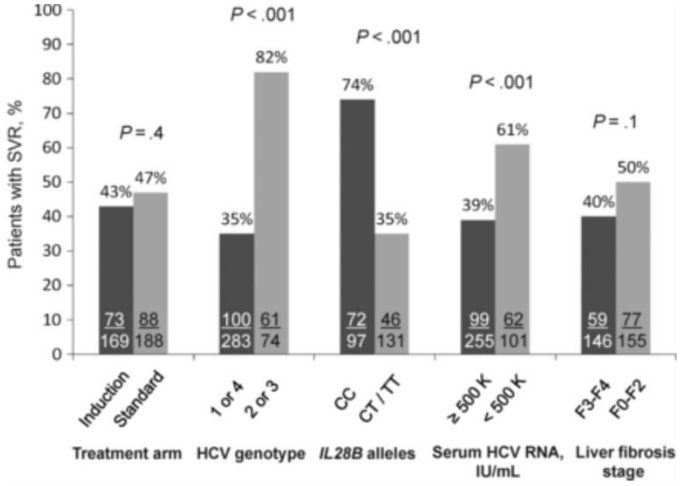

Figure 1. Predictors of sustained virological response (SVR) in univariate analysis. HCV, hepatitis C virus.

Viral responses at weeks 4 and 12 of therapy, and on completion of treatment, did not differ significantly between treatment arms. In contrast, viral response was strongly influenced by HCV genotype. For instance, of 330 patients with a valid HCV RNA measurement at week 4, 89 (27%) attained rapid virological response, with 16% infected with HCV genotype 1 or 4 and 68% with HCV genotype 2 or 3 ($P < .001$). Similar differences were seen at other time points (Figure 2).

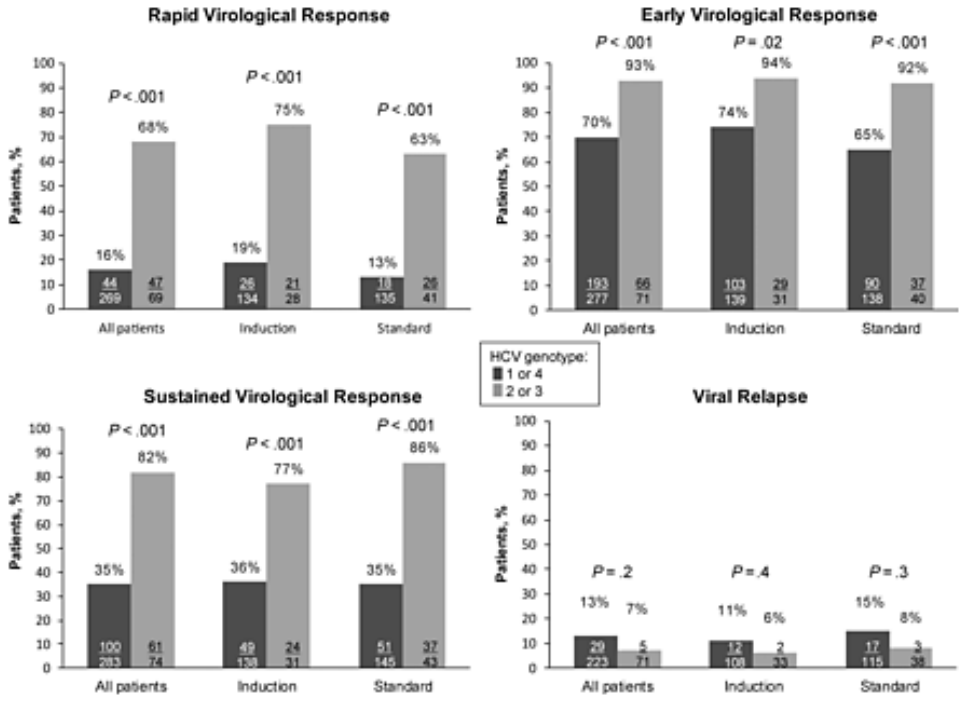

Figure 2. Viral response at different time points by treatment arm and hepatitis C virus (HCV) genotype.

A total of 163 patients discontinued pegIFNα-RBV therapy prematurely. This was because of suboptimal virological response in 91 (25%), reflecting failure to achieve at least a 2-log reduction in viral load at week 12 in 63 patients (18%) or failure to reach undetectability at week 24 in 28 patients (8%). Early treatment discontinuation in the remaining cases was due to adverse events in 29 (8%), voluntary withdrawal in 33 (9%) or loss to follow-up in 10 (3%). Overall, 34 (9%) patients experienced viral relapse after having attained undetectability at the end of treatment.

Predictors of Treatment Response

Figure 1 depicts the influence of several baseline variables on the proportion of patients who achieved SVR. Whereas treatment arm did not affect significantly the SVR rate, it was strongly influenced by HCV genotypes, *IL28B* alleles, and baseline serum HCV RNA level. In contrast, liver fibrosis staging only marginally influenced the SVR.

Table 2 records the representation of different characteristics in patients with or without SVR, as well as their impact on treatment outcome after adjustment for other variables. In multivariate analysis considering only baseline variables, serum HCV RNA level <500 000 IU/mL (odds ratio [OR], 6.67; 95% confidence interval [CI], .91–4.35; $P = .09$), HCV genotype 2 or 3 (OR, 20.1; 95% CI, 4.55–100; $P \leq .001$), *IL28B* genotype CC (OR, 4.85; 95% CI, 2.38–9.89; $P < .001$), and lack of advanced liver fibrosis (OR, 2.40; 95% CI, 1.27–5.02; $P = .009$) were associated with SVR.

Table 2. Predictors of Sustained Virological Response in Multivariate Analysis

Predictor	Sustained Virological Response		*P*	OR (95% CI); *P*	
	Yes (n = 161 [45%])	No (n = 196 [55%])		Baseline Variables	Baseline Plus On-Treatment Variables
Age, mean, y	43.1 ± 5.5	42.9 ± 5.5	.7	…	…
Male sex	113 (70)	148 (76)	.2	…	…
BMI, mean, kg/m^2	24.1 ± 4.0	24.07 ± 3.8	.8	…	…
HCV RNA level, mean, log IU/mL	5.88 ± 0.87	6.31 ± 0.71	<.001	…	…
HCV RNA level <500 000 IU/mL (%)	62 (38)	39 (20)	<.001	6.67 (.91–4.35); .09	1.16 (.42–3.23); .7
HCV genotype 2 or 3	61 (38)	13 (7)	<.001	20.1 (4.55–100); <.001	10.3 (2.08–50.2); .004
IL28B CC alleles	72 (61)	25 (23)	<.001	4.85 (2.38–9.89); <.001	2.92 (1.33–6.41); .007
Nonadvanced liver fibrosis	77 (57)	78 (47)	.1	2.40 (1.27–5.02); .009	2.27 (1.06–5.01); .03
On HAART	142 (89)	180 (93)	.2	…	…
Abacavir as part of HAART	26 (20)	34 (21)	.8	…	…
HIV RNA level <50 copies/mL	120 (87)	147 (84)	.4	…	…
CD4 cell count, mean, cells/μL	568 ± 246	542 ± 262	.4	…	…
RBV trough concentration at wk 4, mean, μg/mL	2.35 ± 0.79	2.17 ± 0.74	.4	…	…
Rapid virological response	79 (51)	10 (6)	<.001	…	40.3 (5.1–314.1); <.001

Abbreviations: BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; RBV, ribavirin.
Unless otherwise specified, data represent no. (%) of patients. Empty cells stand for variables not included in multivariable analyses.

When both RBV trough concentration and attainment of HCV RNA levels <10 IU/mL at week 4 were included in the analysis, HCV genotype 2 or 3 (OR, 10.3; 95% CI, 2.08–50.2; *P* = .004), *IL28B* genotype CC (OR, 2.92; 95% CI, 1.33–6.41; *P* = .007), lack of advanced liver fibrosis (OR, 2.27; 95% CI, 1.06–5.01; *P* = .03), and rapid virological response (OR, 40.3; 95% CI, 5.1–314.1; *P* < .001) remained associated with SVR.

Unexpectedly, mean RBV trough concentrations at week 4 were comparable in the 2 treatment arms (2.48 ± 0.83 μg/mL in the RBV induction plus erythropoietin arm vs 2.14 ± 0.76 μg/mL in the control arm; *P* = .2). Moreover, mean RBV plasma trough concentrations were comparable in patients who reached SVR (2.35 ± 0.79 μg/mL) and the rest (2.17 ± 0.74 μg/mL) (*P* = .3).

Numerical differences were observed in the proportion of patients who achieved SVR between those with HCV subtype 1a and those with subtype 1b (31% vs 42%; *P* = .1). In 229 patients with available *IL28B* genotypes, significant differences in SVR were noted between CC and CT/TT carriers (74% vs 35%; *P* < .001). The influence of these respective *IL28B* allelic variants was mainly recognized in HCV genotype 1 or 4 carriers (62% vs 29%; *P* < .01) rather than in patients infected with HCV genotype 2 or 3 (91% vs 92%; *P* = .9).

Treatment Safety

There were a total of 1191 episodes of toxicity affecting all 357 patients recruited in the study. They were mostly flulike symptoms (19%), gastrointestinal disturbances (11%), and psychiatric alterations (10%). Grade 3–4 side effects occurred in 100 patients (28%); the most common were anemia (5.3% of all patients), neutropenia (5.0%), thrombocytopenia (2.3%), respiratory tract infections (4.8%), and neuropsychiatric alterations (1.4%) (Table 3). The incidence of adverse events was comparable in the 2 treatment arms. The mean drop in hemoglobin concentration within the first month of therapy was lower in the RBV induction arm supplemented with erythropoietin than in the control arm (−1.7 ± 0.3 vs −2.3 ± 0.2 mg/dL, respectively; *P* = .005).

Table 3. Adverse Events in the PERICO Trial

		Patients, No. (%) (n = 357)	
Adverse Effect	Episodes of Any Grade, No.	Grade 3–4	Treatment Discontinuation
Anemia	92	19 (5.3)	4 (1.1)
Neutropenia	54	18 (5.0)	1 (0.3)
Thrombocytopenia	35	9 (2.5)	1 (0.3)
Infection	48	17 (4.8)	3 (0.8)
Psychiatric	117	5 (1.4)	1 (0.3)
Others	830	31 (8.7)	19 (5.3)
Total	1191	100 (28.0)	29 (8.1)

DISCUSSION

The achievement of SVR using pegIFNα-RBV therapy in HIV/HCV-coinfected patients remains a challenge [1]. In agreement with previous studies conducted in Europe using weight-based RBV in HIV/HCV-coinfected patients [6, 7], 35% of our patients infected with HCV genotype 1 or 4 achieved SVR. This figure increased to 82% in HCV genotype 2 or 3 carriers, which unfortunately only represent a fifth of the coinfected population in our region. It should be noted that our results are much better than those obtained using flat low-dose RBV dosing (800 mg/d), where SVR rates across studies ranged from 14% to 29% for HCV genotype 1 or 4, and from 44% to 73% for HCV genotype 2 or 3 [3–5]. In the PERICO trial we explored whether higher RBV dosing (2000 mg/d) during the first 4 weeks of therapy, along with preemptive erythropoietin, could enhance the virological response while preventing the development of severe anemia. Interestingly, although anemia was ameliorated using the growth factor, the antiviral effect did not improve. Thus, other approaches should be tested to improve treatment outcomes in the coinfected population, in which progression of liver-related disease is accelerated [1].

Although treatment arm did not significantly influence the rate of SVR, 4 baseline parameters did. Patients with low viral load, favorable *IL28B* alleles, HCV genotype 2 or 3, and lack of advanced liver fibrosis responded significantly better to therapy. Interestingly, when viral response at week 4 was also considered, it became the strongest predictor of SVR with an OR >40. The relatively high treatment discontinuation rate due to early suboptimal response recorded in our study might be due to the high proportion of subjects with an unfavorable baseline profile. Our findings are in agreement with the results from other recent studies that have examined the impact of baseline variables on SVR in HIV/HCV-coinfected patients, based on which a predictor index named "Prometheus" has been proposed to support therapeutic decision making, providing information about the likelihood of SVR to pegIFNα-RBV therapy [28]. This freely available index (www.fundacionies.com/prometheusindex.php) has recently been endorsed by the European AIDS Clinical Society as a tool to support treatment decisions of hepatitis C in the coinfected population [29]. Currently clinicians mainly debate on whether treatment should be deferred until the arrival of new direct acting antivirals or, alternatively, be given with pegIFNα-RBV alone as soon as possible.

Although several reports have stressed the importance of RBV exposure to maximize the antiviral effect against HCV, especially in the HIV-coinfected population [16, 17], our trial failed to prove it. Patients receiving standard weight-based RBV showed virological responses at weeks 4 and 12 as well as SVRs comparable to responses in those treated with RBV (2000 mg/d) plus erythropoietin. Unexpectedly, we did not find differences in the plasma concentration of RBV in the 2 treatment arms. On the other hand, the hemoglobin concentration was lower in patients who received preemptive erythropoietin. Altogether, these findings suggest that the administration of erythropoietin in the RBV induction arm could have blunted the RBV plasma overexposure initially pursued, because of an increasing erythrocyte RBV uptake. Once in plasma, RBV is actively taken up at the membrane of erythrocytes through the equilibrative nucleoside transporter 1, so that the ratio between intracorpuscular and plasma RBV concentration is 60:1 [30, 31]. Thus, expansion of the red blood cell compartment with erythropoietin since the very beginning of RBV therapy could have produced increased sequestration of the extra amount of RBV given, rendering free RBV plasma concentrations no greater than in the control group.

A direct correlation seems to exist between RBV plasma concentrations, the incidence of anemia, and SVR rates [13, 16, 32]. The development of anemia could act as a surrogate of increased RBV plasma exposure, as free RBV is the one active. Several studies have pointed out that anemia during therapy predicts the chances of SVR [33, 34]. We hypothesize that anemia may not only be a surrogate marker for increased likelihood of SVR but may directly affect treatment outcome by facilitating free RBV exposure in the liver. In this regard, a smaller red blood cell compartment might indirectly favor a greater concentration of circulating free RBV to reach the hepatocytes. The inclusion of a third arm in our study, testing elevated RBV dosing along with erythropoietin on demand only in case of severe anemia, would have provided further insights to answer this hypothesis. Given the high interindividual variability in RBV plasma concentrations, which is influenced by body weight, sex, and kidney glomerular function,

we cannot exclude the possibility that these or other factors for which we did not adjust might have acted as confounders in our study. Furthermore, we did not consider drug adherence in our analyses.

In summary, the administration of greater than approved doses of RBV along with erythropoietin does not improve the antiviral efficacy of hepatitis C therapy in HIV/HCV-coinfected individuals. The use of preemptive erythropoietin may have blunted the increased disposition of free RBV by promoting erythrocyte sequestration. While awaiting for the arrival of new direct acting antivirals against HCV, it seems worthwhile to ensure maximal RBV exposure when treating HIV/HCV-coinfected patients, limiting the indication of erythropoietin only to patients who develop severe anemia on therapy.

Notes

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