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

Predictive Value of Early Virologic Response in HIV/Hepatitis C Virus–Coinfected Patients Treated With an Interferon-Based Regimen Plus Ribavirin

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Background: As a result of adverse events, a moderate rate of virologic response, and high costs associated with hepatitis C virus (HCV) therapy, finding early markers of sustained treatment response is a clinical priority. In the HCV-monoinfected population, a reduction ≥2 log in plasma HCV RNA at week 12 of therapy (early virologic response [EVR]) predicts a sustained virologic response (SVR). Few data are available in HIV/HCV-coinfected patients, however.

Methods: A subanalysis of data from HIV/HCV-coinfected patients treated with pegylated interferon-α-2b (PEG, 100–150 μg/wk) or interferon-α-2b (IFN, 3 MIU 3 times per week) plus ribavirin (RBV, 800–1200 mg/d) was conducted in a randomized single-center clinical trial. The duration of treatment was 48 weeks (only 24 weeks for HCV genotype 2 or 3 with a baseline HCV RNA level <800,000 IU/mL).

Results: Ninety-five patients were randomized (43 assigned to IFN + RBV and 52 assigned to PEG + RBV). Eighty patients completed at least 12 weeks on therapy and were included in the EVR analysis. Thirty-five (43%) of them attained an SVR (56% and 30% of patients treated with PEG and IFN, respectively; $P = 0.026$). An EVR occurred in 55 (69%; 80% of PEG + RBV group and 56% of IFN + RBV group). Overall, 35 of 55 patients with an EVR were sustained responders, yielding a positive predictive value of 64% (70% in PEG + RBV arm and 55% in IFN + RBV arm). None of the patients who demonstrated an HCV RNA decline of <2 logs at week 12 reached an SVR (negative predictive value of 100%).

Conclusion: Our results confirm the utility of an EVR to predict the chance of the lack of an SVR in HIV/HCV-coinfected patients, particularly those treated with PEG.

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Chronic infection with hepatitis C virus (HCV) and complications associated with its clinical course represent an important cause of morbidity and mortality in HIV/HCV-coinfected patients after the widespread use of highly active antiretroviral therapy (HAART).[1–3] In addition, HIV/HCV-coinfected patients have been shown to exhibit an accelerated progression to liver fibrosis.[4] Moreover, HCV coinfection may limit the adequate treatment of HIV and is associated with increased toxicity of antiretroviral drugs.[5] Thus, improved therapeutic management of HCV-related chronic liver disease has become a major concern in this set of patients.

Current therapies for chronic HCV based on pegylated interferon-α (PEG) associated with ribavirin (RBV) have demonstrated good rates of success in HIV/HCV-coinfected patients, eliminating the virus in nearly 40% of patients.[6–9] Nevertheless, this treatment is not well tolerated in coinfected patients and also has the potential to interact with some antiretroviral drugs.[6–14]

Several studies have evaluated potential predictive factors of virologic response to monitor an effective response to therapy. For example, baseline demographic data, such as female gender and age <40 years, or data related to the HCV characteristics, such as genotype 2 or 3 and a low baseline viral load (<800,000 IU/mL), have been associated with a better response.[6–8,15,16] Similarly, some authors have analyzed potential early markers to predict the final virologic response; among them, it seems that a reduction of ≥2 logs in plasma HCV RNA at week 12 of treatment (early virologic response [EVR]) would have a good predictive value of a sustained virologic response (SVR).[17–19]

Although there are some discordant results,[20] the clearance of HCV RNA seems to occur more slowly in HIV/HCV-coinfected patients than in HCV-monoinfected subjects.[21] As a consequence, concern has arisen over the feasibility of following the rules derived from HIV-negative patients and whether they can be applied in HIV/HCV-coinfected patients.

The objective of our study was to asses the utility of an EVR to predict an SVR to HCV therapy in a group of HIV/HCV-coinfected patients.

PATIENTS AND METHODS

We analyzed the EVR in a cohort of HIV/HCV-coinfected patients included in a randomized, prospective, single-center, open-label clinical trial designed to evaluate the efficacy and tolerability of 2 interferon-based therapeutic regimens: (1) interferon-α-2b (IFN) at a dose of 37 iu administered subcutaneously 3 times per week plus daily oral RBV, or (2) PEG administered subcutaneously at a dose of 100 μg when the patient's body weight was 75 kg or at a dose of 150 μg when the patient's body weight was 75 kg or more each week plus oral RBV each day. The dose of RBV, 800 to 1200 mg, was adjusted to body weight and administered in 2 divided doses per day. The duration of treatment was 48 weeks, but only 24 weeks when the HCV genotype was 2 or 3 and the baseline HCV RNA level was <800,000 IU/mL. The study design and primary results have been published previously.[9]

The efficacy of the therapy was defined as undetectable HCV RNA in serum at 24 weeks after cessation of the treatment (SVR) by an intent-to-treat analysis. An EVR was defined as a reduction of plasma HCV RNA levels ≥2 logs at week 12 of treatment compared with baseline. In addition, a qualitative assay of HCV RNA at week 4 was performed, and a very early virologic response (vEVR) was defined if HCV RNA was undetectable at this time.

Serum HCV RNA was measured by a quantitative polymerase chain reaction (PCR) assay at baseline, before starting treatment, and 12 weeks after starting therapy (Cobas AmpliPrep/Cobas Amplicor HCV Monitor Test, version 2.0, with a sensitivity of 500 copies/mL; Roche Molecular Systems, Branchburg, NJ). During treatment, at weeks 4, 24, 36, and 48 as well as 24 weeks after cessation of therapy, HCV RNA was measured by a qualitative PCR assay (Cobas AmpliPrep/Cobas Amplicor HCV Monitor Test, version 2.0, with a sensitivity of 50 copies/mL; Roche Molecular Systems).

A descriptive analysis of the continuous variables at baseline was conducted looking at the median and central tendency measures and at the interquartile range (IQR) as a dispersion measure. Categoric variables at baseline were describing using percentage of the total group. These values were compared between the 2 therapy groups with the aim of ensuring that the demographic, epidemiologic, clinical, biochemical, and histopathologic characteristics did not differ. Continuous variables were compared between groups by means of the Wilcoxon rank sum test. Quantitative variables were compared using the χ^2 or Fisher exact test. Analyses were done by intention to treat on all patients who achieved at least 12 weeks on therapy.

Positive predictive value (PPV) was defined as the probability that an SVR would occur in those patients with evidence of an EVR. Conversely, negative predictive value (NPV) was defined as the probability that patients without evidence of an EVR would not achieve an SVR.

All tests were 2-tailed and based on a confidence level of 0.05. The analyses were performed using STATA (StataCorp 2003 STATA Statistical Software, release 8.0; Stata Corporation, College Station, TX).

RESULTS

A total of 95 subjects (68% male with a median age of 40 years) were included in the study (43 assigned to the IFN + RBV group and 52 assigned to the PEG + RBV group), as reported previously.[9] Baseline characteristics were similar between the 2 groups (Table 1). In the global intent-to-treat analyses, 34% of patients attained an SVR (44% in the group receiving PEG + RBV compared with 21% for the IFN + RBV treatment group; $P = 0.017$).

Eighty patients in our study completed at least 12 weeks of therapy and were included in the EVR study. Of this group, 55 patients (69%) showed a reduction of ≥2 logs in plasma HCV RNA at week 12 of treatment. The frequency of an EVR was significantly higher in patients treated with PEG than in those treated with IFN (80% vs. 56%; $P = 0.030$; Fig. 1).

Regarding the HCV genotype, an EVR was detected in 54% of patients infected with genotypes 1 through 4 (71% of patients treated with PEG vs. 38% of patients treated with IFN), whereas an SVR was detected in 31% of patients (50% in the PEG + RBV group vs. 12.5% in the IFN + RBV group). In those patients infected with genotypes 2 and 3, an EVR was seen in 93% of patients and an SVR was attained in 63% of patients. There were no significant differences between the 2 treatment groups.

TABLE 1. Baseline Characteristics of the Patients

	PEG + RBV (N = 52)	IFN + RBV (N = 43)	Total (N = 95)
Age (y)*	40	40	40
Male gender (%)	63	74	68
Body weight (kg)*	62	64	63
HIV-1 risk factor (% IDUs)	75	91	82
Duration of HIV infection (y)*	10	12	11
Patients on ART (%)	94	81	88
Baseline CD4 count (cells/mm^3)*	570	556	560
Baseline HIV viral load (copies/mL)*	199	199	199
HCV genotype (%)	55	43	49
1	4	2	3
2	33	33	33
3	8	21	14
4	0	2	1
Not typable			
HCV RNA level (% <800,000 IU/mL)	53	38	46
Duration of HCV infection (y)*	17	17,5	17
Inflammatory Scheur's score*	3	4	3
Fibrosis Scheur's score (%)			
0–2	71	69	70
3–4	29	31	30

None of the differences were statistically significant.
*Median.
ART indicates antiretroviral therapy; IDUs, intravenous drug users.

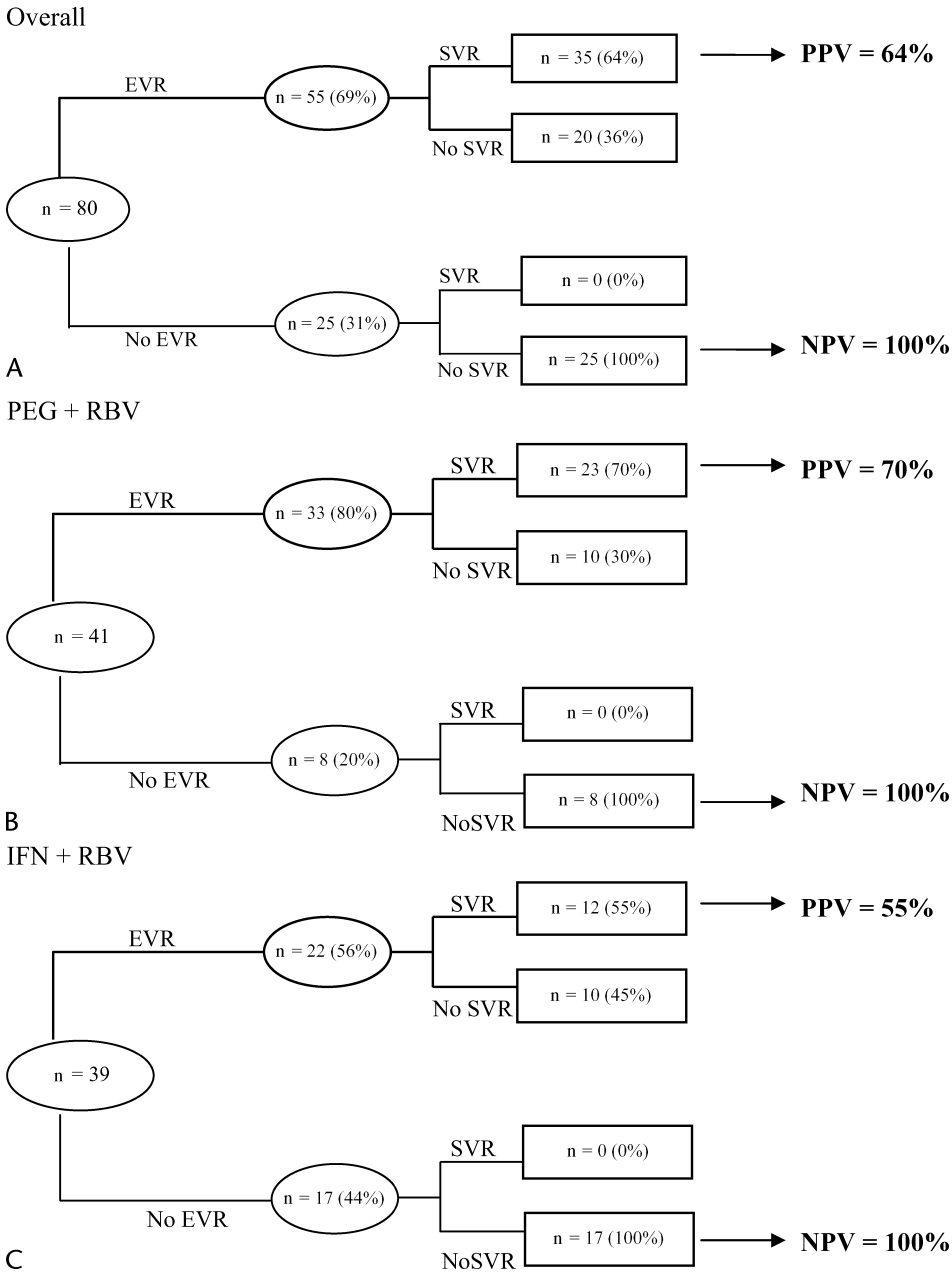

FIGURE 1. EVR as a predictor of SVR in those patients who achieved 12 weeks on therapy (n = 80).

The overall PPV of the SVR for individuals showing an EVR was 64% (Table 2). Regarding the kind of interferon used in the therapy, the PPV value of an EVR was 55% in the case of IFN-based therapy and 70% in the case of the PEG-based regimen (see Table 2; see Fig. 1). Conversely, none of the patients treated with any kind of interferon who demonstrated a decline in HCV RNA level <2 logs at week 12 reached an SVR (NPV of 100%).

In 19 patients, HCV RNA was undetectable at week 4. The PPV achieved with this vEVR was 89%, and the NPV was 70%. Considering the kind of interferon used, the PPV of the vEVR was 67% when a patient was on IFN-based therapy and 100% when a patient was on the PEG-based regimen.

DISCUSSION

The high morbidity, moderate rate of SVR, and high cost of treatment with interferon and RBV–based HCV therapy have prompted research to evaluate factors that may predict the final outcome therapy. Previous studies have shown that in HCV-monoinfected patients, an EVR could be useful in indicating which patients are likely to respond to the therapy.[16–19] There are few data in the literature that confirm an EVR's usefulness in predicting treatment outcome in HIV/HCV-coinfected patients, however.[6–8,21,22]

In our series, an EVR was reached in 69% of those 80 patients who completed 12 weeks on therapy, and 44% of them attained an SVR; the PPV for this cohort was 64%. There were

TABLE 2. Percentages of EVR and SVR by Intent-to-Treat Analysis in Those Patients Who Completed 12 Weeks on Therapy (n = 80)

	EVR	SVR	PPV	NPV
Overall (n = 80)	69	44	64	100
IFN (n = 39)	56	31	55	100
PEG (n = 41)	80	56	70	100
Genotypes 1 + 4 (n = 48)	54	31	58	100
IFN (n = 24)	38	12.5	33	100
PEG (n = 24)	71	50	71	100
Genotypes 2 + 3 (n = 30)	93	63	68	100
IFN (n = 14)	93	64.2	69	100
PEG (n = 16)	94	62.5	67	100

IFN indicates interferon-α-2b; PEG, pegylated interferon-α-2b.

also clear differences between treatment groups; the rates of SVR are intimately related to the EVR, and we could detect how patients treated with PEG demonstrated a better response than the patients who received IFN. A possible pathogenic explanation would be a better initial decrease of HCV plasmatic viremia when we used this new interferon formulation compared with the classic formulation.[23] This idea seems to be confirmed when we analyze the results of vEVR; clearly, the response is better in the group of patients treated with PEG.

In the same way as the SVR, the EVR in the coinfected patients is lower than that obtained in similar studies in monoinfected patients;[17,18] in addition, the chances of an SVR tend to be lower in early virologic responders in the setting of HIV/HCV coinfection, possibly because of a greater number of relapses.[22]

If we focus our attention on the group of patients with a better rate of virologic response, those treated with PEG, we must emphasize the high PPV related to an EVR, which reaches 70% even in those patients with genotype 1 or 4.

Similar to previously published studies in monoinfected patients[18] as well as to the few data available on coinfected populations,[7,22] no patients in our study achieved an SVR in the absence of an EVR. In light of potential toxicities and costs, the high NPV allowed us to stop the treatment for those patients who did not achieve an EVR. Nevertheless, individual decisions regarding discontinuation of antiviral treatment in patients with advanced fibrosis should consider the possible beneficial effects of maintaining the therapy (ie, decreasing necroinflammatory activity and slowing the progression of fibrosis),[7,8] even in the absence of a viral response.[7,25]

At the present time, increasing interest exists in analysis of the kinetics of viral elimination after beginning treatment with interferon so as to determine the optimal time point for evaluation of the HCV RNA level and to predict the final response as early as possible. Some examples of these studies in monoinfected patients are the evaluation of the HCV response at week 2 in a new course of treatment in relapsed patients[26] or evaluation of the EVR at week 4 in a group of previous nonresponding patients.[27] Similarly, a recent study from Cargnel et al[28] shows that the EVR in coinfected patients at week 8 is strongly associated with a likelihood of achieving an SVR. Our results at week 4 are in agreement with these data; HCV RNA levels in almost 90% of the patients with an vEVR remain undetectable at the end of the follow-up period. Nevertheless, we are aware that new studies with a large number of patients are necessary to validate all these data and to express a consensus rule to establish the best point time for evaluation of the EVR.

In conclusion and considering the limited size of this cohort, the results of our study suggest that the rules of reduction of 2 log of the viral load at week 12 of HCV therapy in coinfected patients have the same value as those in monoinfected patients. The high PPV provides a goal to motivate adherence during the therapy and stimulates patients to continue the treatment. In the same way, the high NPV forces us to consider discontinuation of anti-HCV treatment in HIV/HCV-coinfected patients who do not achieve an EVR.

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