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Response predictors and clinical benefits of hepatitis C retreatment with pegylated interferon and ribavirin in HIV/HCV coinfection

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ABSTRACT

Background. Hepatitis C is a leading cause of mortality among HIV-infected individuals. Therefore, eradication of HCV in this population is a priority. There are scarce data regarding retreatment efficacy of HIV/HCV coinfected patients. The aim of our study was to evaluate efficacy, predictors of response, and long term clinical benefits of sustained virological response (SVR) after hepatitis C retreatment in a population of HIV/HCV coinfected patients. **Material and methods.** We evaluated efficacy, safety, and clinical benefits of peginterferon(alfa-2a or alfa-2b) and ribavirin in a restrospective, observational, multicentric study, including 47 HIV/HCV coinfected patients, non-responders to previous treatment with conventional interferon alfa-2a and ribavirin. The primary endpoint of efficacy was SVR, defined as undetectable viral load 24 weeks after end of treatment. Death, liver disease progression, CD4 counts, and AIDS defining illness were the endpoints to access clinical benefits of treatment response. **Results.** In our analysis, 31.9% patients reached SVR. Genotypes 2/3 had a significant better SVR (66.7%) compared to genotypes 1/4 (33.3%) (p = 0.022). During follow-up, deaths (6.89%) and hepatic decompensation (28.6%) occurred only in the nonresponder group, while there were no cases of death or hepatic decompensation among the responder group(p = 0.037). **Conclusion.** Nearly one third of patients (mainly those with genotypes 2/3) reached SVR after hepatitis C retreatment in this group of HIV/HCV coinfected patients. SVR was protective against hepatic decompensation and death in a two-year follow-up period. Retreatment may be an effective and safe way to eradicate HCV until new anti-HCV drugs become available to this group of patients.

Key words. Non-responders. HIV-HCV coinfected. AIDS. Efficacy. Treatment.

INTRODUCTION

Hepatitis C virus (HCV) infection progresses faster to cirrhosis and is characterized by a lower response to interferon (IFN)-based treatments in patients coinfected with the human immunodeficiency virus (HIV) than in HCV-monoinfected individuals. It is currently one of the leading causes of death among HIV individuals, where the prevalence of coinfection is high due the shared routes of transmission.[1-3]

Initially, clinical trials investigating the efficacy of peginterferon and ribavirin in HCV-HIV coinfected patients demonstrated overall sustained virological response (SVR) rates ranging from 27% to 44% after 48 weeks of therapy.[4-6] More recently, the highest SVR rate reported to date in coinfected individuals (49.6%) was achieved in a large trial involving the adoption of response-guided treatment and

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weight-based ribavirin dosing.[7] Still, a large number of HIV-HCV coinfected patients have failed to achieve SVR following a first course of hepatitis C therapy. In this group, hepatic decompensation has been shown to be the leading cause of non-AIDS-related mortality.[8-10]

The effectiveness of interventions, such as liver transplantation, to reduce mortality from end-stage liver disease in HIV-HCV coinfected patients have limited outcomes in the mid-term, when HCV reinfection arises as the main cause of mortality. Additionally, successful management of the interactions between imunnosuppressants and anti-HIV regimens can be difficult to achieve.[11-14] Although newly approved anti-HCV drugs targeted at patients monoinfected with HCV genotype 1 may also benefit coinfected individuals, data from trials using these drugs in the latter group are still preliminary.[15,16] Moreover, their limited efficacy at inhibiting only HCV genotype 1, phamacokinectic and pharmacodinamic interactions between these new drugs and antiretroviral regimens for HIV[17,18] represent an additional obstacle for their use in HCV-HIV coinfected patients.

There are only a few studies demonstrating efficacy of retreatment in coinfected patients who have not responded to a previous course of an IFN-based regimen.[19-23] These studies reported SVR rates from 16 to 40%, which were shown to depend on genotype (genotype 3 was a predictor of response in three studies[21,22,23]), the presence of IL-28B CC polymorphism[23] and prior relapse (those who relapsed following the first treatment were more likely to achieve SVR than non-responders[22]). Similarly, the investigation of the long-term clinical benefits of HCV retreatment for co-infected individuals has been also restricted to a few studies.[24-27]

The primary objective of the present study was to determine SVR rates and putative predictors of response to hepatitis C retreatment in a group of HIV-HCV coinfected individuals considered difficult to treat. Additionally, we compared the clinical outcome and progression of HIV and liver disease between retreatment responders and non-responders. Our study also intends to reveal long term clinical benefits of hepatitis C retreatment in a coinfected population of HIV/HCV patients.

MATERIAL AND METHODS

Study design

To determine the efficacy and possible predictors of virological response following HCV retreatment we conducted retrospective cross-sectional analyses of patients from five tertiary care centers in Sao Paulo, Brazil. To this end, electronic and print databases containing medical information from all patients treated at these institutions were used.

The study protocol was approved by the Ethics Committee of all centers, and all patients still being followed provided informed consent for participation.

Enrolled patients were selected from those registered at these centers. All patients received treatment from January 2004 to February 2009. To evaluate the clinical outcomes of retreatment and benefits of SVR in this population we also conducted a cross-sectional analysis of their medical records as of March 2011.

All medical records were initially reviewed to identify those patients who received at least two treatments for hepatitis C. We included in the analyses those patients who received an initial treatment with conventional interferon and ribavirin and who did not achieve SVR, and were next submitted to a second treatment with peginterferon and ribavirin.

All patients received either 180 mg/week of Peg-IFN alfa-2a (Pegasys, Roche, Basel, Switzerland) or 1.5 mg/kg/week of Peg-IFN alfa-2b (PegIntron, Schering-Plough, Kenilworth, NJ, USA) and ribavirin during retreatment, for 48 weeks, according to the Brazilian Guidelines published by the Ministry of Health, which provided the medication used in this study.[28]

Variables examined

Medical records were reviewed to determine the age, gender, and weight of patients, their clinical characteristics, and laboratory findings during and after retreatment with peginterferon and ribavirin. HCV genotype, HCV RNA (viral load) levels, presence of cirrhosis (as based on the METAVIR classification), and ribavirin dose were recorded for each patient. Additionally, CD4 cell counts at the beginning and after the end of retreatment, HIV viral load, and the adoption of antiretroviral treatment were recorded. We also gathered information on each patient's virological response to the previous HCV treatment (non-response, relapse, interruption).

Efficacy of retreatment

Serum HCV RNA was detected using a qualitative PCR test with a detection limit of 50 IU/mL (Cobas Amplicor HCV v2.0; Roche Molecular Systems,

Branchburg, NJ, USA) at weeks 24 and 48. Patients with HCV RNA < 50 IU/mL at week 24 completed 48 weeks of treatment; otherwise, they were considered non-responders and treatment was discontinued. The primary outcome analyzed was SVR, defined as HCV RNA below the limit of detection 24 weeks after completion of treatment. An additional analysis identified pre-treatment variables associated with SVR.

Clinical benefits of SVR

The following clinical and laboratory parameters were evaluated: survival, liver disease progression, including presence of liver decompensation (defined by the presence of ascitis, hepatic encephalopathy, jaundice), and/or variceal bleeding and/or hepatocelular carcinoma, change in antiretroviral therapy due to virological or clinical failure, occurrence of an AIDS-defining illness (as based on the criteria established by the Centers for Diseases Control[29] and CD4 count levels at the end of follow up. Death, liver disease progression, or the occurrence of an AIDS-defining illness were indicative of a poor clinical outcome after retreatment. In the case of patients who reported more than one of these outcomes, only the first was considered for the assessment of the clinical benefits of SVR. In all cases, the time from the end of retreatment until the last follow-up visit was at least 24 months.

Data analysis

The prevalence of sustained virological response (SVR) and its associated 95% confidence interval (95% CI) were calculated. To explore putative predictors of SVR, its association with the independent factors measured was examined in univariate (chi-squared tests) and multivariate analyses. In the latter case, logistic regression models were used, including all variables for which $p < 0.25$ in the univariate analysis. Statistical significance was set at $p < 0.05$. Data were analyzed using STATA, version 11.0 (StataCorp LP, College Station, Texas, USA).

RESULTS

Population characteristics

A total of 76 treatment rechallenges were identified among those patients who did not respond to a first course of HCV treatment. Of these, 47 patients were included in the analyses. A total of 29 patients were excluded from the analysis due to lack of clinical information (negative/unavailable HCV RNA at the end of treatment and lack of information regarding duration of treatment).

Thus, 47 patients were included in the final analysis. No significant difference in age, sex and degree of liver fibrosis was found between patients included or not included in the analysis.

The demographic and clinical characteristics of the patients are summarized in table 1. HCV genotype 1 was the most frequently detected (54.3%). HCV viral load was measured only in approximate-

Table 1. Characteristics of 47 patients retreated for HCV infection with Peg-IFN and ribavirin.

Variables	N (%)
Age (years)	44.1 (29.0-66.8)*
Male	37 (78%)
Weight (kg)	69 (49-101)*
Former treatment	
• IFN + RBV	47 (100%)
Former virological response	
• Non-response	42 (89.4%)
• Relapse	4 (8.5%)
• Interruption	1 (2.1%)
Serum HCV RNA	
> 500,000 IU/mL	13 (81.2%)
HCV genotype	
• 1	25 (54.3%)
• 2	2 (4.4%)
• 3	18 (39.1%)
• 4	1 (2.1%)
• Unknown	1 (2.1%)
Liver cirrhosis**	22 (47.8%)
Ribavirin dose (mg/kg)	15.1 (11.1-20.0)*
CD4 count pre treatment	582.5 (142-1,836)*
• CD4 count < 200	2 (4.2%)
• CD4 count 200-499	14 (29.7%)
• CD4 count > 500	28 (59.7%)
• CD4 unknown	3 (6.4%)
Antiretroviral treatment (ART)	46 (97.9%)
HIV RNA not detectable (in all patients receiving ART)	46 (97.9%)

IFN: interferon. RBV: ribavirin. ART: antiretroviral treatment. *Continuous variables are expressed as medians and interquartile ranges. **All patients underwent liver biopsy. Both F3 (numerous septa without cirrhosis) and F4 (cirrhosis) scores (as based on the Metavir scoring system) were considered as cirrhosis.

ly a third of all patients, and was > 500,000 UI/mL in most cases. All patients underwent liver biopsy and nearly half had cirrhosis, indicating a difficult-to-treat population. Only one patient was not under a highly active anti-retroviral therapy (HAART), with detectable HIV-RNA. AIDS-defining illnesses were previously identified in 20 of the 47 patients. Median ribavirin dose in this group was 15.1 mg/kg.

Predictors of retreatment efficacy

At the end of the retreatment, 42.6% of the patients (20/47) were HCV RNA-negative. However, six months after treatment completion 5 of these patients relapsed and the SVR was found in 31.9% (IC95%: 19.1-47.1) of patients. In those patients who maintained SVR, HCV genotypes were distributed as follows: genotypes 1/4, 19.2% (5 out of 26 patients)

Table 2. Analysis (chi-square) of gender, indicators of HIV and HCV infection, and HCV treatment as predictors of SVR in HCV-HIV coinfected patients.

Predictors	Total	Responders	OR (95% CI)	P-value
Sex				0.176
Male	37	14 (37.8)	1.00	
Female	10	1 (10.0)	0.26 (0.04-1.81)	
Total	47			
Age				0.230
< 45 y.o.	25	10 (40.0)	1.00	
≥ 45 y.o.	22	5 (22.7)	0,44 (0,09; 1,85)	
Total	47			
CD4 nadir				0.816
< 200	24	8 (33.3)	1.00	
≥ 200	20	6 (30.0)	0.90 (0.37-2.18)	
Total*	44			
HCV genotype				0.040
1 or 4	26	5 (19.2)	1.00	
2 or 3	20	10 (50.0)	2.60 (1.04-6.47)	
Total**	46			
AIDS-defining illness				0.140
Yes	20	4 (20.0)	1.00	
No	26	11 (42.3)	2.12 (0.78-5.73)	
Total**	46			
Fibrosis grade (metavir)				0.914
0, 1, or 2	24	8 (33.3)	1.00	
3 or 4	22	7 (31.8)	0.95 (0.41-2.22)	
Total	46			
Pre-retreatment CD4				0.972
< 400	10	3 (30.0)	1.00	
≥ 400	34	10 (29.4)	0.98 (0.33-2.92)	
Total*	44			
Post-retreatment CD4				0.670
< 400	5	1 (20.0)	1.00	
≥ 400	30	9 (30.0)	1.50 (0.23-9.67)	
Total***	35			
Length of HCV retreatment (weeks)				0.665
< 48	21	6 (28.6)	1.00	
48	26	9 (34.6)	1.21 (0.51-2.88)	
Total	47			
Ribavirin dosis				0.921
> 15 mg/kg/day	21	6 (28.6)	1.00	
≤ 15 mg/kg/day	20	6 (30.0)	1.05 (0.40-2.75)	
Total****	41			

Missing data: *3. **1. ***12. ****6.

and genotypes 2/3, 50% (10 out of 20 patients). In the relapsers group, genotypes 3 and 1 were identified in 3 and 2 patients, respectively. Indeed, SVR was significantly more likely among patients with genotypes 2/3 (p = 0.04) OR (95% CI) 2.60 (1.04-6.47). No other factor (Table 2) was significantly associated with SVR response.

The logistic regression including HCV genotype, gender, and the presence of an AIDS-defining illness confirmed the effect of genotype on SVR, showing that the probability of eradicating HCV infection was nearly 3-fold higher among patients with genotypes 2 or 3 than in patients with genotypes 1 or 4 [p = 0.022, adjusted odds ratio (aOR): 2.78; 95% CI: 1.16-6.68].

There was also a trend towards an effect of a previous AIDS-defining illness in non-responders [p = 0.08, aOR: 2.31; 95% CI: 0.90-5.94].

Tolerance and safety

Retreatment was prematurely discontinued in one patient due to an adverse psychiatric event. Neither HIV virological failure nor opportunistic infections were observed during the study.

Clinical benefits of SVR

The medical records of the 47 patients were available in March 2011 (25 to 79 months between the end of treatment and the last follow-up visit). They indicated that 42 patients were still being followed. From them, 14 patients were responders, 28 were treatment failures (either did not achieve SVR or had interrupted) treatment. As demonstrated in table 3, hepatic decompensation was identified in eight non-responders (28.6%), but not among responders (p = 0.037). Similarly, in the non-responder group, the presence of an AIDS-defining illness post-treatment occurred in one patient while two patients died by hepatic decompensation. The same was not observed in any of the 14 patients in the responder group. There was no incidence of HCC in the observed patients and no incidence of variceal bleeding, but three patients in the non-responder group underwent variceal encoscopical treatment.

We also evaluated CD4 counts at least 24 months after the end of treatment. There was a trend towards higher CD4 count levels in the responder group, but the difference was not significant (Table 4).

DISCUSSION

This study determined SVR rates and putative predictors of response to hepatitis C retreatment in a population of HIV-HCV coinfected individuals who did not respond, or relapsed, to a previous treatment with standard interferon and ribavirin.

Similarly to a previous report,[21] SVR was achieved by 31.9% of retreated patients, particularly those with HCV genotypes 2 or 3. Consistent findings were also recently reported in a subset of patients previously treated with peginterferon and ribavirin.[22,23] Importantly, the present results strongly support the long-term benefits of SVR, as

Table 3. Clinical benefits of SVR.

SVR	n	Hepatic decompensation or death (%)	CI	P value
Yes	14	0	1	
No	28	8 (28.6)	*	0.037

*Impossible to calculate odds ratio due the absence of hepatic decompensation endpoint among SVR patients.

Table 4. Median CD4 counts before and after HCV retreatment in HCV-HIV coinfected patients, as based on their virological response.

Period	Sustained virological response				P-value*
	No		Yes		
	n	Median (range)	n	Median (range)	
Before retreatment	30	578 (192-1,353)	13	571 (142-1,418)	0.689
After retreatment (≥ 24 months)	27	610 (273-1,207)	14	734.5 (352-1,296)	0.073

*Student t-test.

nearly one fourth of non-responders had hepatic decompensation post-treatment. Conversely, no event of hepatic decompensation, AIDS-defining illness, or death was identified among the group of patients that achieved SVR during the follow-up period. These results are in line with a previous report showing that SVR prevented hepatic decompensation and death in a larger cohort of HCV-HIV coinfected individuals treated with peginterferon and ribavirin.[24] Mathematical models have also been used to demonstrate that SVR prevents end-stage liver disease and is cost-effective.[25-27]

Our analysis also identified a trend towards higher CD4 counts, which are inversely related to HIV illness and mortality in SVR patients, after a follow-up of two years ($p = 0.07$). These findings contribute to the idea that HCV may influence HIV disease progression. As while many studies have focused on how HIV affects HCV disease progression[31-34] in co-infected individuals, few have investigated the immune mechanisms whereby HCV influences HIV disease progression.[35-40]

The fact that repeating HCV treatment leads to SVR in some patients who did not respond to previous treatment should be considered by practitioners. Although new anti-HCV targeted agents, such as NS3 protease inhibitors, represent a promising therapeutic strategy for HIV-HCV coinfected patients,[15,16] drug interactions with HAART must be studied further and are likely to delay their use in this population.[17,18] Additionally, these new drug therapies are currently not effective for HCV genotypes 2 and 3. New agents directed at these genotypes are under development, but will not be available in the short-term.

Besides its observational and retrospective nature, one limitation of the present study is its small sample size. Although sample size was similar to that used by previous studies, the low number of subjects eligible for analysis may have limited the power of the tests in detecting significant associations. Therefore, if on the one hand the present results were consistent with previous research on the efficacy of retreatment of coinfected individuals, on the other we failed to demonstrate statistical significance between SVR and potential predictors of response to retreatment. In addition, other putative predictors were not investigated, such as the effect of plasma level of ribavirin.[30] Labarga, *et al*. have also demonstrated that IL-28 CC polimorphysm and higher viral load prior to treatment predicted SVR in coinfected patients with genotypes 1 and 4 submitted to a treatment rechallenge,[23] also demonstrating retreatment efficacy in those previously treated with peginterferon plus ribavirin.

In summary, although HCV infection is difficult to treat in HCV-HIV coinfected individuals, the present results show that an important proportion of patients who did not respond to a first course of standard IFN-based treatment achieved sustained virological response in a treatment rechallenge, which in turn prevented end-stage liver disease. While new anti-HCV drugs are under development, all efforts must be made to ensure SVR and prevent hepatic decompensation and death in the mid- and long-term. In this scenario, optimized retreatment with peginterferon and ribavirin remains as a safe approach to treat HIV-HCV coinfected individuals (especially those with HCV genotypes 2 and 3), even if they failed to respond to a standard IFN-based regimen.

The present study is among the first to reveal the long-term clinical benefits of hepatitis C retreatment in a coinfected population of HIV/HCV patients and may help in developing effective and safe strategies to eradicate HCV in this population of individuals.

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