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Sustained virological response according to the type of early virological response in HCV and HCV/HIV

Paulo R. Lerias de Almeida,*,*** Angelo Alves de Mattos,** Cristiane Valle Tovo**,***

* Secretaria Estadual de Saúde do Rio Grande do Sul (SES-RS). ** Post-Graduation Course-Hepatology Sector of Fundação Universidade Federal de Ciências da Saúde de Porto Alegre. *** Hospital Nossa Senhora da Conceição-Porto Alegre-Brazil.

ABSTRACT

Background. The most important factors to predict the sustained virological response (SVR) are the genotype and the fibrosis grade, although there are other predictive factors to be considered, mainly in HCV/HIV coinfected patients. **Aim.** To evaluate different prognostic factors to obtain the SVR in HCV monoinfected and HCV/HIV coinfected genotype 1 patients emphasizing the type of early virological response (EVR)-complete or partial. **Methods.** This is a cohort study, retrospective, where the registers of HCV monoinfected or HCV/HIV coinfected patients, genotype 1, treated with pegylated interferon + ribavirin were reviewed. The prognostic factors: age greater than 40 years, viral load higher than 600,000UI/mL, and fibrosis grade (score METAVIR) were evaluated pre-treatment, and also the EVR considering the reduction of 100 times of the basal viral load (partial EVR) or negative PCR (complete EVR) in the week 12. In the statistical analysis, multivariate analysis was used. The significance level adopted was 5%. **Results.** There were 323 HCV monoinfected and 59 HCV/HIV coinfected. The SVR was 35.3% in monoinfected and 23% in coinfected patients. The worst results was observed in those with age greater than 40 years, high viral load, pronounced fibrosis (F4) and partial EVR, with an expected probability of 1.9% for SVR in those coinfected and 3.8% in monoinfected. In conclusion, patients with cirrhosis HCV genotype 1, age greater than 40 years, high viral load, coinfected with HIV or not, will present a low SVR if did not obtain negative PCR in week 12, and should be evaluated for discontinuation.

Key words. HCV Treatment. HCV/HIV coinfection. Prognostic factors.

INTRODUCTION

At present, therapy with pegylated interferon associated to ribavirin (PEG+RBV) has created a new perspective for patients with hepatitis C virus (HCV) because of the rate of sustained virological response (SVR) reported.

However, few studies have assessed all the negative predictors of SVR,[1-5] mainly related to the type of early virological response (EVR), i.e. the impact of partial EVR (drop of 2 logs in viral load from baseline) compared to complete EVR (when there is negative PCR-HCV) in week 12 of treatment.[6-8] In this respect, the data reported in the literature are scarce when evaluating HCV/HIV coinfected patients.

As HCV genotype 1 appears to be the main predictor of failure to achieve SVR, the objective of this study is to evaluate different prognostic factors in the SVR in monoinfected by HCV and also in coinfected by HCV/HIV patients infected by genotype 1.

METHODS

This is a cohort study, retrospective, where the registers of patients monoinfected by HCV or coinfected by HCV/HIV, genotype 1 treated with PEG and RBV during 48 weeks were reviewed.

The criteria for inclusion, according to the Brazilian Public Health Program protocol,[9] included: positive PCR-HCV; genotype 1; elevated aminotransferases; liver biopsy with septal fibrosis (greater than or equal to F2, according to the METAVIR score);[10] age between 18 and 70 years; platelets count greater than 75,000/mm^3 for cirrhotics and 90,000/mm^3 for non-cirrhotics and a neutrofile count higher than 1,500/mm^3.

Correspondence and reprint request: Paulo Almeida,
Rua Cel Aurelio Bitencourt 115 apto 201 Porto Alegre-RS Brazil
CEP 90430-080
Ph. and Fax: 55-51-3332-5706
E-mail: paulorlalmeida@terra.com.br

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The exclusion criteria were: previous treatment with interferon associated or not with ribavirin; abusive consumption of alcohol and regular consumption of illicit drugs; transplanted patients; decompensated chronic liver disease, cardiopathy, thyroid disease, and diabetes mellitus type I; presence of neoplasia; uncontrolled convulsions; men and women without adequate contraceptive control; pregnancy and non-agreement with the terms of informed consent. Coinfection with hepatitis B virus was also excluded.

By this protocol, patients with fibrosis stage 0 or 1 are not treated.

The available treatment was PEG alpha-2a 180 mcg or alpha-2b at a dose of 1.5 μg/kg, administered subcutaneously once a week associated with RBV 1,000 mg/day for patients with less than 75 Kg or 1,250 mg/day for patients with 75 Kg or more, for a period of 48 weeks.

The main prognostic factors were evaluated pretreatment (age greater than 40 years, viral load higher than 600,000UI/mL and fibrosis stage-score METAVIR), and also the EVR partial or complete.

The HCV-RNA was detected through the PCR technique using the *AMPLICOR HCV Test, version 2.0* (Roche Diagnostics; Nutley, NJ; detection limit: 50 IU/mL).

The quantification of HCV-RNA was done using *AMPLICOR HCV MONITOR ™ Test, version 2.0* (Roche Diagnostics; Nutley, NJ; detection limit: 600 IU/mL).

The genotype was tested using the technique of restriction fragment link polymorphism (RFLP-PCR).

Antibodies for HIV-1/HIV-2 were detected by the ELISA II and Immune Chromatographic Assay Determine (Abbott Axsym System, N.Chicago/IL, USA). Positive samples were submitted to confirmation through the immunofluorescence test (Fundação Oswaldo Cruz, Rio de Janeiro/RJ). Indeterminate results were confirmed by the *western-blot* test.[11]

Assessment of liver fibrosis was made using the METAVIR score.[10]

Those with clinical/laboratory and ultrasonographic diagnosis of cirrhosis could undergo treatment without the need of a liver biopsy, and patients with extrahepatic manifestations of HCV were treated regardless of the stage observed after the classification by METAVIR.

The study was submitted to and approved by the Research Ethics Committee of Hospital Nossa Senhora da Conceição.

In order to evaluate the strength of the association between the factors in the study and the SVR, the odds ratio (OR) was used with its respective confidence interval. Chi-squared was used for significance among categorical variable and Mann-Whitney test for significance among continuous variables. To estimate probabilities of SVR considering simultaneously the effects of several factors we used a logistic regression model. The significance level used was $p = 0.05$. The data were processed and analyzed with the help of the SPSS version 13.0 software.

RESULTS

There were 323 HCV monoinfected and 59 HCV/HIV coinfected.

The baseline characteristics of both groups can be observed in table 1.

In this study, the HCV viral load was defined as high when greater than 600,000 UI/mL. It was not possible to evaluate the fibrosis stage in 09 patients of the HCV group and in 04 from the HCV/HIV group because of coagulability impediments. It is possible to observe that there was a high percentage of patients with advanced fibrosis (F3 and F4) in both groups.

Table 1. Characteristics of patients included in the study: demographic data, count of CD4 cells and histopathology.

	HCV n = 323	HCV/HIV n = 59	P
Male - n (%)	180 (55.7)	45 (76.3)	0.004
Age, years (average ± DP)	51 ± 10	42 ± 9	0.29
BMI* (average ± DP)	27 ± 04	24 ± 03	0.16
CD4, cells/mm^3 (average)	-	432	-
Viral load (IU/mL) - average	645,000	1,178,786	0.003
Viral load > 600,000 (IU/mL) - n (%)	184 (57)	39 (66)	0.24
F3 + F4 - n (%)	232/314 (74)	37/55 (67)	0.25

*** BMI:** body mass index.

In the HCV group, 323 patients began treatment. In 33 (10.2%) treatment was suspended due to adverse events. Another 75 (23.2%) patients did not obtain EVR at week 12, and treatment was interrupted. Thus, 236 (73.1%) patients proceeded beyond week 12. Two-thirds of the patients (215; 66.6%) completed the 48 weeks of treatment, most with end of treatment response (ETR) (169; 52.3%). In the 24th week of follow up, it was not possible to contact 03/169 patients who had obtained ETR, thus losing the SVR information for 0.9% of the cohort. Among the others 166 patients, 52 presented a relapse and 114 presented negative PCR. Thus, in the analysis by intention to treat, SVR was obtained in 114 (IC95% 30.1 - 40.8) patients.

Among the 236 patients proceeding beyond week 12, 215 presented EVR (in 21 the virological response at week 12 was not assessed). Of them, 105 (48.8%) reached SVR. In relation to the type of EVR obtained, 180 (83.7%) presented complete EVR and 35 (16.3%) a partial EVR. Among those with undetectable viremia, 99/180 reached SVR in comparison to only 6/35 of those who presented a 2 log reduction ($p < 0.01$). Thus, the subtype of the EVR presented by patients in week 12 proved to be strongly predictive of SVR (OR 6.05).

Among the coinfected group, 7/59 (12%) had treatment discontinued due to adverse reactions, and other 27/59 (46%) patients interrupted the treatment since did not present EVR at week 12. Thus, 25 (42%) patients completed treatment and had the ETR evaluated: 04 with HCV-RNA positive and 21 with HCV-RNA negative. Among these, there was loss of contact with one patient, and other 20 patients had their SVR measured, 14 patients had HCV-RNA negative and 06 positive HCV-RNA at week 24 of the follow-up. Thus, by intention to treat, the SVR was achieved in 14/59 of those HCV/HIV coinfected.

The EVR was evaluated in 51 patients, and was obtained in 27/51 (53%) patients: 21 with complete EVR and 06 with partial EVR. The SVR was obtained in 12 (57%) patients from those with complete EVR, and in no patients from those with partial EVR ($p < 0.05$).

Combining the effects of several factors (mono/coinfection, age, viral load of HCV, fibrosis stage, type

Table 2. Logistic regression model for sustained viral response (SVR).

	Coefficient	OR for SVR	95% CI	P
Age < 40 yrs	0.515	1.67	0.85 to 3.30	0.137
HIV coinfection	-0.737	0.48	0.20 to 1.14	0.095
Viral load < 600,000UI/mL)	0.352	1.42	0.84 to 2.42	0.193
Fibrosis level:				
F1 + F2		1.00	-	0.003
F3	-0.495	0.61	0.34 to 1.11	0.104
F4	-1.288	0.28	0.13 to 0.58	0.001
Negative PCR 12th week	2.439	11.46	6.12 to 21.45	< 0.001

HIV: Human immunodeficiency virus. **PCR:** polymerase chain reaction. **OR:** odds ratio. **P:** statistical significance.

Table 3. HCV monoinfected.

Viral load	*Fibrosis stage	Age (yr)	Partial EVR RVS (%)	Complete EVR RVS (%)
	F1 + F2	< 40	25.5	79.7
		> 40	17.0	70.0
< 600	F3	< 40	17.3	70.5
		> 40	11.1	58.8
	F4	< 40	8.6	52.0
		> 40	5.3	39.3
	F1 + F2	< 40	19.4	73.4
		> 40	12.6	62.2
> 600	F3	< 40	12.8	62.7
		> 40	8.1	50.1
	F4	< 40	6.2	43.2
		> 40	3.8	31.3

600 = viral load 600,000 UI/mL. *: fibrosis stage (score METAVIR).

Table 4. HCV/HIV coinfected.

Viral load	* Fibrosis stage	Age	↓ 2 log RVS (%)	PCR (-) RVS (%)
	F1 + F2	< 40	14.1	65.3
		> 40	8.9	52.9
< 600	F3	< 40	9.1	53.4
		> 40	5.6	40.6
	F4	< 40	4.3	34.1
		> 40	2.6	23.6
	F1 + F2	< 40	10.3	56.0
		> 40	6.4	44.1
>600	F3	< 40	6.6	44.6
		> 40	4.0	32.5
	F4	< 40	3.1	26.7
		> 40	1.9	17.9

600 = viral load 600,000 UI/mL. *: fibrosis stage (score METAVIR).

of EVR) in a logistic regression model, we were able to predict the SVR in different clinical situations (Table 2). When the EVR was complete, the OR for SVR was 11.46.

The expected probabilities of SVR among monoinfected and coinfected patients can be found in tables 3 and 4 respectively. It is possible to notice that the worst results expected are for those patients presenting the following clinical characteristics: coinfection with HIV, age greater than 40 years, high viral load, pronounced fibrosis (F4) and partial EVR.

DISCUSSION

It has been pointed in the literature that the SVR to anti-HCV treatment is lower depending on factors such as male gender, older age, genotype 1, high viral load and coinfection with HIV.[2-6] However, when there is just partial EVR, the treatment appears to be very inefficient. A recent study by Poynard et al[6] showed SVR of 56% and 12% with complete or partial EVR respectively.

HCV/HIV coinfection is known to decrease the SVR. Several studies have reported these results, such as studies APRICOT,[12] RIBAVIC,[13] NIH,[14] Laguno et al,[15] Crespo et al[16] and PRESCO.[17] On reviewing the literature, we found no study that evaluated the SVR in coinfected patients depending on the type of EVR (whether partial or complete).

In this study, when there was partial EVR the SVR was low, ranging from 1.9 to 14.1% in the population of coinfected patients and 3.8 to 25.5% in those HCV monoinfected. It should be noted that worse outcomes were observed in patients above 40 years of age, high viral load and with cirrhosis (1.9% in coinfected and 3.8% in monoinfected). In contrast, when the EVR was complete, the chance of SVR was more than 10 times higher when compared to those with partial EVR (OR 11.46).

Why the importance of SVR? No conclusive evidence for randomized controlled trials of anti-HCV therapy has demonstrated a beneficial impact on the main clinical outcomes because cirrhosis, hepatocellular carcinoma (HCC) and death often do not occur for many years after infection with HCV and would therefore require long-term evaluation of therapy to demonstrate benefit. As a consequence, most published reports of anti-HCV therapy use SVR to infer the likelihood of long-term benefit.

The Di Marco group[18] studied 102 patients with advanced liver disease related to HCV treated with PEG and RBV and reported a 32% risk reduction in the incidence of liver-related complications, HCC and death in those achieving viral clearance.

El Braks et al[1] evaluated a cohort of 113 French patients with HCV compensated cirrhosis between 1989 and 2006. They also suggested that virological cure seems to be associated with a strong decrease in the incidence of complications, particularly HCC.

Thus, it has been standard practice to treat patients with compensated cirrhosis. It is important to understand the limitations of this practice when assessing potential benefit. Anyway, when we evaluate the trials treating patients with compensated cirrhosis, the SVR ranges from 9% to 52%,[19-21] generally lower than that of patients with lesser stages of fibrosis. Otherwise, some authors[22] suggests that besides the SVR the tolerability to treatment is consistently lower in cirrhotic patients than in those with earlier stage of fibrotic liver disease.

The HALT-C trial[21] evaluated the impact or severity of disease in the SVR in 1,046 patients, and demonstrated that SVR rates ranged from 23% in

patients with the mildest disease to only 9% in those with more advanced features-cirrhosis with low platelets. They conclude that cirrhosis is the major independent determinant factor for non-responding. These results emphasize the urgent need for new and better drugs to eradicate HCV in those with advanced liver disease. Logistic regression analysis showed that the trendlines for diminished virologic responses with increasing disease severity were highly significant for both virological response in week 20 and SVR.

It is noteworthy that the treatment results obtained in real life are lower than those obtained when patients are enrolled in clinical trials.[23-25]

Thus, when evaluating a population of patients with negative predictors of SVR, it must be taken into account the value of treatment maintenance in those where the chance of the virus turning to negative is low. This fact becomes more relevant when evaluating the adverse effects inherent to the therapy in question and the economic impact that it reflects, when the prospects of therapeutic success are low.

The present study demonstrates that the SVR can vary from 3.8 to 52.0% in cirrhotic monoinfected and from 1.9 to 34.1% in cirrhotic HCV/HIV coinfected, depending of the factors involved (age, viral load, and type of EVR).

We conclude that patients with cirrhosis HCV genotype 1, age greater than 40 years and high viral load will present a very low SVR if did not obtain negative PCR in week 12 of treatment. Thus, treatment maintenance must be questioned specially in those coinfected patients, since treatment is less tolerated in this population as a result of adverse events, including those resulting from existing drug interactions.

ABBREVIATIONS

- **PEG:** Pegylated interferon.
- **RBV:** Ribavirin.
- **HCV:** Hepatitis C virus.
- **HIV:** Human immunodeficiency virus.
- **SVR:** Sustained virological response.
- **EVR:** Early virological response.
- **RFLP-PCR:** Restriction fragment link polymorphism.
- **OR:** Odds ratio.
- **BMI.** Body mass index.
- **ETR.** End treatment response.
- **HCC.** Hepatocelular carcinoma.
- **PCR**. Polymerase chain reaction.

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