Article/Artigo

# Gender influence on treatment of chronic hepatitis C genotype 1

## Influência do gênero no tratamento da hepatite C crônica genótipo 1

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**ABSTRACT**

**Introduction:** Although various studies have been published regarding the treatment of chronic hepatitis C (CHC) with peginterferon (Peg-IFN) and ribavirin, little is known regarding the real impact of gender on the characteristics that influence the effectiveness and safety of antiviral treatment for CHC patients. The objective of this study was to evaluate the influence of gender on HCV treatment outcomes. **Methods:** A retrospective analytical study was conducted among selected carriers of CHC genotype 1, who were treated with Peg-IFN α-2b at a dose of 1.5 μg/kg or Peg-IFN α-2a at a dose of 180 μg/week plus a ribavirin dose of 1,000-1,250 mg/day, according to weight, between 2001 and 2007. **Results:** Among 181 patients undergoing treatment, the mean age was 46.4 ± 11.0 years and 46% were women. At baseline, 32% of the patients had advanced fibrosis (F3-F4 Scheuer), and 83% of the subjects had viral load > 400,000 IU/ml, without significant difference between the genders (p = 0.428 and p = 0.452, respectively). When compared with men, women had higher incidence of many adverse events such as anemia (p < 0.001) and higher need for dose reduction, for both Peg-IFN (p = 0.004) and ribavirin (p = 0.006). However, the rate of sustained virological response (SVR) did not differ between the genders: 45% (female) vs 41% (male); p=0.464. **Conclusions:** This study suggests that women and men react differently to combined therapy, especially in relation to the incidence of adverse events and the need for dose modification. Nevertheless, these differences do not influence the SVR rate.

**Key-words:** Hepatitis C. Pegylated interferon. Ribavirin. Gender. Women.

**RESUMO**

**Introdução:** Apesar dos vários estudos publicados a respeito do tratamento da hepatite C crônica (CHC) com Peg-Interferon (Peg-IFN) e ribavirina, se desconhece o real impacto do gênero sobre as características que influenciam a eficácia e a segurança da terapia antiviral em portadores de CHC. O objetivo deste estudo foi avaliar a influência do gênero no tratamento da CHC. **Métodos:** Foi realizado um estudo analítico retrospectivo de portadores de CHC genótipo 1 tratados com Peg-IFN α-2b na dose de 1,5μg/kg ou Peg-IFN α-2a na dose de180μg/ sem associado à ribavirina 1.000-1.250 mg/dia, de acordo com o peso, entre 2001 e 2007. **Resultados:** Entre 181 pacientes submetidos ao tratamento, a média de idade foi de 46,4±11,0 anos e 46% eram mulheres. No pré-tratamento, 32% dos pacientes apresentavam fibrose avançada (F3-F4 Scheuer), e 83% dos indivíduos apresentavam carga viral >400.000IU/mL, sem diferença significativa entre os gêneros (p=0,428 e p=0,452, respectivamente). Quando comparadas aos homens, as mulheres exibiram maior incidência de eventos adversos como anemia (p<0,001) e maior necessidade de redução de dose tanto do Peg-IFN (p=0,004) quanto da ribavirina (p=0,006). Entretanto, as taxas de resposta virológica sustentada (RVS) não diferiram entre os gêneros (45% (mulheres) . vs 41% (homens); p=0,464). **Conclusões:** Este estudo sugere que homens e mulheres reagem à terapia combinada de forma diferente, especialmente com relação aos eventos adversos e à necessidade de modificação de dose. No entanto, essas diferenças não influenciam as taxas de RVS.

**Palavras-chaves:** Hepatite C. Interferon peguilado. Ribavirina. Gênero. Mulheres.

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## INTRODUCTION

Hepatitis C virus (HCV) infection remains highly prevalent, and it is estimated that 170 million people worldwide are chronic carriers[1]. Despite recent advances, few studies have evaluated the characteristics of HCV infection in women. Some authors have demonstrated that women have less altered hepatic biochemical tests and lower rates of fibrotic progression[2-5]. It is believed that these findings are related to the protective effects of estrogen, which possesses anti-fibrotic activity[6] and blocks fibrogenesis in the hepatic stellate cells[7]. The idea that estrogen has a protective role was also suggested by a study on chronic HCV patients that observed a greater chance of progression to hepatic cirrhosis among asymptomatic women older than 50 years of age[8]. Furthermore, that study demonstrated that female patients with chronic hepatitis had a lower risk of developing hepatocarcinoma than did men[8]. The menopause appears to be associated with an accelerated rate of fibrotic progression, and hormone replacement therapy may minimize this effect[6].

Spontaneous clearance of HCV infection appears to be more frequent among women after acute infection[9-11]. It is possible that the higher prevalence of viral clearance among women is associated with immunological factors[12] and genetics (in particular, the HLA DRB1*01[13], HLA-Bw35, HLA-DRB1*8[14] and GG genotypes[15]).

To date, the only study that evaluated the influence of gender on the treatment for chronic hepatitis C genotype 1 concluded that the response to combined therapy with pegylated interferon alpha (Peg-IFN) and ribavirin (RBV) was poorer among female than among male hepatitis C-infected patients aged 50 years or older, irrespective of compliance (32% vs 63%)[16]. Previously, Hayashi et al assessed gender importance in relation to the response to conventional interferon alpha treatment (IFN) alone and concluded that women younger than 40 years of age had higher rates of sustained virological response (SVR) than did men (75% vs 33%)[17].

It may be intuitively concluded that women suffering from chronic hepatitis C have specific characteristics that potentially affect the course and outcome of antiviral therapy. However, despite several published studies on the treatment of hepatitis C with Peg-IFN and RBV, little is known about the real impact of gender on the characteristics that influence the efficacy and safety of treatment for chronic hepatitis C. Thus, this study aimed to evaluate the influence of gender on relevant pre-treatment characteristics of HCV patients, as well as the impact of gender on the tolerability profile and efficacy of combination therapy with Peg-IFN and RBV.

## METHODS

### Patients

This cross-sectional study was carried out in a single tertiary care centre (Hepatitis Section, Hospital São Paulo, Brazil) and included consecutive adult naïve patients with biopsy-proven chronic hepatitis C genotype 1, who were treated with Peg-IFN and RBV between January 2001 and December 2007. HCV infection was defined as a positive HCV RNA finding from PCR (> 50 IU/ml). Patients with HBV and/or HIV coinfection, end-stage renal disease or incomplete data on blood counts and/or liver panel were excluded.

### Methodology

Demographic, laboratory and other clinical variables were reviewed and extracted from medical records. Parenteral risk factor for HCV acquisition was defined as history of blood transfusion (if received before 1993) or injection drug use. Patients without parenteral risk factors were considered to present sporadic or unknown risk regarding the mode of infection. Patients with ethanol consumption greater than 50 g/day were considered to be alcohol abusers. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and gamma glutamyltransferase (GGT) were expressed as multiples of the upper limit of normalcy (ULN). The other parameters were expressed as absolute values. Only laboratory results performed within one month from the start of treatment were used for this study.

### Histological analysis

All patients underwent liver biopsy irrespective of ALT levels. The liver biopsies were performed using a Tru-Cut 14-gauge biopsy needle, after the patients had given their written informed consent. The liver biopsy samples were fixed in formalin and embedded in paraffin. Slides were stained with hematoxylin and eosin, Masson's trichrome, Perls' Prussian blue, and Gomori reticulin. A single experienced pathologist who was unaware of the clinical data evaluated all the liver biopsy slides. Hepatitis C liver disease was classified according to Scheuer's classification[18]. Fibrosis was staged as follows: 0= no fibrosis; 1= enlarged, fibrotic portal tracts; 2= periportal or portal-portal septa but intact architecture; 3= fibrosis with architectural distortion but no obvious cirrhosis; 4= probable or definite cirrhosis. Portal/periportal necroinflammatory activity was graded on a scale ranging from 0-4: 0= none or minimal; 1= portal inflammation; 2= mild limiting plate necrosis; 3= moderate limiting plate necrosis; 4= severe limiting plate necrosis. Advanced fibrosis was defined as stages 3 or 4, and significant periportal activity was defined as grades 3 or 4.

### Treatment regimens and outcomes

All patients received Peg-IFN alpha-2a (180 μg/week) or 2b (1.5 μg/kg/week) and RBV at a dose of 1 or 1.25 g/day (dictated by weight less than or greater than 75 kg) for a minimum of 12 weeks and maximum of 48 weeks. The criteria for inclusion in the Peg-IFN treatment group were: age 18-70 years, HCV infection defined by the presence of positive HCV-RNA (> 50 IU/ml), as confirmed by qualitative polymerase chain reaction (PCR); HCV infection with genotype 1; liver biopsy performed not more than 24 months prior to inclusion, with Scheuer's[18] fibrosis stage and inflammatory grade ≥ 2.

The following were considered to be contraindications for treatment: current liver decompensation, immunosuppressive treatment within the last six months, associated liver diseases (especially autoimmune hepatitis) and other associated serious diseases such as systemic autoimmune disease, neoplasia, cardiac arrhythmias and ischemic vascular disease.

Treatment was discontinued if HCV-RNA was detectable after six months of therapy. Patients were evaluated every two weeks during the first month and monthly thereafter. Complete blood count and serum biochemical parameters were assessed at least every 15 days during the first month, then monthly during treatment and post-treatment follow-up at 3 and 6 months.

### Efficacy assessments

Sustained virological response was defined as undetectable HCV-RNA in a qualitative PCR evaluation (AMPLICOR® Hepatitis C Virus Test, version 2.0, Roche Molecular Systems, Branchburg, NJ, USA) performed six months after the end of treatment, using intention-to-treat analysis. The lower limit of detection was 50 IU/ml.

### Safety assessments

During the treatment, patients were seen at the outpatient clinics every two weeks for the first month and then monthly until the end of the treatment. A standardized questionnaire on adverse events was routinely applied to every patient, in order to document any of the following occurrences: flu-like symptoms, anemia (hemoglobin less than 10 g/dl), neutropenia (neutrophil count less than 1,500/mm$^3$), thrombocytopenia (platelet count less than 50,000 platelets/mm$^3$), psychiatric events (dizziness, panic attacks, depression, irritability), significant weight loss (weight loss exceeding 10% of baseline body weight), anorexia, nausea, insomnia, dermatitis or itching, alopecia, decreased visual acuity, diarrhea, dyspnea, bacterial infection and hypothyroidism (defined by TSH greater than 10 mIU/l).

Peg-IFN and RBV dose reduction and either treatment interruption or treatment suspension were also evaluated in order to evaluate tolerance to combined therapy.

### Statistical analysis

Continuous variables were compared using Student's t-test, or the Mann-Whitney U test when appropriate. Categorical variables were compared using Pearson's chi-square test ($\chi^2$) or Fisher's exact test. A p value of less than 0.05 was considered statistically significant. A comparative analysis of all data was performed with regard to gender identity. Univariate and logistic regression analysis were used to identify variables associated with SVR. All tests were two-tailed and performed using the SPSS software version 15.0 (SPSS Inc., Chicago, Illinois, USA).

### Ethical

The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by our institutional review board.

## RESULTS

### Characteristics of the patients

From January 2001 to December 2007, 181 patients were included in the study. Their mean age was 46.4 ± 11.0 years; 46% were women; 39% had a previous history of blood transfusion; and 11% had a history of intravenous drug use.

Compared with men (**Table 1**), women presented higher mean age (p = 0.003) and higher frequency of previous blood transfusion (p < 0.001). In contrast, histories of alcohol abuse (p < 0.001) and intravenous drug use (p < 0.001) were less common among women than among men. Despite similar BMI (p = 0.069), women showed lower mean baseline weight than presented by men (p < 0.001). No differences between the genders were identified in relation to biochemical and hematological parameters, except that women presented lower baseline neutrophil counts (p = 0.009). At baseline, 83% of all the patients had HCV viral loads greater than 400,000 IU/ml, but there was no statistically significant difference between genders (81% of women vs 85% of men; *P* = 0.452). Histologically, 32% of all the individuals had advanced fibrosis (F3 or F4), and 40% had evidence of significant periportal necroinflammatory activity (A3 or A4). No difference was identified with respect to fibrosis between men and women (35% of women vs 29% of men; p = 0.428) or necroinflammatory activity (43% of women vs 38% of men; p = 0.533).

### Efficacy

Overall, 77 patients (43%) achieved SVR after combination therapy with Peg-IFN and RBV. Women received higher mean ribavirin doses per kg than did men (16.0 ± 2.9 vs 13.1 ± 2.1; p < 0.001). However, the proportions of individuals treated with Peg-IFN alpha-2a was similar between genders (32.5% of women vs 37.8% of men, p = 0.064). In univariate analysis, advanced fibrosis, treatment suspension due to adverse events and thrombocytopenia were associated with treatment failure (**Table 2**). Nevertheless, in a multiple logistic regression model (**Table 3**), only suspension of treatment due to adverse events remained independently associated with failure to achieve SVR [odds ratio (OR): 9.006, 95% confidence interval (CI): 1.096-74.026; p = 0.041]. SVR rates were similar between women and men (45% vs 41%, p = 0.464).

### Safety

In general, women had a higher incidence of anemia (p < 0.001), dizziness (p = 0.011), anorexia (p < 0.001), nausea (p = 0.005), alopecia (p = 0.002), decreased visual acuity (p = 0.025), bacterial infection (p = 0.025) and hypothyroidism (p = 0.036), in relation to men. The adverse events are detailed for each cohort in **Table 4**. Women had higher rates of change in dosage of Peg-IFN (p = 0.004) and RBV (p = 0.006) during treatment, as demonstrated in **Table 5**. There were no significant differences between genders with regard to interruption (p = 0.190) or suspension (p = 0.383) of antiviral treatment.

**TABLE 1 - Baseline characteristics of 181 patients with chronic hepatitis C (genotype 1), treated with pegylated interferon and ribavirin, according to gender.**

| | Gender | | | |
|---|---|---|---|---|
| | Total | Female | Male | $P^{\ddagger}$ |
| | n = 181 | n = 83 | n = 98 | |
| Characteristics | | (46%) | (54%) | |
| Age (years)* | 46.4 ± 11.0 (47.0) | 49.0 ± 11.7 (51.0) | 44.1 ± 10.0 (44.0) | 0.003 |
| Caucasian, n (%) | 130 (71.8) | 60 (72.3) | 70 (71.4) | 0.898 |
| BMI (kg/m²)*# | 25.6 ± 3.9 (25.3) | 25.3 ± 4.2 (24.8) | 25.8 ± 3.6 (25.6) | 0.438 |
| Weight (kg) | 71.9 ± 1.0 (71.8) | 64.1 ± 11.1 (62.5) | 71.5 ± 12.3 (76.3) | < 0.001 |
| Alcohol abuse, n (%) | 32 (17.7) | 2 (2.4) | 30 (31.6) | < 0.001 |
| Previous depression, n (%) | 14 (7.7) | 8 (9.6) | 6 (6.1) | 0.371 |
| Mode of infection | | | | |
| Transfusion, n (%) | 71 (39.2) | 47 (56.6) | 24 (24.5) | < 0.001 |
| IV drug use, n (%) | 20 (11.0) | 1 (1.2) | 19 (19.4) | < 0.001 |
| Sporadic/others, n (%) | 90 (49.7) | 35 (42.2) | 55 (56.1) | 0.061 |
| AST (xULN)* | 1.84 ± 1.08 (1.56) | 2.02 ± 1.22 (1.63) | 1.69 ± 0.93 (1.50) | 0.108 |
| ALT (xULN)* | 2.41 ± 1.58 (2.01) | 2.24 ± 1.58 (1.84) | 2.55 ± 1.57 (2.12) | 0.072 |
| DB (mg/dl)* | 0.38 ± 0.22 (0.30) | 0.37 ± 0.20 (0.30) | 0.38 ± 0.24 (0.30) | 0.701 |
| AP (xULN)* | 0.71 ± 0.38 (0.66) | 0.72 ± 0.29 (0.70) | 0.70 ± 0.44 (0.63) | 0.109 |
| GGT (xULN)* | 2.78 ± 2.86 (1.80) | 2.67 ± 2.42 (1.79) | 2.87 ± 3.20 (2.00) | 0.660 |
| Prothrombin activity (%)* | 93.91 ± 10.35 (100) | 93.2 ± 10.9 (100) | 94.5 ± 9.8 (100) | 0.400 |
| Hemoglobin (g/dl)* | 14.84 ± 1.46 (14.9) | 13.89 ± 1.24 (14.0) | 15.66 ± 1.10 (15.8) | 0.141 |
| Neutrophils (/mm³)* | 3.177 ± 1.459 (3.008) | 2.871 ± 1.124 (2.866) | 3.438 ± 1.656 (3.130) | 0.009 |
| Platelets (/mm³)* | 192.005 ± 67.437 (190.000) | 196.578 ± 73.115 (189.000) | 188.052 ± 62.231 (190.500) | 0.400 |
| VL ≥ 400,000 IU/ml, n (%)& | 150 (82.9) | 67 (80.7) | 82 (84.7) | 0.452 |

BMI: body mass index, #Available for 144 patients, *Mean ± standard deviation and median, IV: intravenous, ‡ Student's t test, Mann-Whitney test and $\chi^2$ test when appropriate for comparison of groups, ULN: upper limit of normalcy. AST: aspartate aminotransferase, ALT: alanine aminotransferase, DB: direct bilirubin, AP: alkaline phosphatase, GGT: gamma-glutamyltransferase, VL: viral load, *Mean ± standard deviation and median.

**TABLE 2 - Univariate analysis on variables associated with treatment failure among patients with chronic hepatitis C (genotype 1), treated with pegylated interferon and ribavirin.**

| Characteristics | SVR n = 77 (43%) | Not SVR n = 104 (57%) | $P^{\ddagger}$ |
|---|---|---|---|
| Female gender, n (%) | 37 (48.1) | 46 (44.2) | 0.610 |
| Age (years)* | 44.8 ± 10.8 (46.0) | 47.5 ± 11.1 (47.0) | 0.107 |
| Caucasian, n (%) | 57 (74.0) | 73 (70.2) | 0.571 |
| BMI (kg/m²)*# | 24.9 ± 3.6 (25.3) | 26.1 ± 4.0 (25.5) | 0.069 |
| Alcohol abuse, n (%) | 14 (18.2) | 18 (17.3) | 0.879 |
| Previous depression, n (%) | 5 (6.5) | 9 (8.7) | 0.591 |
| Advanced fibrosis, n (%) | 18 (23.0) | 40 (38.5) | 0.028 |
| Viral load ≥ 400,000 IU/ml, n (%)& | 46 (79.3) | 72 (85.7) | 0.317 |
| Peg-IFN alpha-2a, n (%) | 26 (33.8) | 38 (36.5) | 0.700 |
| Ribavirin dose mg/kg* | 14.0 ± 2.9 (14.1) | 14.2 ± 2.9 (13.8) | 0.291 |
| Peg-IFN dose modification, n (%) | 8 (10.4) | 10 (9.6) | 0.863 |
| Ribavirin dose modification, n (%) | 15 (19.5) | 23 (22.1) | 0.667 |
| Treatment interruption, n (%) | 4 (5.2) | 6 (5.8) | 1.000 |
| Treatment suspension due to AE, n (%) | 3 (3.9) | 19 (18.3) | 0.005 |
| Anemia, n (%) | 23 (29.9) | 30 (28.8) | 0.881 |
| Neutropenia, n (%) | 20 (26.0) | 22 (21.4) | 0.469 |
| Thrombocytopenia, n (%) | 3 (3.9) | 18 (17.3) | 0.005 |

SVR: sustained virological response, BMI: body mass index, Peg-IFN: pegylated interferon, AE: adverse events, #Available in 144 patients, &Available in 142 patients, *Mean ± standard deviation and median; ‡Student's t test, $\chi^2$ test or Fisher's exact test when appropriate for comparison of groups.

**TABLE 3 - Factors associated with failure to achieve sustained virological response (SVR), according to multivariate analysis.**

| Factors | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Suspension of treatment due to AE | 9.006 | 1.096 – 74.026 | 0.041 |
| Body mass index | 1.078 | 0.981 – 1.185 | 0.118 |
| Thrombocytopenia | 2.339 | 0.528 – 10.371 | 0.263 |
| Age | 1.005 | 0.973 – 1.739 | 0.747 |
| Fibrosis stage 3 or 4 | 1.079 | 0.981 – 1.185 | 0.863 |

CI: confidence interval, AE: adverse events.

**TABLE 4 - Adverse events in patients with chronic hepatitis C (genotype 1) who were treated with pegylated interferon and ribavirin, according to gender.**

| | Gender | | | $P^{\ddagger}$ |
|---|---|---|---|---|
| | Total | Female | Male | |
| **Adverse events** | n = 181 | n = 83 | n = 98 | |
| Flu-like symptoms, n (%) | 170 (93.9) | 77 (92.8) | 93 (94.9) | 0.551 |
| Anemia, n (%) | 53 (29.3) | 40 (48.2) | 13 (13.3) | < 0.001 |
| Neutropenia, n (%) | 42 (23.3) | 22 (26.5) | 20 (20.6) | 0.352 |
| Thrombocytopenia, n (%) | 21 (11.6) | 9 (10.8) | 12 (12.2) | 0.478 |
| Dizziness, n (%) | 28 (15.5) | 19 (22.9) | 9 (9.2) | 0.011 |
| Panic attacks, n (%) | 3 (1.7) | 1 (1.2) | 2 (2.0) | 1.000 |
| Depression, n (%) | 65 (35.9) | 34 (41.0) | 31 (31.6) | 0.192 |
| Irritability, n (%) | 48 (26.5) | 20 (24.1) | 28 (28.6) | 0.497 |
| Significant weight loss, n (%) | 66 (36.5) | 31 (37.3) | 35 (35.7) | 0.820 |
| Anorexia, n (%) | 36 (19.9) | 26 (31.3) | 10 (10.2) | < 0.001 |
| Nausea, n (%) | 34 (18.8) | 23 (27.7) | 11 (11.2) | 0.005 |
| Insomnia, n (%) | 25 (13.8) | 12 (14.5) | 13 (13.3) | 0.817 |
| Dermatitis or itching, n (%) | 95 (52.5) | 49 (59.0) | 46 (46.9) | 0.104 |
| Alopecia, n (%) | 24 (13.3) | 18 (21.7) | 6 (6.1) | 0.002 |
| Decreased visual acuity, n (%) | 8 (4.4) | 7 (8.4) | 1 (1.0) | 0.025 |
| Diarrhea, n (%) | 33 (18.2) | 20 (24.1) | 13 (13.3) | 0.060 |
| Dyspnea, n (%) | 12 (6.6) | 8 (9.6) | 4 (4.1) | 0.134 |
| Infection, n (%) | 35 (19.3) | 22 (26.5) | 13 (13.3) | 0.025 |
| Hypothyroidism, n (%) | 12 (6.6) | 9 (11.0) | 3 (3.0) | 0.036 |

Peg-IFN: pegylated interferon, ‡ Fisher's exact test and $\chi^2$ test when appropriate for comparison of groups.

**TABLE 5 - Modifications of pegylated interferon or ribavirin dose, and interruption or suspension of treatment, in patients with chronic hepatitis C (genotype 1), according to gender.**

| | Gender | | | |
|---|---|---|---|---|
| | Total | Female | Male | $P^{\ddagger}$ |
| | n = 181 | n = 83 | n = 98 | |
| Modification of Peg-IFN dose, n (%) | 18 (10.0) | 14 (17.0) | 4 (4.0) | 0.004 |
| Neutropenia, n (%) | | 5 (6.0) | 2 (2.0) | 0.250 |
| Thrombocytopenia, n (%) | | 2 (2.4) | 2 (2.0) | 1.000 |
| Significant weight loss, n (%) | | 3 (3.6) | 0 (0.0) | 0.095 |
| Other adverse events, n (%) | | 4 (4.8) | 0 (0.0) | 0.042 |
| Modification of ribavirin dose, n (%) | 38 (21.0) | 25 (30.0) | 13 (13.0) | 0.006 |
| Anemia, n (%) | | 23 (27.7) | 9 (9.2) | 0.001 |
| Other adverse events, n (%) | | 2 (2.4) | 4 (4.1) | 0.689 |
| Treatment interruption due to AE, n (%) | 10 (5.5) | 7 (8.0) | 3 (3.0) | 0.190 |
| Anemia, n (%) | | 4 (4.8) | 0 (0.0) | 0.042 |
| Thrombocytopenia, n (%) | | 0 (0.0) | 1 (1.0) | 1.000 |
| Other adverse events, n (%) | | 3 (3.6) | 2 (2.0) | 0.662 |
| Treatment suspension due to AE, n (%) | 42 (23.2) | 12 (14.4) | 10 (10.2) | 0.383 |
| Anemia, n (%) | | 1 (1.2) | 1 (1.0) | 1.000 |
| Thrombocytopenia, n (%) | | 2 (2.4) | 0 (0.0) | 0.209 |
| Other adverse events, n (%) | | 9 (10.8) | 9 (9.2) | 0.710 |

Peg-IFN: pegylated interferon, AE: adverse events, $^{\ddagger}$Fisher's exact test and $\chi^2$ test when appropriate for comparison of groups.

## DISCUSSION

Treatment with Peg-IFN and RBV for 48 weeks has been recommended for patients infected with HCV genotype 1, which is the most common variant not only in Brazil, but also in the United States and Europe[19-20]. Whereas SVR can be achieved in 81% to 84% of patients infected with HCV genotype 2 or 3 after 24 weeks of combination therapy, the rate of SVR is much lower in patients with HCV genotype 1 infection, ranging from 34% to 52% after 48 weeks of combination therapy with Peg-IFN and RBV[21-23]. In a retrospective study on Southern Brazilian patients with chronic hepatitis and HCV genotype 1 infection, SVR was achieved in only 35.3% of patients (114/323), although this may have occurred because a large proportion of the patients presented advanced fibrosis (F3/F4 = 74%)[24]. However, previous Brazilian studies have demonstrated SVR rates of 44-52% in genotype 1 HCV infection among patients who were not enrolled in medical trials[25-27].

Improvements in the management of patients with chronic HCV genotype 1 infection are essential. Every effort needs to be directed towards an increase in SVR rates. A number of host and viral factors have been studied as possible predictors of treatment outcomes, such as gender, age, body weight, alcohol consumption, advanced fibrosis, basal viral load and treatment compliance.

Despite a previous large analysis (n = 1744) on two trials involving standard IFN plus RBV therapy that showed a significant positive correlation between female gender and SVR ($p < 0.004$)[28], no such difference has been confirmed in studies involving Peg-IFN plus RBV[21-24,29-31]. Kogure et al[32] observed that among Asian patients, the SVR rate among females was significantly lower than the rate among males (17% vs 50%, p = 0.026). Furthermore, the SVR among older females was remarkably low (17.4%), compared with all the females included in the study (36%). Similarly, in another Asian study, Sezaki et al[16] concluded that women older than 50 years of age had worse rates of SVR than did men (32% vs 63%, p = 0.016). In accordance to Western studies[21-24,29-31], no differences in SVR have been shown between genders ($p = 0.464$), not even among patients older than 50 years of age (40% of women vs 38% of men; p = 0.859; *data not shown*).

In all large prospective studies on Peg-IFN and RBV combination therapy, younger age correlated significantly with SVR and patients younger than 40–45 years showed the best response rates[21,22,28]. Recently, Reddy et al evaluated 569 genotype-1 patients who underwent Peg-IFN alpha-2a + RBV for 48 weeks, and demonstrated that the SVR rate among patients ≤ 50 years of age was greater than the rate among patients older than 50 years (52% vs 39%; p = 0.007)[33].

Although high BMI has been previously identified as an independent risk factor for non-response to antiviral treatment with standard IFN plus RBV[29], the results relating to pegylated presentation are controversial. While in both types of Peg-IFN combination therapy (alpha-2a/2b) with RBV, lower baseline body weight has formely been associated with achieving SVR[21,22,34], this has not been confirmed in other large studies on HCV-infected patients in which multilogistic regression analyses including BMI and body weight were conducted[30,35].

Alcohol consumption is possibly underestimated in most retrospective analyses. Hence, limited data are available on its impact on antiviral treatment outcome. In a large, prospective multicenter trial, it was observed that patients who drink alcohol discontinue therapy more often and therefore achieve lower SVR rates. Nevertheless, individuals with alcohol consumption who finished treatment had response rates comparable to those of non-drinkers[36].

The presence of advanced liver fibrosis and cirrhosis has long been accepted as associated with lower response rates to IFN-based treatment[28]. Furthermore, advanced fibrosis and cirrhosis have been shown to be major independent predictors of non-response[37]. In a recent study that evaluated the efficacy and safety of Peg-IFN alpha-2a

+ RBV in 341 genotype 1/4 patients, it was demonstrated that SVR rates decreased progressively from 60% in genotype 1/4 patients without advanced fibrosis to 51% in those with bridging fibrosis and 33% in those with cirrhosis ($p = 0.003$)[38].

Although HCV-related liver injury and disease progression have not been associated with viral load, HCV-RNA quantification before, during and after therapy is an essential tool for predicting treatment outcome. Low baseline viral load has been shown to be an independent predictor of SVR, regardless of genotype in numerous studies[21,28,34,35]. Initially, 800,000 IU/ml was recommended as the decision threshold for high vs low viremia[39]. However, subsequent data have suggested that a baseline level of 400,000 IU/ml is the most effective cutoff point between high and low likelihood of achieving SVR in genotype 1-infected patients[40,41].

In addition to host and viral characteristics, certain treatment features may influence SVR, such as ribavirin dose and adherence. Nevertheless, no significant differences regarding SVR rates and tolerability have been demonstrated between the two available peginterferons[31]. A detailed analysis on the relationship between bodyweight and SVR suggests that ribavirin dose per kilogram may be the determining factor for the response among genotype 1 patients, with a 40-50% increase in the likelihood of SVR for a 12-16 mg/kg dose[42]. With regard to adherence, HCV-1-infected patients who can be maintained on > 80% of their Peg-IFN + RBV dosage for the duration of treatment in a clinical trial setting exhibit enhanced sustained response rates[43].

In this study, women had some favorable pretreatment-related variables, including lower mean weight and less frequent history of alcohol abuse than shown by men. However, women presented higher mean age as a negative pretreatment predictor of SVR. Nevertheless, women and men presented equivalent BMI means, similar proportions of high viral load and comparable histological characteristics (advanced liver fibrosis and significant necroinflammatory activity). Despite similar SVR rates between genders, it was demonstrated that the women presented higher incidence of several adverse events and, consequently, Peg-IFN dose modifications were more frequent among women. Even though adherence *per se* was not evaluated in this study, no significant differences were observed between women and men with regard to interruption or suspension of antiviral therapy. This could reflect adequate management of adverse events, which made it possible to avoid a negative impact on SVR rate.

Although some adverse events from combined therapy have previously been described in association with female gender, such as hypothyroidism[44] and anemia[45,46], most of the findings from this study have never been correlated with gender. The higher incidence of alopecia among women, for instance, could be associated with hypothyroidism[44], but this relationship was not evidenced ($p = 0{,}201$; *data not shown*).

Even though baseline hemoglobin levels and mean BMI were similar between genders, women weighed less than men did and thus received higher doses of RBV per kg. Although current data suggest that SVR increases linearly with ribavirin doses (which equate to > 10 mg/kg), there is also a simultaneous linear increase in the anemia rate (< 10 g/dl hemoglobin)[42], which may possibly explain the higher incidence of anemia among women. It is well established that anemia can cause dizziness, asthenia and worsened quality of life, and may result in reduction, suspension or interruption of the RBV regimen[47,48]. In this study, anemia was the most common reason for RBV dose modification and treatment interruption among women; this probably reflects the higher incidence of anemia and its clinical manifestations such as dizziness.

The limitations of this study include the possible selection bias due to retrospective data collection. Nevertheless, the data were collected from standardized medical records, and the treatment used has also been standardized by the Brazilian Public Health System, thus minimizing potential sources of bias. Secondly, the number of patients included was far smaller than in most published treatment studies, which have included 500-1,500 patients[21-23]. However, the characteristics of the patients included in the present study are comparable to those reported in the literature and represent a true picture of the chronic hepatitis C patients treated in Brazil.

This study concluded that, while women and men exhibit similar clinical, histological and virological disease characteristics before beginning treatment, they react differently to combined therapy, especially with regard to the incidence of adverse events, which are more frequent among women. Furthermore, women required modifications to their antiviral therapy dose with greater frequency than men did, due to higher incidence of adverse events (particularly, anemia). Recognition of these features, which are unique to females, is fundamental for crafting a suitable approach towards treating these patients and optimizing the chances of cure for chronic hepatitis C infection.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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