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Original Article

Therapeutic effectiveness of biosimilar standard interferon versus pegylated interferon for chronic hepatitis C genotypes 2 or 3

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ABSTRACT

Background: Pegylated interferon (Peg-IFN) and standard interferon (IFN) play a significant role in the treatment of hepatitis C virus (HCV) infection. Biosimilar standard IFN is widely available in Brazil for the treatment of HCV infection genotypes 2 or 3, but its efficacy compared to Peg-IFN is unknown.

Objective: To compare the sustained virological response (SVR) rates following treatment with biosimilar standard IFN plus ribavirin (RBV) versus Peg-IFN plus RBV in patients with HCV genotypes 2 or 3 infection.

Methods: A retrospective cohort study was conducted in patients with HCV genotypes 2 or 3 infection treated with biosimilar standard IFN plus RBV or with Peg-IFN plus RBV. SVR rates of the two treatments were compared.

Results: From January 2005 to December 2010, 172 patients with a mean age of 44 +/- 9.3 years were included. There were eight (4.7%) patients with HCV genotype 2 infections. One hundred fourteen (66.3%) were treated with biosimilar standard IFN plus RBV, whist 58 (33.7%) patients were treated with Peg-IFN plus RBV. Between the two groups, there were no significant differences regarding age, gender, glucose level, platelet count, hepatic necroinflammatory grade, and hepatic fibrosis stage. Overall, 59.3% (102/172) patients had SVR. In patients treated with Peg-IFN plus RBV, 79.3% (46/58) had SVR compared to 49.1% (56/114) among those treated with biosimilar standard IFN plus RBV ($p = 0.0001$).

Conclusion: In patients with HCV genotypes 2 or 3 infection, a higher SVR was observed in patients receiving Peg-IFN plus RBV related to patients treated with biosimilar standard IFN plus RBV.

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Introduction

Hepatitis C virus (HCV) infection has a high prevalence worldwide and is the leading cause of cirrhosis and hepatocellular carcinoma.[1,2] The antiviral treatment for HCV infection, a combination of interferon α (pegylated or non-pegylated) and ribavirin (RBV), reduces liver disease progression and improves the quality of life of patients who obtain sustained virological response (SVR).[3,4]

Among patients with HCV genotype 1 infection, SVR rates are higher in those treated with pegylated (Peg) interferon (IFN) (pegylated interferon alpha 2a or 2b) plus RBV than in those treated with standard IFN (interferon alpha 2a or 2b) plus RBV.[5,6] However, among patients with HCV genotypes 2 or 3 infection, some large studies showed no difference in SVR rates when patients were treated with Peg-IFN plus RBV or with standard IFN plus RBV. It is important to consider that the cost of treatment with Peg-IFN is higher than that with non-Peg-IFN.

In 2000, according to the national guidelines for hepatitis C treatment from the Brazilian Ministry of Health, patients with chronic HCV infection became eligible to receive antiviral treatment, fully covered by government-funded healthcare.[7] In 2007, according to a new protocol from the Brazilian Ministry of Health, patients with genotype 1 infection were to be treated with Peg-IFN plus RBV, and patients with genotypes 2 or 3 infections should be treated with standard IFN plus RBV.[8] Since 2000, biosimilar standard IFN has been used in Brazil for genotypes 2 or 3 infections. The main objective of this study is to compare the SVR rates of the biosimilar standard IFN plus RBV with that of Peg-IFN plus RBV in patients with HCV genotypes 2 or 3 infections.

Patients and methods

Patient enrollment

Patients with HVC genotypes 2 or 3 infections, treated for the first time with biosimilar standard IFN plus RBV or with Peg-IFN plus RBV at the Hospital de Clínicas, Universidade Estadual de Campinas, state of São Paulo, Brazil from January 2005 to December 2010, were included in this study. Chronic hepatitis C was defined as the presence of HCV antibody (Abbott AxSYM Anti-HCV 3.0, Abbott Laboratories – Wiesbaden, Germany) and detectable serum HCV RNA (Amplicor HCV 2, Roche Diagnostics Systems Inc – Branchburg, USA). Patients with HIV infection, detectable hepatitis B surface antigen, evidence of other liver disease (e.g., autoimmune hepatitis and primary biliary cirrhosis), previous treatment for HCV infection, and/or previous therapy with immunosuppressive drugs were excluded from the study.

Patients received Peg-IFN alpha-2a (180 µg) or Peg-IFN alpha-2b (1.5 µg/Kg) subcutaneously once a week, or biosimilar standard IFN (3 million units) three times a week. All patients also received RBV, 1,000 mg to 1,250 mg a day according to the patient's weight. SVR was defined as negative HCV RNA six months after treatment.

Data collection

Baseline data were collected from medical records. They included demographic information, HCV genotype, and liver histological data. Prior to initiation of treatment, serum biochemical analyses using commercial tests were carried out. These included fasting glucose level and platelet count. Amplicons generated by the Amplicor® HCV test were used, applying a commercially available assay (Line Probe assay, LIPA HCV, Innogenetics – Gent, Belgium) to determine HCV genotype.

Histological evaluation

Hepatic histological evaluation was graded and staged according to the Metavir scoring system.[9] The Metavir score incorporates five progressive stages of fibrosis, F0 (absence of fibrosis) to F4 (cirrhosis), and four grades of necroinflammatory activity, A0 (no activity) to A3 (severe activity), taking into account the severity of portal and lobular necroinflammatory lesions. For analysis purposes, the diagnosis of cirrhosis was made upon histological examination (F4 stage) or by the combination of clinical and laboratorial parameters (presence of hyperbilirrubinemia, esophageal varices, ascites, and splenomegaly).

Statistical analysis

Continuous variables were analyzed as mean and standard deviation, and categorical variables as frequency, unless otherwise stated. Study patients were categorized into biosimilar standard IFN or Peg-IFN groups. Analysis of variance (standard or nonparametric, as appropriate) was used for continuous variables whereas the chi-square test was used for categorical variables. All analyses were performed with Epi Info software version 3.5.1. (Centers for Disease Control – Atlanta, GA, USA). A significance level of 5% ($p < 0.05$) was considered statistically significant.

Results

Pretreatment demographic and clinical characteristics

A total of 172 patients were included in the study. Patients' characteristics are presented in Table 1: 71% were male, and the median age at the beginning of follow up was 44 years (range: 17-69). Only eight (4.7%) patients were infected by HCV genotype 2.

Liver biopsy was performed in 158 patients. Fibrosis was staged as F1 or F2 in 95 (55.2%) patients, and as F3 or F4 in 77 (44.8%). In 14 patients, the diagnosis of cirrhosis (F4) was based on clinical and laboratorial parameters alone. Histological analysis showed necroinflammatory grade as no activity (A0) or mild (A1) in 27 (17.1%) patients, and moderate (A2) or severe (A3) in 131 (82.9%).

Table 1 - Characteristics of 172 study patients with chronic hepatitis C virus infection (January 2005–December 2010)

Characteristic	Value*
Male – n (%)	123 (71.5%)
Age (years)	44.0 ± 9.3
Weight (kg)	71.0 ± 14.2
Glucose (mg/dL)	85.0 ± 18.8
Platelets (x 10^9/L)	171.0 ± 70.8
Genotype 2 – n (%)	8 (4.7%)
Necroinflammatory grade[1] – n (%)	
A0 / A1	27 (17.1%)
A2 / A3	131 (82.9%)
Fibrosis stage – n (%)	
F1 / F2	95 (55.2%)
F3 / F4	77 (44.8%)
Cirrhosis – n (%)	41 (23.8%)

*Data presented as mean and standard deviation, unless otherwise noted; [1]available for 158 patients.

Patients' characteristics in Peg-IFN plus RBV and biosimilar standard IFN plus RBV treatment groups were similar (Table 2). There were no significant differences between the two groups in respect to demographic characteristics, fast glucose level and platelet count. Similarly, the number of patients with genotype 2 infection, advanced fibrosis (F3 or F4), and cirrhosis were similar in the two treatment groups. The only significant difference was body weight: patients treated with biosimilar standard IFN plus RBV had a higher body weight when compared with those treated with Peg-IFN plus RBV (p = 0.03).

Treatment

Fifty-eight (33.7%) patients were treated with Peg-IFN plus RBV, and 114 (66.3%) with biosimilar standard IFN plus RBV. Out of 172 patients, 157 received Peg-IFN plus RBV or biosimilar standard IFN plus RBV for 24 weeks. Ten patients received Peg-IFN plus RBV for 48 weeks. Treatment was discontinued in five (3%) patients, three (5.2%) in Peg-IFN plus RBV treated group with, and two (1.8%) in the group treated with biosimilar standard IFN plus RBV (p = 0.2). The dose of IFN or Peg-IFN was reduced in nine (5.2%) patients; this reduction was more frequent in patients treated with Peg-IFN plus RBV than in those treated with biosimilar standard IFN plus RBV, in six (10.3%) and three (2.6%) patients, respectively (p = 0.03). The dose of RBV was reduced in 13 (7.6%) patients; it was more frequent in patients treated with Peg-IFN plus RBV than in those treated with biosimilar standard IFN plus RBV, in eight (13.8%) and five (4.4%) patients, respectively (p = 0.02).

Virological response

Of 172 patients treated for 24 or 48 weeks, 102 (59.3%) patients had SVR. There was an association between receiving Peg-IFN plus RBV and having SVR. Among patients treated with Peg-IFN plus RBV, 79.3% (46/58) had SVR, in contrast, in patients who were treated with biosimilar standard IFN plus RBV, 49.1% (56/114) had SVR (p = 0.0001). When considered only patients treated for 24 weeks, among patients treated with Peg-IFN plus RBV, 79.2% (38/48) had SVR; and in patients who were treated with biosimilar standard IFN plus RBV, 49.1% (56/114) had SVR (p = 0.0004).

Table 2 - Univariate analysis of pretreatment characteristics of patients treated with Peg-IFN plus RBV or IFN plus RBV

Variable*	Peg-IFN (2a or 2b) + RBV (n = 58)	Biosimilar standard IFN + RBV (n = 114)	p-value
Male – n (%)	36 (62.1%)	87 (76.3%)	0.05
Age (years)	50.0 ± 9.7	42.0 ± 8.3	0.16
Weight (kg)	70.0 ± 14.0	72.0 ± 14.0	0.03
Glucose (mg/dL)	84.0 ± 9.3	87.0 ± 21.9	0.07
Platelets (x 10^9/L)	170.0 ± 67.1	172.0 ± 72.8	0.77
Genotype 2 – n (%)	1 (1.7%)	7 (6.1%)	0.19
Necroinflammatory grade[1] – n (%)			
A0 / A1	9 (16.4%)	18 (17.5%)	0.85
A2 / A3	46 (83.6%)	85 (82.5%)	0.85
Fibrosis – n (%)			
F1 / F2	33 (56.9%)	62 (54.4%)	0.75
F3 / F4	25 (43.1%)	52 (45.6%)	0.75
Cirrhosis – n (%)	12 (20.7%)	29 (25.4%)	0.48

Peg-IFN, pegylated interferon; RBV, ribavirin; IFN, interferon. *Data presented as mean and standard deviation, unless otherwise noted; [1]available for 158 patients.

Among patients with stage 1 or 2 fibrosis, in comparison to biosimilar standard IFN plus RBV Peg-IFN plus RBV was associated with significantly more SVR (p = 0.01) (Fig. 1). The same was observed among patients with stage 3 or 4 fibrosis (p = 0.003) (Fig. 1).

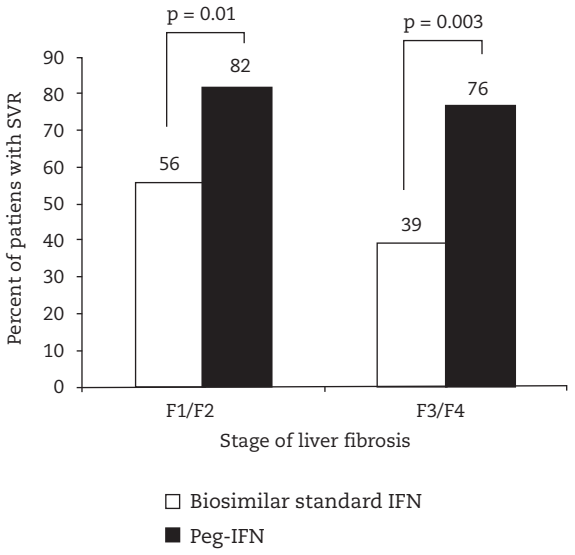

Fig. 1 - Sustained virological response according to stage of liver fibrosis. SVR, sustained virological response; IFN, interferon; Peg-IFN, pegylated interferon.

Discussion

In the present study, Peg-IFN plus RBV was significantly more effective than biosimilar standard IFN plus RBV for treating patients with HCV genotypes 2 or 3 infection, irrespective of fibrosis stage. According to the present findings, although the presence of advanced fibrosis (F3 or F4) is associated with lower SVR rates than those with mild or moderate fibrosis (F1 or F2), both groups of patients benefited from being treated with Peg-IFN plus RBV.[10]

Both IFN and RBV doses have a major impact on SVR rates. Patients who receive the optimal dose of Peg-IFN or standard IFN and RBV for the planned duration have higher rates of SVR than those who require dosage reductions.[11] Although RBV and IFN dosage reduction were more frequent in patients treated with Peg-IFN and RBV than those treated with biosimilar standard IFN and RBV, SVR rate was higher in the Peg-IFN group.

Overall, the rate of SVR found in this study was similar to that reported with Peg-IFN plus RBV in patients with HCV genotypes 2 or 3 infection. Studies have shown SVR rates ranging from 76% to 81%, and in the current study the SVR rate was 79.3%.[5,6,12] In contrast to previous reports, that showed SVR rates ranging from 61% to 79% in patients with genotype 2 or 3 infection treated with standard IFN plus RBV, a SVR rate of 49.1% was found in this study.[5,6,13]

Other studies have shown no consistent advantage of Peg-IFN over standard IFN in patients with viral genotypes 2 or 3 infections.[5,6,14] In addition, although the SVR rate found in the present study among patients treated with Peg-IFN is similar to that of previous studies, it is lower in the non-Peg-IFN treated group. The reason for this finding is unknown.

Biosimilar Peg-IFN is not available, the only Peg-IFN formulations currently available are Peg-IFN alpha-2a (Pegasys®) or alpha-2b (Peg Intron®). Therefore, the Peg-IFN used in this study are the same formulations used in studies reported in the literature. However, with respect to standard IFN, there are several biosimilar formulations available. In the present study, patients were treated with biosimilar standard IFN, and the high SVR rates of IFN reported in previous studies were the original trademark.[5,6,13,14]

In Brazil, previous studies in patients with genotype 2 or 3 treated with biosimilar standard IFN plus RBV showed SVR rates ranging from 39 to 46%, similar to that found in the present study.[15-17] On the other hand, one Brazilian study on patients with genotypes 2 or 3 infections who were treated with Peg-IFN plus RBV found a SVR rate of 67%.[18] Biosimilar standard IFN plus RBV treatment is routinely used in Brazilian patients with genotype 2 or 3 infections and, according the present study findings, it was less effective regarding SVR than what would be expected according to the literature.

The present study has some limitations. Due to retrospective nature of this study, some patients were treated for more than 24 weeks, and levels of HCV RNA were not available. In addition, it was not possible to randomize patients. However, this study provides an important clinical data in real life practice, and to the authors' best knowledge, it is the first comparative study of biosimilar standard IFN and Peg-IFN for HCV genotypes 2 or 3 infections.

In conclusion, regarding the SVR rate among the studied patients, Peg-IFN plus RBV was better than biosimilar standard IFN for genotype 2 or 3 infections regardless of fibrosis stage, and the SVR rate associated with biosimilar standard IFN was low. Therefore, Peg-IFN is a better option for genotype 2 or 3 infections than biosimilar standard IFN.

Conflict of interest

All authors declare to have no conflict of interest.

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