Peginterferon Alfa-2a (40KD) (PEGASYS®) Plus Ribavirin (COPEGUS®) in Retreatment of Chronic Hepatitis C Patients, Nonresponders and Relapsers to Previous Conventional Interferon Plus Ribavirin Therapy

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Peginterferon alfa plus ribavirin is currently the treatment of choice for chronic hepatitis C. Peginterferon alfa-2a (40KD) plus ribavirin has given an overall sustained virological response of 18% in F3/F4 previous nonresponder US patients. We evaluated the effectiveness of peginterferon alfa-2a (40KD) plus ribavirin in Brazilian patients who were relapsers or nonresponders to previous interferon-based therapy. One-hundred-thirty-four patients with biopsy-proven chronic hepatitis C, HCV RNA positive, elevated ALT and who were either relapsers (n=37) or nonresponders (n=97) to at least 24 weeks of conventional interferon/ribavirin therapy were retreated with peginterferon alfa-2a (40KD) 180mg/qw and ribavirin 800mg bid for 48 weeks. Efficacy was assessed as virological response (defined as undetectable HCV RNA) at the end of treatment (EoT) and at the end of follow-up (SVR - Sustained Virological Response). Safety assessments consisted of clinical and laboratory evaluations. In the patient sample, 72% were genotype 1 and 34% were cirrhotic. In an intention-to-treat analysis, relapser patients showed 78% EoT response and 51% SVR. Nonresponders showed 57% EoT response and 26% SVR. Positive predictive factors of SVR were non-1 genotype and relapser state. Six percent of the patients interrupted treatment because of adverse events and 45% had dose reduction (mainly associated with leucopenia and anemia). Brazilian patient relapsers and nonresponders to conventional interferon and ribavirin treatment can achieve a sustained virological response when retreated with peginterferon alfa-2a (40KD) and ribavirin. The safety profile is similar to that of naive patients.

Key Words: Peginterferon alfa, ribavirin, hepatitis C, safety, efficacy.

Chronic infection with hepatitis C virus (HCV) is the leading cause of liver cirrhosis and hepatocellular carcinoma worldwide [1]. HCV-associated liver disease is the most common indication for liver transplantation [2]. Therefore, new therapeutic strategies to avoid the progression of HCV-related liver disease are eagerly awaited. A 48-week course of conventional interferon (IFN) therapy at the standard dose of 3 MU tiw combined with ribavirin (1000-1200 mg daily) yielded a sustained virological response (SVR) of approximately 40% in naive patients [3,4]. Recently, two randomized controlled trials have shown that the combination of peginterferon alfa-2a (40KD) plus the standard dose of ribavirin, or of peginterferon alfa-2b (12KD) plus a low dose of ribavirin, are significantly more effective than the combination of conventional IFN plus ribavirin in previously untreated patients with an overall SVR of 56% and 54%, compared to approximately 45%, respectively [5,6]. A later prospective controlled trial showed that the HCV genotypes and baseline viral load are also the most important predictive variables to peginterferon alfa-2a (40KD) and ribavirin combined treatment in naive patients. The overall sustained virological response in this trial was 63% [7].

Choosing the correct strategy for retreating chronic hepatitis C patients, who were nonresponders to a first course of antiviral therapy, is the biggest challenge in routine practice. A meta-analysis that evaluated the efficacy of conventional IFN and ribavirin combination therapy in previous

Received on 27 October 2005; revised 17 January 2006.
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Funding Information: This study was partially supported by Roche, São Paulo, Brazil.

The Brazilian Journal of Infectious Diseases 2006;10(1):11-16.

nonresponders reported only 13% SVR, thus indicating the need for better therapeutic options [8].

We evaluated the efficacy and tolerability of peginterferon alfa-2a (40KD) plus ribavirin combination therapy in patients with chronic hepatitis C who had previously failed to respond or who responded and subsequently relapsed after conventional IFN plus ribavirin therapy.

Material and Methods

Patients. One hundred and thirty-four patients from 20 to 71 years old with chronic hepatitis C who had previously received one course of conventional IFN (3-6 MU tiw) plus ribavirin (800-1200 mg qd) for at least 24 weeks were considered eligible for this study. Among these, 97 patients never achieved undetectable HCV RNA levels (qualitative PCR testing) during the first treatment (nonresponders, group A) and 37 patients showed undetectable HCV RNA during the first therapy but became HCV RNA positive after discontinuing medication (relapsers, group B). At the baseline, the patients were HCV RNA positive, had elevated ALT (defined as ALT above the upper limit of normal) and had a liver biopsy consistent with chronic hepatitis C. Exclusion criteria were previous course of conventional IFN monotherapy, age below 18 years, HBV or HIV virus infection, platelet count <75,000cells/mm^3, neutrophil count <1500cells/mm^3 and hemoglobin levels <12g/dL, evidence of decompensated liver disease, alcohol or drug abuse, metabolic or autoimmune liver disease, severe psychiatric conditions, seizures, other poorly controlled clinical diseases, pregnancy or unwillingness to practice contraception.

Study design. This was an open-label non-randomized trial conducted at 14 Brazilian centers. The study was approved by the Institutional Ethics Committee of each participating center and a written informed consent was obtained from every patient. Enrollment began in 2000 and lasted 18 months. Eligible patients were consecutively included in the study and received peginterferon alfa-2a (40KD) (PEGASYS®), subcutaneously at a dose of 180 mcg/weekly plus ribavirin (COPEGUS®) administered orally twice a day at a total dose of 800 mg for 48 weeks (group A nonresponders and group B relapsers). Clinical and laboratory evaluations were performed at screening, baseline, week 2, week 4, monthly thereafter, and at follow-up weeks 4, 12 and 24. All patients had HCV genotyping before study entry. Qualitative HCV RNA and HCV RNA quantification were done by in house or Roche Amplicor methodologies. Liver biopsies were graded according to METAVIR criteria.

Assessment of efficacy. The primary efficacy end point was sustained virological response (SVR), defined as the absence of detectable HCV RNA in serum by polymerase chain reaction (detection limit of 100 copies per milliliter) 24 weeks after cessation of treatment. A secondary end point was used to compare the efficacy of combination therapy in genotype 1 *versus* non-1 genotype patients (nonresponders and relapsers), to evaluate the percentage of relapsers (patients with negative HCV RNA at the end of therapy and a positive HCV RNA test at the end of follow-up) and to evaluate predictive variables associated with a better outcome.

Assessment of safety. The safety profile was assessed by evaluation of adverse events and by laboratory tests. Adverse events were graded as mild, moderate, severe or life threatening, according to the modified World Health Organization (WHO) grading system. Therapy adjustments were allowed and performed whenever there were changes in hemoglobin, or in white blood cell or platelet counts, using standard guidelines for peginterferon alfa-2a (40KD) plus ribavirin combination treatment. If the abnormalities were resolved, the doses were increased towards the initial dose. Patients skipping more than four consecutive treatment weeks were withdrawn from the study. All patients prematurely withdrawn were followed for safety reasons during 12 weeks after the last study medication dose.

Statistical analysis. Efficacy analysis was performed on an intention-to-treat basis; therefore all patients who received at least one study dose were considered for the primary end point. Response rate was calculated as the number of patients with a sustained virological response divided by the number of patients who started treatment. Patients who did not have week-24 follow-up assessments were classified as nonresponders. Comparisons were made at a significance level of 0.05. Changes from baseline variables were analyzed using analysis of covariance with the baseline value as a covariate. The following parameters were examined as potential prognostic factors for treatment success: gender (male vs female), age (< 40 years *versus* > 40 years), viral load (= 800.000 IU *versus* > 800.000 IU), histological status (no cirrhosis vs cirrhosis), HCV genotype (1 and 4 *versus* 2 and 3) and adherence (adherent *versus* nonadherent). An exact 95% confidence interval from the binomial distribution was determined for each prognostic variable.

Results

Patient characteristics. One-hundred-thirty-four patients agreed to participate, gave a written informed consent and were enrolled in the study; 97 nonresponders to previous IFN treatment were allocated to group A, and 37 relapsers to previous IFN treatment were allocated to group B. Baseline demographic, virological and histological characteristics of patients in the two treatment groups were similar (Table 1). Overall, 111 (83%) patients were men, median age was 48 years (range 20-71), 111 (83%) patients were Caucasian, 96 (72%) patients were genotype 1 and histological evidence of cirrhosis was observed in 44 (34%) patients. Bridging fibrosis was observed in 29 (22%) patients. Among patients with non-1

Table 1. Patients baseline characteristics

	All patients (n = 134)	Group A (n = 97)	Group B (n = 37)
Gender			
Male	111 (83)	81 (84)	30 (81)
Age (years)			
Median (range)	48 (20 - 71)	48 (20 - 71)	50 (28 - 70)
Race			
White	111 (83)	79 (82)	32 (86)
Mulato	18 (13)	13 (13)	5 (14)
Other	5 (4)	5 (5)	0 (0)
Histological diagnosis*			
Noncirrhotic	86 (64)	58 (60)	29 (78)
Cirrhotic	44 (33)	36 (37)	8 (22)
HCV genotype			
1	96 (72)	69 (71)	27 (73)
2	1 (0,7)	1 (1)	0 (0)
3	36 (27)	26 (27)	10 (27)
4	1 (0,7)	1 (1)	0 (0)
Serum HCV RNA			
>800.000	53 (39)	48 (50)	16 (43)
≤800.000	64 (48)	39 (40)	14 (38)
Missing	17 (13)	10 (10)	7 (19)

Group A = nonresponders; Group B = relapsers. Values expressed as number of patients (percentage). *Data was missing in 3 patients in group A and in 1 patient in group B.

Table 2. Virological response rates

HCV RNA clearance	All patients (n = 134)	Group A (n = 97)	Group B (n = 37)
End of therapy (week 48)	84 (63)	55 (57)	29 (78)
End of follow-up (week 72)	44 (33)	25 (26)	19 (51)

Group A = nonresponders; Group B = relapsers. Values expressed as number of patients (percentage).

genotype, 1 (1%) was genotype 2, 36 (27%) were genotype 3 and 1 (1%) was genotype 4. HCV RNA quantification was performed before treatment in 117 patients (87.3%).

Outcomes according to treatment groups. The percentage of patients with undetectable serum HCV RNA at the end of the treatment period was 57% in group A (nonresponders) and 78% in group B (relapsers). At the end of follow-up, the rate of sustained virological response was 26% for group A and 51% for group B (Table 2).

SVR was more frequent in non-1 genotype compared to genotype 1 patients (Table 3). In the nonresponders group, 46% of non-1 genotype achieved an SVR (*versus* 17% for genotype 1, p = 0.0048), and in the relapsers group, 70% of non-1 genotype achieved an SVR (*versus* 44% for genotype 1, p = 0.2691). SVR was also more frequent in non-cirrhotic compared to cirrhotic patients in nonresponders (group A, 33% *versus* 11%, p = 0.0269). However SVR was similar in non-cirrhotic and cirrhotic patients among relapsers (group B, 48% *versus* 50%, p = 1.0000). Among nonresponders, patients with low baseline serum HCV RNA (< 800,000 IU/mL) showed the same SVR as patients with high baseline serum HCV RNA (> 800,000 IU/mL, 21% for both). Among relapsers, patients with low baseline serum HCV RNA showed higher SVR, when compared to patients with high baseline serum HCV RNA (71% *versus* 37%, p = 0.0813). The complete subgroup analysis is presented in Table 3.

Table 3. Patients with sustained virological response as a function of baseline variables and treatment group

	All patients (n = 134)	Group A (n = 97)	Group B (n = 37)
HCV genotype			
Genotype 1	24/96 (25)	12/69 (17)	12/27 (44)
Genotype non-1	20/38 (53)	13/28 (46)	7/10 (70)
Histological diagnosis			
Noncirrhotic	34/90 (38)	20/61 (33)	14/29 (48)
Cirrhotic	8/44 (18)	4/36 (11)	4/8 (50)
Histological diagnosis (genotype 1)			
Noncirrhotic	19/63 (30)	10/42 (24)	9/21 (43)
Cirrhotic	5/33 (15)	2/27 (7)	3/6 (50)
Histological diagnosis (genotype non-1)			
Noncirrhotic	15/27 (56)	10/19 (53)	5/8 (63)
Cirrhotic	3/11 (27)	2/9 (22)	1/2 (50)
Baseline serum HCV RNA			
≤800.000	18/51 (35)	8/37 (22)	10/14 (71)
>800.000	16/64 (25)	10/48 (21)	6/16 (38)
Baseline serum HCV RNA (genotype 1)			
≤800.000	10/33 (30)	4/24 (17)	6/9 (67)
>800.000	9/49 (18)	4/37 (11)	5/12 (42)
Baseline serum HCV RNA (genotype non-1)			
≤800.000	8/18 (44)	4/14 (29)	4/4 (1 0 0)
>800.000	7/15 (47)	6/11 (55)	1/4 (25)

Group A = nonresponders; Group B = relapsers. Values expressed as number/total number of patients (percentage).

A bivariate logistic regression analysis identified genotype non-1 (OR 4.02 – CI 1.5-10.5), relapser state (OR 4.2 – CI 1.6-11.2) and adherence (OR 5.8 – CI 1.8-19), as the significant baseline variables associated with an SVR.

Safety and tolerability. Overall, 23 patients (17%) prematurely discontinued treatment. The reasons were adverse events or laboratory abnormalities in 6 (4.5%) patients, noncompliance in 8 (6%) patients and absence of response in 9 (6.7%) patients (Table 4).

Dose reduction because of laboratory abnormalities and/or adverse events was required in 60 patients (45%), with a similar proportion among groups A and B. Reasons for dose

Table 4. Incidence of discontinuation of treatment and dose reduction

	All patients (n = 134)	Group A (n = 97)	Group B (n = 37)
Dose discontinuation for			
Any adverse event	6 (4)	6 (6)	0 (0)
Insufficient response	9 (7)	6 (6)	3 (8)
Lost to follow-up	8 (6)	7 (7)	1 (3)
Dose modification for**			
Any adverse event	60 (45)	40 (41)	20 (54)
Anaemia	6 (4)	4 (4)	2 (5)
Neutropenia	22 (16)	14 (14)	8 (22)
Thrombocytopenia	10 (7)	7 (7)	3 (8)
ALT Elevation	6 (4)	3 (3)	3 (8)

Group A = nonresponders; Group B = relapsers. Values expressed as number of patients (percentage). †Dose reduction was defined as the reduction or omission of one or more doses. ‡Some patients required dose reduction for both laboratory abnormalities and other adverse events.

Figure 1. Virological response rates (end of treatment)

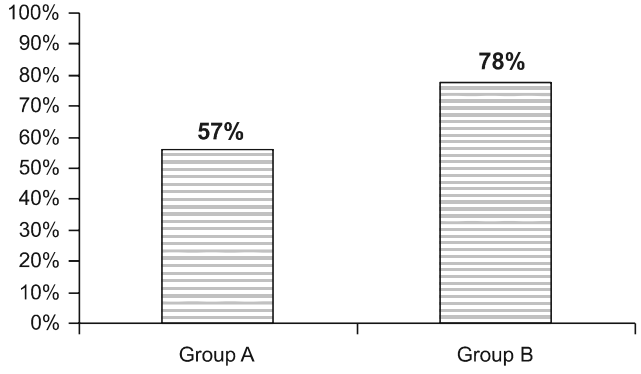


Figure 2. Virological response rates (end of follow-up)

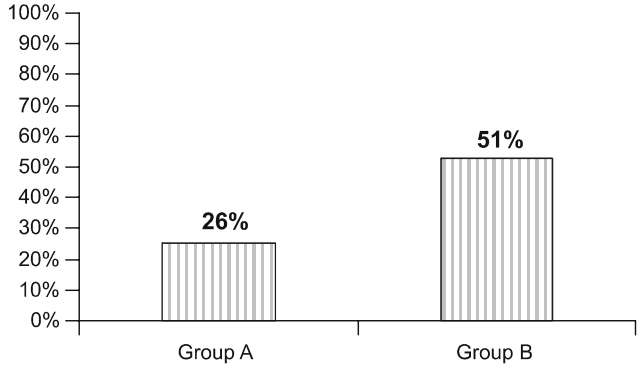


Table 5. Adverse events

Adverse event	Group A (n=97)	Group B (n=37)
Headache	42	14
Myalgia	31	11
Fever	29	08
Irritability	16	14
Nausea	22	04
Fatigue	16	10
Imsomnia	19	06
Weight loss	19	04
Asthenia	17	05
Malaise	22	07
Depression	14	06
Diarrhea	14	05
Dizziness	13	04
Anorexia	20	08
Cough	09	06
Flu-like	17	09
Pruritus	9	04
Dispepsia	9	04
Anxiety	10	03

* Adverse events that occurred in more than 10% of patients.

Figure 3. Sustained virological response (genotype 1)

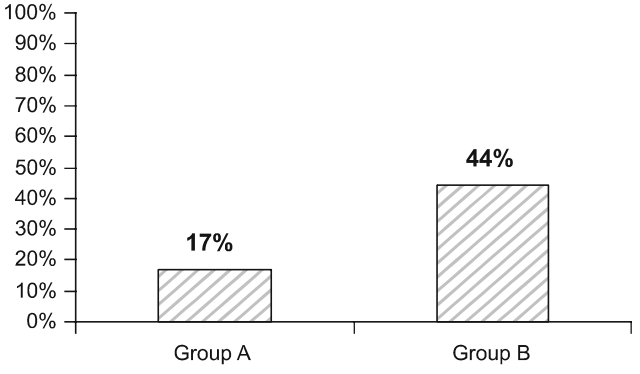
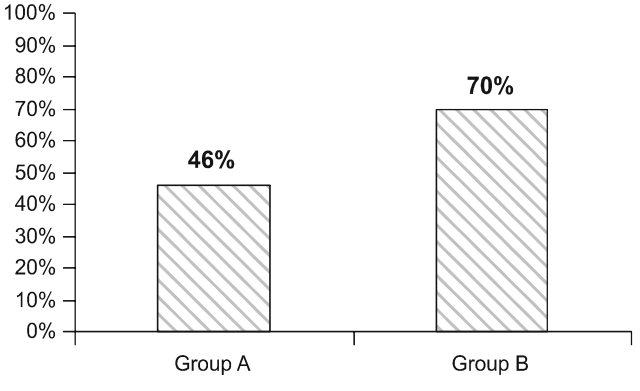


Figure 4. Sustained virological response (genotype non- 1)



reduction are listed in Table 4. Overall, the most frequent cause for peginterferon alfa-2a (40KD) dose modification was neutropenia which occurred in 14 group A patients (14%) and in 8 group B patients (22%). Ribavirin was reduced mostly because of hemolytic anemia, which was observed in 4% of patients from group A and 5% of patients from group B. There were no severe infection or cardiac events associated with laboratory abnormalities.

Most of the adverse events reported during treatment showed the same profile as already known for peginterferon alfa-2a (40KD) plus RBV, and they were graded as mild or moderate. Flu-like symptoms was the most common among the adverse events (Table 5). Both adverse events and laboratory abnormalities returned to baseline after the medication was interrupted.

Discussion

Information on the use of peginterferon alfa in patients who are nonresponders or relapsers to conventional interferon is still limited. Herrine et al. [9] reported the results of retreating patients who are relapsers to conventional IFN plus RBV. They found 37% SVR in 32 patients retreated with peginterferon alfa-2a (40KD) plus ribavirin. An even better SVR was observed in 31 patients who also received amantadine at a rate of 200 mg/day (45%).

Truly chronic hepatitis C patients who are nonresponders to conventional IFN plus ribavirin represents one of the most difficult challenges in clinical routine. Shiffman et al. [10] reported the first analysis from the HALT-C trial, designed to look at the histological end points in patients without virological responses. They examined only nonresponder patients with advanced fibrosis or cirrhosis (F3/F4) who received a full 48-week course of peginterferon alfa-2a (40KD) plus ribavirin. Overall, they found an SVR of 18% (N = 604). In the nonresponders in the conventional IFN plus ribavirin group, the SVR was 12%. The non-1 genotype patients had responses of at least 54%.

We found that nonresponders to at least 24 weeks of conventional IFN and ribavirin combination therapy achieved 26% of SVR when retreated with peginterferon alfa-2a (40KD) plus ribavirin for 48 weeks. This result is higher than previously reported results. On the other hand, our results on relapsers (SVR of 51%) are quite similar to what was reported by Herrine et al. [9] (37 to 45%). Probably, the more advanced histological disease observed among HALT-C patients contributed to lowering the rates of SVR observed by Shiffman et al. [10]. However, one has to consider that the conventional interferon normally used in the Brazilian public health services comes from various countries, with no prospective and controlled evaluation of virological responses. Observational studies have suggested that virological responses could be inferior to those obtained in the registration trials reported by some investigators [11,12]. This should bring the issue that Brazilian nonresponders may be an easier group to be retreated compared to non Brazilian patients, since there is a lack of quality assurance in the first antiviral therapy in Brazil.

A genotype subanalysis of our studied population showed that 17% and 44% of genotype 1 nonresponders and relapser patients, respectively, achieved a SVR. Among the non-1 genotype nonresponders and relapsers, 46% and 70% of patients achieved a SVR, respectively. The response rate in our non-1 genotype relapsers group was close to what was reported for naive patients submitted to the same therapeutic regimen (84%) [7].

We also found significantly higher response rates in nonresponder patients without cirrhosis compared to cirrhotic patients (33% *versus* 11.%). This difference was not observed in relapsers (48% *versus* 50%), in whom histological diagnosis seemed not to influence treatment outcome. Furthermore, only 7% of genotype 1 nonresponder patients with cirrhosis achieved SVR, as compared to 50% of relapser patients with the same characteristics. Therefore, non-1 genotype infection, along with a relapser state and good adherence, were the best independent predictive factors to achieve an SVR in our study. Pretreatment serum HCV RNA levels were not available for every patient. We observed a higher rate of SVR (71%) in relapser patients with low baseline serum HCV RNA levels, when compared to patients with high baseline serum HCV RNA levels (37%), although there were few patients with such characteristics in our study. Indeed, this group of patients had a better chance to respond to their first course of antiviral therapy. Surprisingly, in the group of nonresponder patients, baseline viral load did not influence the outcome and SVR rates were identical in low and high baseline serum HCV RNA (21%) patients. Sample size error must be considered as an explanation for these unexpected results.

It is very important to consider that patients in our study took a low dose of ribavirin (800 mg/day). It is becoming clearer that SVRs are better when there is a full exposure to ribavirin, which is particularly important in difficult to treat genotype 1 patients at the beginning of therapy [13]. We believe that if we had used a higher dose of ribavirin we could have achieved a better sustained virological response.

Overall, peginterferon alfa-2a (40KD) plus ribavirin as retreatment for 48 weeks showed the safety and tolerability profile seen in naive patients. The rate of discontinuation linked to side effects was 4% in our study, which compares favorably to 12% observed in a peginterferon alfa-2a (40KD) plus ribavirin registration trial made with naive patients [7]. Dose reduction rates for adverse events or laboratory abnormalities were also similar to what was observed in a naive patients registration trial (45% *versus* 62%).

In summary, we suggest that Brazilian hepatitis C patients who are nonresponders and relapsers to conventional IFN plus ribavirin can be successfully retreated with peginterferon alfa-2a (40KD) plus ribavirin combination therapy. The safety profile is acceptable, and non-1genotype, relapser state and good adherence are important predictive variables for a SVR.

Abbreviation Notes

ALT = alanine aminotransferase. ETVR = end of therapy virological response. HCV = hepatitis C virus. IFN = interferon. MU = million units. SVR = sustained virological response. TIW = three times weekly. WHO = World Health Organization; RT-PCR = reverse transcription-polymerase-chain reaction assay. Brazilian Pegasys Cooperative Study Group: Oliveira A; Chebli J; Villanova M; Lima L; Borges S; Teixeira R; Gomes A; Silva R; Pereira L.

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