Response to Treatment with Interferon-alpha and Ribavirin in Patients with Chronic Hepatitis C Virus Genotypes 2 and 3 Depends on the Degree of Hepatic Fibrosis

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The combined therapy with interferon alfa plus ribavirin (INF+RBV) is considered the most appropriate treatment for patients with chronic hepatitis C virus genotypes 2 and 3 in Brazil. However, wide variations in the rates of sustained viral response (SVR) have been reported among such patients. We evaluated, retrospectively, factors associated with SVR in subjects with chronic hepatitis C virus genotypes 2 and 3 and that received medication from the Health Secretariat of the state of São Paulo. One-hundred-seventy-seven consecutive patients with chronic hepatitis C were treated for 24 or 48 weeks according to the viral genotype. Patients co-infected with associated hepatic diseases or who had problems with alcohol abuse were excluded. The genotype of the HCV-RNA was identified through restriction analysis, the viral load through quantitative PCR (Amplicor, Roche) and the degree of hepatic fibrosis according to the Metavir score. Demographic, virological and histological parameters were submitted to binary logistic regression analysis to identify the variables associated with SVR. The overall rate of SVR was 36.4% for the 177 patients, and genotype 2 or 3 was the main parameter independently associated with SVR. Among the 77 patients with these viral genotypes, only the stage of fibrosis had a significant effect on the SVR (odds ratio (OR) = 3.035; 95% CI (confidence interval) = 1.196-7.699; p=0.019). The rate of SVR among the subjects with fibrosis at an advanced stage (F3-F4) was 38%, compared to 75% for patients with fibrosis at an initial stage (F0-F2). Consequently, other therapeutic options should be considered for patients with genotypes 2 and 3 who have advanced fibrosis.

Key Words: Interferon alpha, ribavirin, treatment of chronic C hepatitis, genotype 2 and 3, hepatic fibrosis.

Combined treatment with interferon alfa (INF-α) plus ribavirin (RBV) has revolutionized the therapy of chronic hepatitis caused by the hepatitis C virus (HCV) [1-2]. However, with the introduction of pegylated INF, which has greater therapeutic efficacy, is easier to use, and has a lower incidence of side effects [3-5], the combined treatment of pegylated INF plus RBV has become the chosen therapy for infected subjects in several developed countries [6,7]. Unfortunately, the high cost of this medicine has limited its use in replacing conventional INF-α. In some countries, such as Brazil, the option has been to limit the use of this medicine to naive subjects with genotype 1 chronic C hepatitis. This option is due to the significantly higher rates (60% to 70%) of sustained virological response (SVR) that can be obtained with the use of INFa in carriers of genotypes 2 and 3 [1,2].

Various retrospective analyses conducted in Brazil have shown contrasting results for the SVR rates found in carriers of HCV genotypes 2 and 3 who have chronic hepatitis and are treated with combined INF-α+RBV [8,9]. On the other hand, studies on the retreatment of such non-responder and relapser patients reported high levels of SVR when pegylated INF-α+RBV was used [10].

We conducted a retrospective analysis of the factors associated with SVR in subjects with genotypes 2 and 3 who had chronic C hepatitis and had been treated with conventional therapy (INF-α+RBV).

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Material and Methods

We included consecutive adult patients with chronic hepatitis C virus, with detectable HCV-RNA in the peripheral blood detected by PCR, who received a combined therapy of INF-α+RBV, which was provided by the Health Secretariat of the state of São Paulo from July of 1999 to December 2003. Subjects were treated for 24 to 48 weeks, according to a protocol defined by the Secretariat and international guidelines [1,2]. Patients with other associated hepatic diseases, co-infected with HBsAg, HIV, active alcohol drinkers during the previous six months, or with contraindications to the use of INF and/or RBV were excluded from our study.

Aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) serum concentrations were determined through the automatic kinetic method. The genotype of the HCV-RNA was identified through restriction analysis of the amplified sequences of the non-coding 5' region. The viral load was determined with the quantitative PCR method (Cobas Amplicor, Roche Diagnostics).

The stage of the hepatic lesion was determined by evaluating fragments from percutaneous hepatic biopsies stained with hematoxylin and eosin (HE), reticulin and Masson's trichrome, and by applying the Metavir criteria (11), where F0 = absence of fibrosis, F1 = fibrous portal expansion, F2 = portal fibrosis with incomplete septa, F3 = bridging fibrosis, and F4 = cirrhosis.

Intention-to-treat analysis was used, and the response to the treatment was evaluated; this was determined by a sustained virological response (SVR), indicated by undetectable levels of HCV-RNA in the peripheral blood 24 weeks after ending the treatment. The data obtained was presented as a percentage or as a mean ± standard deviation. Statistical analysis was conducted by binary logistic regression to identify the independent variables associated with response to treatment, which was considered as a dependent variable. The variables were categorized according to previously-established criteria [1,2], which were: age (< or ≥ 40 years), gender (male or female); genotype (1a/1b x 2,3), viral load (< or ≥ 850,000 IU), and stage (F0-F2 x F3-F4).

The level of significance was set at <0.05 (5%) for all statistical analyses [12].

Results

One-hundred-seventeen subjects were evaluated in our study. The demographic, virological, biochemical and histopathological characteristics are shown in Table 1. Of the 117 patients, 19 showed clinical, ultrasonography and endoscopy signs compatible with hepatic cirrhosis; because of alterations in their blood clotting ability, no biopsies were performed. Most of the subjects had viral genotypes 1a or 1b, were males, with elevated hepatic enzymes, had a viral load below 850,000 IU/mL and showed fibrosis at an advanced stage on hepatic biopsy.

Overall, 36.4% of the subjects showed SVR to the treatment with INF-α+RBV. The parameters that were independently associated with the response to treatment were genotypes 2 and 3 and a low stage of fibrosis, F0-F2 (Table 2).

The factors involved in the SVR of the subjects with genotypes 2 and 3 were evaluated. Only the stage of fibrosis appeared to significantly influence SVR (Table 3). The rates of SVR were 75.7% for subjects with fibrosis at the initial stage (F0 to F2), and 38.6% for those with bridging fibrosis or cirrhosis (Figure 1).

The rate of discontinuation of treatment due to side effects did not differ between genotype 2 and 3 patients with advanced fibrosis compared to those with initial staging (16% x 9%, p=0.574)

Discussion

Treatment of chronic hepatitis C virus with pegylated INF-α, combined with RBV, which has greater therapeutic efficacy

Table 1. Demographic, biochemical, virological and histopathological characteristics of the subjects with chronic hepatitis C virus

Characteristics	N=177
Age (years)	48.1 ± 11.9
Male gender	69.9% (121:52)
ALT (x ULN)	3.61 ± 6.89
Genotype 1a/1b	56.5% (100: 77)
Viral load < 850,000 IU/mL	60.0% (106:71)
Structural F3, F4	59.3% (105:72)

ULN = upper limit of normality; IU = international units; ALT = alanine aminotransferase.

Table 2. Logistic regression analysis of the demographic, virological and histopathological parameters in subjects with chronic hepatitis C virus submitted to treatment with interferon alfa plus ribavirin

Parameter	RR	95% CI	P
Structural (F0-F2 x F3,F4)	4.536	2.194-9.380	<0.001
Genotype (2,3 x 1)	5.575	2.680-11.598	<0.001

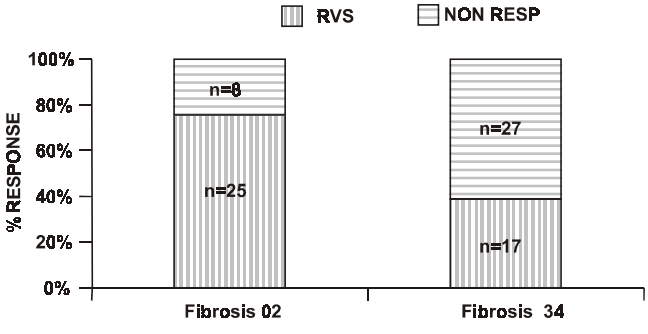
Age, gender, genotype, viral load, and stage (fibrosis) parameters were included in the regression analyses. RR = relative risk

Table 3. Logistic regression analysis of data on patients with chronic hepatitis C virus genotypes 2 and 3 (n= 77), evaluating the parameters associated with a sustained viral response in patients treated with interferon alfa plus ribavirin.

Parameter	RR	95%CI	P
Age (< or ≥ 40 years)	1.017	0.974-1.062	0.440
Gender (male:female)	0.916	0.640-5.865	0.242
Viral load (< or ≥850,000 IU/mL)	0.972	0.669-4.891	0.243
Structural (F0-F2 x F3, F4)	3.297	1.317-8.256	0.011*

CI = confidence interval. * = significant.

Figure 1. Virological response to treatment with interferon alpha and ribavirin in patients with chronic hepatitis C, genotypes 2 and 3, according to the fibrosis staging. RVS: sustained virological response. NON RESP: non responders.



than unpegylated INF-α, is easier to use, and has a lower incidence of side effects [3-5] has become the chosen therapy for subjects infected with this virus in several developed countries [5-6]. On the other hand, conventional INF-α is an economically viable alternative for developing countries with significant portions of their populations infected with this virus. However, the cost-benefit analysis needs to be considered, especially in the case of patients that do not respond to an initial treatment, who could require a second or third treatment, or where the disease could progress to a more advanced forms, which would increase the overall cost of treatment. Therefore, it is necessary that the treatment cost take into account the optimization of results, especially in Brazil, where the medicines provided by the Heath Secretariat vary in potency, depending on their commercial origin.

Even in the classic studies on the use of INF-α+RBV, traits such as age and gender of the subject, the viral load, the HCV-RNA genotype, and the stage of fibrosis observed through hepatic biopsy [1,2,13], were known to be predictive factors for the response of patients to treatment. Based on the evaluation of the 117 cases, only the genotype and structural alteration (stage of the fibrosis) were found to be independent factors associated with response to treatment. These results are similar to those found by Pariente et al. [13], who made a similar study. Thus, we conclude that clinical and virological factors associated with the response to the combined treatment have different influences. In the 'a la Carte' treatment proposed by Poynard et al. [14], the same importance is given for all five predictive variables associated with SVR (age, gender, viral load, genotype and stage of structural lesion). These factors are known to have different impacts, with genotype being the most important factor in all casuistic studies and the one that shows the highest odds ratios, even in studies with pegylated INF [1-5,13-15]. The larger the group analyzed, the greater the chance of identifying other factors that have a small impact.

The analysis of subjects with genotypes 2 and 3 who had chronic C hepatitis showed that the only factor that could be associated with SVR was the stage of fibrosis observed in the hepatic biopsy. This result was expected since the regression analysis of the 177 patients identified this structural alterations as an response factor independent from the genotype.

The importance of the stage of fibrosis in SVR to treatment with INF-α+RBV has been documented in many studies [13,14,16,17]. Several factors could be associated with the low response observed in subjects who have advanced stage fibrosis. These could include a greater prevalence of side effects and the need to reduce the dosage of medications; even viral kinetics appears to be different in patients with more advanced fibrosis [16,18].

In addition, our study allowed some insight on the discrepancies found in the success of treatment of patients with genotypes 2 and 3 in Brazil, who have a widely ranging rate of SVR (between 20 and 80%) [8,9]. These discrepancies may be a function of the spectrum of the case study. Medical groups working in hepatitis C reference centers primarily attend patients with initial stages of the disease, who will attain more favorable results, when compared to a Liver Unit, which has the tendency to work with the disease at more advanced stage [19,20].

The SVR values of around 40% found in our study are close to those reported in 2003 at the European Congress of Hepatic Diseases (EASL). An evaluation of the therapeutic response to the treatment with pegylated INF-α+RBV was conducted in subjects with fibrosis at an advanced stage, in a multicenter study. A group treated with INF+RBV during 48 weeks was the control. The authors found SVR in 45% of the subjects in the control group and in 75% of the patients treated with pegylated INF-α, independent of the dosage of RBV and the period of treatment [21]. These data suggest that the use of pegylated INF-α doubles the therapeutic response in these subjects.

These results raise a serious question about the decision to generalize a treatment based only on the viral genotype, without considering the individual differences of subjects. Even though the number of patients in our study was small when compared to international studies, an important variance in response was caused by differences in the hepatic staging of the disease, indicating that this factor is an important variable.

Therefore, our data indicate that in Brazil, subjects with chronic hepatitis due to HCV genotypes 2 or 3 and who have a low degree of fibrosis are ideal candidates for treatment with INF-α+RBV. On the other hand, patients with advanced stage fibrosis had low rates of response to this combined therapy, and a criterion of treatment with pegylated interferon as a first alternative should be considered.

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