Results of the treatment of chronic hepatitis C genotype 4. A comparative analysis with genotype 1


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ABSTRACT

Introduction: nearly all the data on the efficacy of combined antiviral therapy on chronic hepatitis C genotype 4 have been obtained in countries of the Middle East. Genotype 4 is quite unusual in Spain. We report our experience in a group of Spanish patients treated with homogeneous criteria.

Patients and methods: between 2001 and 2007 we have treated 30 patients with chronic hepatitis C genotype 4 (20 males) with pegylated interferon α-2b (26 cases) or α-2a (4 cases) combined with ribavirin at a weight-adjusted dose. Results of therapy are known in all patients and liver biopsy is available in 24 cases.

Results: ten patients (33.3%) obtained sustained viral response (SVR: HCV-RNA undetectable in blood 6 months after the end of therapy), 12 were primary non-responders, 4 relapsed after reaching undetectable HCV-RNA at the end of therapy and 4 interrupted the treatment due to severe adverse events. These results are very close to those obtained in 355 patients infected with HCV genotype 1.

Conclusion: HCV genotype 4 should be considered as “difficult to treat”. The better results of therapy in other geographical areas (Middle East) may be due to a different distribution of the subtypes of HCV genotype 4.

Key words: Chronic hepatitis C. Hepatitis C virus genotype 4. Pegylated interferon. Ribavirin.
genotype is the most important predictive factor for sustained viral response (SVR) in patients treated with pegylated interferon and ribavirin. Current clinical guidelines recommend grouping genotypes 2 and 3 in one treatment group, and genotypes 1 and 4 in another treatment group when seeking optimal therapy duration: 24 weeks for the first group and 48 weeks for the second group (1-3).

The geographical distribution of the various genotypes is not uniform. The 1a genotype is more frequent in the United States and in Northern Europe. The 1b genotype has a worldwide distribution, and is the most frequent type overall as well as in Spain, where it is responsible for 60-70% of all cases of chronic hepatitis C. Genotype 4 is more frequent in Central Africa and Egypt. The prevalence of this genotype has, however, increased in Europe due to recent immigration trends, and to increasing intravenous use of illicit psychotropic substances (1). This variation in the distribution of HCV genotypes implies that, in Spain, there is a high rate of patients infected by genotype 1, while the number of patients infected with genotype 4 is much lower, which can explain the paucity of studies addressing the issue of therapy in patients infected with genotype 4. The recommended dosage and treatment duration are the same for genotypes 1 and 4 (3). Recently Trapero-Marugán et al. (5) have reported their experience in the treatment of patients infected with HCV genotype 4. Their series included 29 patients conventionally treated with interferon or pegylated interferon, combined in both cases with ribavirin. We report here our experience with a group of patients all of whom were treated with pegylated interferon and ribavirin.

PATIENT AND METHODS

For more than 15 years the Liver Unit of the Gastroenterology Department in our center has been treating patients with chronic hepatitis C. Since 2001 antiviral combination therapy with pegylated interferon (Peg-IFN) plus ribavirin has been used in accordance with recommendations by internationally accepted protocols and under standard clinical practice conditions. We have developed a highly homogeneous database that currently includes 496 patients with chronic hepatitis C who have been treated with Peg-IFN, and for whom there are definitive results regarding effectiveness and tolerance. For the present analysis we have selected the patients infected with viral genotype 4, and have performed the pertinent comparisons with the group of individuals infected with genotype 1 who received the same treatment.

Clinical, biochemical, virological, and histological variables were analyzed in relation to therapy outcomes. These data had been systematically and prospectively recorded in our database as part of our standard practice.

The diagnosis of chronic hepatitis C was based on clinical assessment and the results of biochemical and virological measurements. All patients were positive for anti-HCV, and HCV-RNA was detectable in blood samples of all individuals at therapy onset. Standard serological measurements were used to exclude individuals with active infection with hepatitis B or human immunodeficiency virus.

A quantitative analysis of HCV-RNA was performed with the Cobas Amplicor HCV Monitor® version 2.0 (Roche Molecular Diagnostic). The detection range was 600 IU/mL to 8.5 x 10⁵ IU/mL. Starting from July 2005, viral RNA was extracted automatically using Cobas AmpliPrep, and viral load was detected by real-time polymerase chain reaction (PCR) using Cobas TaqMan® (Roche Diagnostics), which has a detection range of 10 IU/mL to 2 x 10⁸ IU/mL (6).

HCV genotypes were determined by a reverse hybridization assay (INNO-LiPA®; Innogenetics). Genotypes are assigned on the basis of sequence variations in the 5’ untranslated region of HCV following gene amplification using reverse-transcription polymerase chain reaction (RT-PCR).

The treatment of chronic HCV infection was with alpha 2a (40 kD) pegylated interferon at a fixed dose of 180 µg/week, or alpha 2b (12 kD) pegylated interferon at a dose of 1.5 µg/kg/week, combined in both cases with ribavirin at a dose of 1.5 mg/kg/day.

Sustained virological response (SVR) was defined as the absence of detectable RNA-HCV in the serum after six months of treatment. HCV infection relapse was defined as an undetectable viral load at or before week 24 of treatment, which was detected again at six months following therapy completion. Primary failure was defined as the persistence of detectable HCV-RNA at any time during follow-up, and definitely when present at week 24 of treatment. Premature discontinuations or withdrawals because of patient intolerance or unacceptable adverse events during follow-up were recorded.

Statistical analyses

Continuous variables were compared using Student’s t-test, or a Mann-Whitney U-test, as indicated. Dichotomous variables were compared using the χ² test by Mantel-Haenszel or Fisher’s exact test, depending on sample size. Values are expressed and mean ± standard deviation (SD) values or as percentages. All tests of significance were two-tailed. All statistical analyses were performed using the SPSS statistical software package for Windows (version 14.0; SPSS), and Epi-Info® 2002 (Center for Disease Control and Prevention). The null hypothesis was rejected when p-value was < 0.05.
RESULTS

Analysis of patients with genotype 4

There were 30 patients (6.1% of the total sample) infected with genotype 4. The results of treatment are presented in Table I. Pegylated interferon α-2b was administered to 26 patients, and 4 received pegylated interferon α-2a. IFN doses had to be reduced at week 12 for one patient who finally exhibited primary viral failure. The dose of ribavirin had to be lowered in three cases; two achieved SVR (reduction in weeks 20 and 29), and one suffered a secondary relapse (reduction at week 32). The only significant difference in baseline data between patients with SVR and those with primary viral failure were age (36 ± 6.1 vs. 42.2 ± 6.2 years; p = 0.02) and γGT (53 ± 72 vs. 142 ± 115 IU; p = 0.004). Due to small sample size no comparisons were made between those with secondary relapse and those with intolerance.

Comparisons between viral genotypes 4 and 1

There were 355 patients (71.9% of the total) infected with genotype 1. Table I summarizes response to therapy in both groups. There were no statistically significant differences in the frequencies of various response categories.

Table II summarizes the baseline characteristics of both groups. In the group of patients with genotype 4 there was a significant excess of cases secondary to intravenous drug abuse. In the group of patients with genotype 1 age at therapy onset was significantly higher, as were viral load and serum bilirubin. In cases with previous liver biopsy necro-inflammation extent and fibrosis stage, according to Knodell index (7), were significantly higher in the group of patients with genotype 1 infection.

DISCUSSION

Our results indicate that chronic infection by HCV genotype 4 is as refractory to treatment as that induced by HCV genotype 1. There was a very similar rate of sustained viral response in both genotypes (33-35%), despite the higher frequency of factors known to predict a favorable response among genotype 4 patients, i.e., younger age, lower viral load, and less fibrosis in hepatic biopsy samples. Therefore, we must consider that genotype 4 is intrinsically difficult to treat.

Our results are in contrast to those reported in a meta-analysis that included six studies (8) containing 219 patients treated with pegylated interferon plus ribavirin, in which an overall SVR of 55% was reached. The patients who received the recommended dose of ribavirin (1,000-1,200 mg/day) achieved better outcomes. These data are similar to those obtained by Kamal et al. (9) in a study conducted in Egypt. Of the 96 patients treated over 48 weeks with PEG-IFN α-2b and ribavirin at the recommended doses (1-3), 69% achieved SVR. Similar results (66% SVR) were reported in the same study in patients treated over 36 weeks. Equally favorable results were those obtained by Hasan et al. (10), in which 68% of the 66 patients similarly treated achieved SVR. Conversely, three studies conducted in populations of Saudi Arabia (11), Egypt (12), and France (13), with sample sizes similar to that in our study, reported rates of SVR of 43, 32, and 33%, respectively. Trapeño-Marugán et al. (5), in the only previous study conducted in a Spanish population that
could be identified in the literature, reported results in a group of 19 patients treated with recombinant interferon and compared them with a group of 10 patients who received pegylated interferon; overall SVR rate was 55%.

The variations in response observed in these reports could be explained, partly, by the heterogeneity of HCV genotype 4. Several variants have been recognized recently (4) but, at present, their relative importance is unknown. Genotype 4a is prominent in Egypt whereas in France it shares its distribution density with 4d genotype; in sub-Saharan populations there is a wide range of subtypes. These differences have been highlighted recently in a study (14) conducted in 242 patients, which showed that response to therapy was clearly better in patients of Egyptian origin (54.9% SVR) when compared to those who acquired the infection in France (40.3%) or in sub-Saharan Africa (32.4%), albeit the stage of fibrosis in liver biopsy material was significantly lower in the latter population. As such, it is probable that the genetic variability in genotype 4 significantly influences response to treatment.

In conclusion, our data suggest that response to treatment in our Spanish patients infected with HCV genotype 4 is at least as poor as that of patients infected with genotype 1. Given the low prevalence of genotype 4 in our geographic environment, it would be advisable to conduct a multicentered study to evaluate this issue more systematically. A supplementary aim would be to develop appropriate techniques to identify HCV genotype 4 subtypes to be implemented in our hospitals –or in a reference laboratory.

REFERENCES

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