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Five-year follow-up of patients with chronic C hepatitis and sustained virological response

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ABSTRACT

Objective: to assess persistence of sustained viral response at 5 years of follow-up in patients with chronic viral hepatitis C treated with pegylated interferon and ribavirin.

Design: a descriptive study.

Patients: from August 2001 to May 2004, all patients treated at our center with pegylated interferon and ribavirin who achieved a sustained viral response were consecutively enrolled (93 patients). Demographic, histological, biochemical, and virological data were collected during treatment and 5 years after achievement of the sustained viral response. Eighty-six percent of patients enrolled (n = 80) attended the control visit at 5 years.

Results: mean age of enrolled patients was 41 years (standard deviation = 10 years), and 30.1% (n = 28) were women. Liver biopsy had been performed before treatment in 68.8% of patients (n = 64), showing no or mild fibrosis in 62.3% (F0 and F1) and significant fibrosis and cirrhosis in 37.7% (F ≥ 3). Genotype distribution was: 58.1% genotype 1 (n = 54); 8.6% genotype 2 (n = 8); 24.7% genotype 3 (n = 23); 7.5% genotype 4 (n = 7), and indeterminate in one patient. Only one patient experienced virological recurrence. All other patients had negative HCV RNA levels and, in the absence of other liver diseases, normal ALT levels.

Conclusion: in patients treated with pegylated interferon and ribavirin with sustained viral response, long-term recurrence rate was very low.

Key words: Chronic C hepatitis. Pegylated interferon alfa-2a. Pegylated interferon alfa-2b. Ribavirin.

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INTRODUCTION

Chronic viral hepatitis C is a health problem worldwide. It is estimated that 170 million people are currently infected. Hepatitis C prevalence in our environment is approximately 1.6%-2.6% of the population, which means that from 480,000 to 760,000 people may be infected in Spain (1). Hepatitis C is currently the most common cause of liver cirrhosis, hepatocarcinoma, and liver transplant (2).

The only treatment shown to date to be clearly effective for attenuating or reversing hepatic fibrosis is elimination of the causative agent (3). Treatment available for curing infection consists of the combination of pegylated interferon (Peg-IFN) and ribavirin (RBV), given for a period ranging from 24-72 weeks. Treatment is considered to be successful if sustained virological response (SVR) is achieved. SVR is defined as a negative HCV RNA test six months after treatment completion (4,5). These patients do not only have a decreased risk of fibrosis progression, incidence of cirrhosis, and hepatocellular carcinoma (6,7), but may also show histological improvement with decreased inflammation, stabilization, and even improvement in the degree of fibrosis in the long term (8-10). The SVR rates reported range from 54%-56% in the different clinical trials (11-13), and these results may be reproduced in our environment in standard clinical practice (14).

However, few data are available in the literature about long-term follow-up after SVR is achieved, although the number of reports has increased in recent years (Table I). Sustained virological response is maintained at 5 years in 95% (4,15) and 98%-100% (10,16) of patients treated with IFN monotherapy and IFN+RBV respectively. In patients treated with Peg-IFN+RBV, SVR was maintained at 4 years in 99%-100% of cases (17-19). While these studies found highly favorable results, there are other studies including non-naïve patients or using non-conventional

Table I. Studies reporting long-term virological recurrence rates in patients with SVR

Author	*Patients and pretreatment status*	*Treatment (n)*	*Follow-up time*	*Virological recurrence rate*
Cammà C et al (4)	453 naïve patients (meta-analysis of 14 prospective studies)	IFN	>18 months (range 18-93)	8.7%
Ciancio et al (20)	97 non-responders	IFN (3MU/3weeks)+RBV (1,000mg/day), 12 months (21)	7,17 years (mean)	0%
		IFN (5MU/3weeks)+RBV (1,000mg/day), 12 months (37)		13.5%
		IFN (3MU/3weeks)+RBV (1,000mg/day), 6 months (15)		20%
		IFN (5MU/3weeks)+RBV (1,000mg/day), 6 months (24)		12.5%
Desmond et al (33)	147 naïve patients	IFN (34)	2.3 years (mean)	3%
		IFN+RBV (76)		0%
		Peg-IBF+RBV (37)		0%
Formann et al (34)	187 patients (PSNR)	IFN (12)	1.83 years (mean)	0%
		IFN+RBV (73)		
		Peg-INF+RBV (102)		
Fontaine et al (35)	34 naïve patients 7 patients with relapse 3 non-responders	IFN+RBV	1.72 years (mean)	2.3%
George et al (10)	150 patients (PSNR)	IFN+RBV (146)	5 years	0%
		IFN-peg+RBV (4)		
Giannini et al (17)	171 naïve patients 60 non-naïve patients	Peg-INF+RBV (231)	3.15 years (mean)	1%
Kelly et al (16)	42 pediatric patients	IFN+RBV	5 years	2%
Khokhar et al (36)	57 patients (PSNR)	IFN+RBV	1.97 years (mean)	8.77%
Manns et al (37)	366 patients (PSNR)	Peg-INF±RBV	4.8 years (mean)	1%
Maylin et al (19)	94 naïve patients 26 non-responders 37 patients with relapse	IFN (12) IFN+RBV (24) Peg-INF+RBV (121)	4 years (mean)	0%
McHutchison et al (38)	302 patients (PSNR)	IFN±RBV	5 years	0±1%
Moreno et al (39)	132 patients (PSNR)	IFN/Peg-INF±RBV	>1 year	0%
Ponsoda et al (40)	125 (PSNR)	IFN±RBV	1.7 years	0%
Soriano et al (41)	77 HIV+patients	IFN (22)	4.8 years (mean)	0%
		IFN+RBV (17)		
		Peg-INF+RBV (38)		
Swain et al (18)	400 patients (PSNR)	Peg-INF (160)	4 years	0.8%
		Peg-INF+RBV (240)		
Veldt et al (15)	286 naïve patients	IFN	5 years	4.7%

PSNR: pretreatment status not reported.
Virological recurrence rate: HCV RNA detection in patients with SVR

HCV RNA detection methods which reported higher rates of late virological recurrence (20-21). However, there are no studies assessing the virological recurrence rate after SVR.

In this article, the terms proposed by Sánchez-Tapias (22) have been used for adequate interpretation of results. *Recurrence* refers to detection of HCV RNA in serum, using a commercially available method, in a patient who has achieved SVR. The term *relapse* is commonly used to refer to detection of HCV RNA within 6 months of treatment completion. *Recurrence* and *late relapse* are therefore used with the same meaning. However, unlike *late relapse*, *recurrence* does not necessarily imply that the original virus recurs, but could also be due to reinfection or to a false negative result at the time SVR was considered.

Our study was intended to analyze persistence of SVR in patients treated with Peg-IFN and RBV at least five years after the end of treatment.

METHODS

Patients

Study inclusion criteria

All patients infected with hepatitis C virus treated with Peg-IFN and RBV between August 2001 and May 2004 and who had achieved SVR were enrolled into the study.

Treatment regimens

Patients were treated according to the treatment regimens recommended in clinical practice guidelines (23). Patients with genotype 1 or 4 were treated with Peg-IFN alfa 2a (180 mcg/week) or Peg-IFN alfa 2b (1,5 mcg/kg/week) and RBV (based on weight) for 48 weeks. Patients with genotypes 2 and 3 were treated for 24 weeks with the same dosage of Peg-IFN alfa 2a or alfa 2b, but with RBV 800 mg/day in two divided doses. The type of Peg-IFN used for each patient was decided by the treating physician.

Follow-up after treatment

At our center, patients who achieve SVR after treatment and show mild fibrosis (F0 and F1) at biopsy or have no evidence of advanced fibrosis based on non-invasive criteria (24,25) are referred to the family physician for continued follow-up using an agreed protocol. Laboratory tests, including liver function tests (AST/ALT, AP/GGT, and bilirubin), are done annually for 5 years. Five years after SVR, patients are referred again to our hepatology outpatient clinic for a new measurement of HCV RNA. If the family physician detects any change in liver biology during follow-up, patients are again referred to the hepatology outpatient clinic for assessment of the reason for the change. Patients with advanced fibrosis at biopsy or based on non-invasive criteria are followed up at the hepatology outpatient clinic. At 5 years, patients not referred are appointed by post.

Data collection

Demographic characteristics, treatment administered, degree of fibrosis before treatment (according to Knodell index) (26), genotype, ALT levels, and viral load were recorded at the start and end of treatment. At the 5-year visit conducted by a specialist, the following laboratory parameters were tested: liver biology (ALT, AST, bilirubin, FA, GGT, albumin) and HCV RNA. If high transaminase levels were found, etiological laboratory tests (viral serology, autoantibodies, ceruloplasmin, alfa1-antitrypsin, TSH; iron metabolism) and an ultrasound examination were performed to look for the most common causes in our environment (27).

Detection of HCV RNA

Two methods were used in this study for assaying HCV RNA. In the first study phase, during patient treatment, RNA was measured using the Cobas Amplicor technique, with manual RNA extraction followed by amplification and detection in a Cobas Monitor analyzer (Roche Diagnostics) with a detection limit of <600 IU/mL.

In the second phase, in the 5-year follow-up, the Cobas Ampliprep/Cobas Taqman HCV (Roche Diagnostics) test was used. This is a real-time, *in vitro* nucleic acid amplification test for quantitative measurement of HCV RNA in plasma or serum (the Cobas Ampliprep system was used for automated sample processing, and a Cobas Taqman analyzer was used for subsequent automated RNA amplification and detection). The Cobas Ampliprep/Cobas Taqman assay allows for automated sample preparation (RNA isolation), followed by automated reverse transcription, PCR amplification, and RNA detection. The detection limit of the technique is 15 IU/mL.

Statistical analysis

Data were analyzed using SPSS 15.0 software. Continuous variables are given as mean (standard deviation, SD).

RESULTS

Characteristics of patients enrolled

From June 2007 to November 2009, a total of 93 patients who had achieved SVR after treatment with Peg-IFN and RBV at least 5 years before were enrolled into the study. Mean age of patients at treatment start was 41 years (SD = 10 years), and 30.1% were women.

Clinical and virological changes at 5 years

Of the 93 patients enrolled, 33 (41.25%) attended the control visit referred by their general practitioners. A patient died for reasons other than his liver disease. Forty-one (68.3%) of the 59 patients appointed attended the clinic after a first appointment, and 6 (31.6%) of the 18 patients not previously attending were seen after a second appointment. Finally, 80 patients were seen at 5 years (Figure 1).

Baseline ALT levels before the start of antiviral treatment were 114 IU/mL (SD = 67 IU/mL) (normal value

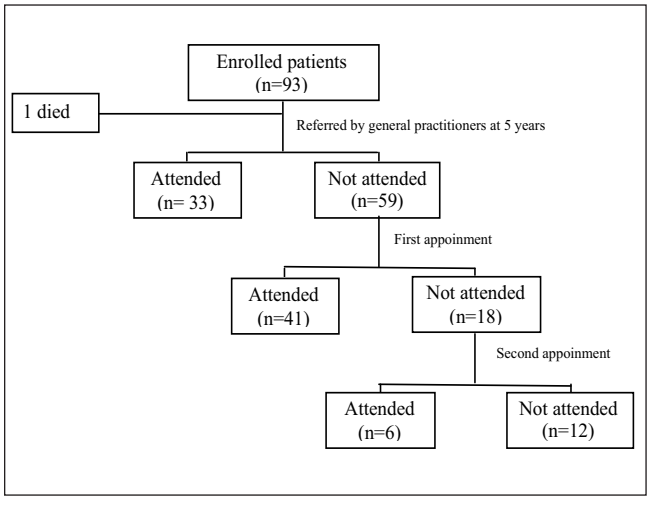

Fig. 1. Patient enrolment flowchart.

< 39 IU/mL). Baseline HCV RNA level was 465,497 IU/mL (SD = 272,070 IU/mL). Liver biopsy had been performed before treatment in 68.8% of patients (n = 64), showing no or mild fibrosis in 62.3% (F0 and F1) and significant fibrosis and cirrhosis in 37.7% (F≥3). Genotype distribution was: 58.1% genotype 1 (n = 54); 8.6% genotype 2 (n = 8); 24.7% genotype 3 (n = 23); 7.5% genotype 4 (n = 7), and indeterminate in one patient.

ALT levels at 5 years of achievement of SVR were 25 IU/mL (SD = 13 IU/mL). Seven patients (8.7%) had ALT levels higher than normal values (<39 IU/mL), with a mean of 55.2 IU/mL (SD = 9.56 IU/mL) (range, 43-68 IU/mL). Transaminase levels were normalized in repeated tests to perform etiological study. Of the remaining five patients, four had a body mass index greater than 25. Of these four patients, three had a negative etiological laboratory study and a liver ultrasound with signs of steatosis, and the fourth patient was lost to follow-up. A single patient (of the initial seven patients with high transaminase levels) had a detectable serum viral load. His genotype was determined and was found to be the same as the one he had before treatment was administered (RNA 8,314,619 IU/mL, genotype 1, ALT 42 IU/mL). Patients with advanced fibrosis or cirrhosis who had SVR seen at our unit showed no decompensation during the 5 years of follow-up.

DISCUSSION

This study showed that virtually all patients with a sustained virological response continued to have negative HCV RNA levels. Only one patient (1.25%) experienced virological recurrence after achievement of SVR.

As regards durability of SVR, currently available data show that this has a positive effect on patients who experience it. Thus, it has been shown that a proportion of patients with liver cirrhosis who achieve a SVR experience histological regression of cirrhosis (8-10,28). Liver disease was not decompensated in any cirrhotic patient in our study. However, an obvious limitation of our study was that no histological samples were collected from patients enrolled during the follow-up period after SVR.

A great source of controversy is whether SVR results in eradication of the virus and no subsequent virological controls are therefore required. The crucial issues in this regard are the methods for assaying HCV RNA and how is this measured (in liver tissue, peripheral mononuclear cells, or peripheral blood).

As regards sensitivity of the different techniques used for considering that SVR has been achieved, a system with a relatively high detection level (<600 IU/mL), and thus with a lower sensitivity, was initially used. In the subsequent 5-year control, a real-time PCR method with a higher sensitivity (<15 IU/mL) was used.

This suggests that the patient with virological recurrence did not possibly experienced a true late relapse induced by the same strain, but a false negative result was found when SVR was assessed (no detection of minimal residual viremia). On the other hand, a reinfection would be less likely because, although we had no serum library available to perform a phylogenetic study of both RNAs, the genotype was the same, clinical history was reviewed, and repeat patient questioning found no epidemiological data suggesting risk of reinfection.

With regard to the different RNA measurement techniques, other more sensitive methods have been reported. A study suggested that transcription-mediated amplification (TMA) was superior to PCR for detecting minimal residual viremia (29). Another group suggested that late virological recurrence could be predicted if sera were retested performing ultracentrifugation before PCR (21). In this study, prior sera with an undetectable viral load were obtained using conventional methods from 13 patients with virological recurrence after achievement of SVR, and ultracentrifugation was performed before PCR. HCV RNA levels were detected in 11 patients. This suggests that if a sufficiently sensitive technique is available, virological controls may be concluded once SVR is achieved.

As regards the way in which HCV RNA is measured, there are studies reporting detection of HCV RNA in mononuclear cells and liver tissue after SVR (8,9,30-32). Thus, Castillo et al. (31) studied 20 patients with SVR followed up for a mean of 47 months and detected HCV RNA in 19 patients and in peripheral mononuclear cells in 13 patients. No patient was found HCV RNA in plasma In this regard, some authors have suggested the concept of subclinical infection. This is defined as detection of HCV by any method in any tissue from patients considered to have a SVR based on the commercially available HCV RNA assays (22). However, its meaning is still uncertain, and clinical significance is still unknown.

On the other hand, most patients who had at 5 years persistently high transaminase levels with negative HCV

RNA were found criteria of hepatic steatosis after a comprehensive etiological study.

In conclusion, the study suggests that patients treated with Peg-IFN + RBV who have a SVR have a very low long-term recurrence rate.

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