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BRIEF ARTICLE

Long-term outcome of chronic hepatitis C patients with sustained virological response to peginterferon plus ribavirin

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Abstract

AIM: To assess the clinical, biochemical and virological long-term outcome in chronic hepatitis C (CHC) patients with a sustained virological response (SVR) after peginterferon (PEG-IFN) plus ribavirin combination therapy.

METHODS: One hundred and fifty three patients with a SVR after treatment with PEG-IFN plus ribavirin were included in a 5-year follow-up study in a single Spanish center, based on standard clinical practice. Clinical anamnesis, biochemical analysis, hepatitis C virus RNA and alpha-fetoprotein measurement, ultrasonography and transient elastography were performed annually.

RESULTS: The mean follow-up period of the 153 patients was 76 ± 13 mo after they obtained a SVR. Five patients (3.26%) presented with cirrhosis before treatment and 116 (75.8%) had genotype 1. No patient showed evidence of hepatic decompensation. One patient (0.65%) developed a hepatocellular carcinoma at month 30 after achieving SVR. There were no virological relapses during this follow-up period. Persistently elevated alanine aminotransferase was found in only one patient (0.65%). At the end of the 5-year follow-up, the mean value of transient elastography was 7 ± 4.3 kPa (F1). There were no deaths and no other tumors.

CONCLUSION: The long-term outcome of 153 CHC patients with SVR to PEG-IFN plus ribavirin was good. No evidence of a virological relapse was seen. One patient (0.65%) developed a hepatocellular carcinoma.

Key words: Chronic hepatitis C; Peginterferon; Ribavirin; Sustained virological response; Long-term effects

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INTRODUCTION

The combination of peginterferon (PEG-IFN) plus ribavirin is the current standard of care for naïve chronic hepatitis C (CHC) patients, achieving a high sustained virological

response (SVR) rate[1-4]. The long-term benefits of CHC combination therapy have been well established in several studies, but the results are limited by differing patient populations or treatment regimens and, importantly, a brief duration of follow-up[5]; in addition, occult hepatitis infection by hepatitis C virus (HCV) has been proposed[6]. The conclusions of long-term studies[7-14] may be compromised by the small number of patients, and most studies using IFN monotherapy or IFN combined with ribavirin, while only 4 studies used PEG-IFN plus ribavirin combination therapy[15-18].

We conducted an open-label cohort study in a single center in Spain from January 2000 to December 2009, and included patients with a SVR after antiviral combination therapy with PEG-IFN plus ribavirin achieved between 2000 and 2003, with a mean follow-up greater than 5 years. Our major aim was to assess the clinical, biochemical and virological outcomes, and the durability of the SVR.

MATERIALS AND METHODS

Study design

A total cohort of 303 CHC consecutive patients (18-65 years) treated with PEG-IFN plus ribavirin in 2000-2003 were included in this cohort study. All patients attended the Hepatology Unit, Hospital Universitario de La Princesa (a tertiary university care centre), CIBERehd, Madrid, Spain.

Patients

Eligible patients were those who achieved a SVR after PEG-IFN plus ribavirin for 24 or 48 wk (in genotypes 2/3 or genotypes 1/4, respectively), defined as negativization of HCV-RNA at the end of treatment and after 6 mo of follow-up. Criteria for exclusion were: alcohol or intravenous drug abuse; liver diseases not related to HCV infection (autoimmune, metabolic or toxicity by drugs); decompensated liver disease; coinfection with HBV or human immunodeficiency virus; and pregnancy.

All patients received the standard of care combination therapy: 60 (39%) patients had been treated with PEG-IFN α-2a (Pegasys, Roche) plus ribavirin (1-1.2 g/d) and 93 (61%) patients with PEG-IFN α-2b (Pegintron, Schering-Plough) plus ribavirin (1-1.2 g/d). Patients with genotypes 1 and 4 were treated for 48 wk and patients with genotypes 2 or 3 were treated for 24 wk[19].

Clinical, biochemical and virological evaluation

We obtained data on patients' sex and age, treatment, virological data (genotype, baseline HCV-RNA), biochemical data [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), α-fetoprotein (AFP)], and length of follow-up. Pre-treatment liver biopsy and transient elastography analysis during the follow-up was obtained in some patients taking into account that this study was performed as routine clinical practice.

Patients were evaluated as outpatients at sequential annual clinical visits (1, 2, 3, 4, 5 years after the completion of antiviral therapy and 6 mo of follow-up). Blood tests with hematological, biochemical and virological assays were performed at the basal visit and thereafter. Serum HCV-RNA levels (IU/mL) were determined with Cobas Amplicor Hepatitis C Monitor Test (v2.0 Roche Diagnostics) and reverse transcription-polymerase chain reaction (RT-PCR), with a limit of detection < 50-100 IU/mL. HCV genotyping was performed by a reverse-hybridization line probe assay (INNO-LiPA HCV; Innogenetics, Zwijndrecht, Belgium).

Liver decompensation or failure was defined if a patient showed any of these findings: bleeding varices, hepatic encephalopathy, jaundice, or ascites. Patients were classified pretreatment by liver biopsy, and the establishment of cirrhosis was done using the METAVIR score for fibrosis stage. In addition, transient elastography was performed during follow-up after achieving the SVR. Hepatocellular carcinoma (HCC) was diagnosed if 2 coincident imaging techniques [ultrasonography, computed tomography (CT) or magnetic resonance imaging] showed a focal lesion larger than 2 cm with arterial hypervascularization or if one imaging technique showed a focal lesion larger than 2 cm with arterial hypervascularization in the presence of an AFP level > 400 ng/mL.

Statistical analysis

Quantitative variables are expressed as mean ± SD. Qualitative variables are expressed as percentage with range. The Student *t*-test with Welch's and Fisher's correction, the chi-squared test, the Mann-Whitney *U* test and the Kruskal Wallis test were used for continuous or discrete variables as appropriate. Logistic regression was used to analyze if baseline factors could be associated with SVR. The Kaplan-Meier method was used to determine the rate of HCC occurrence. A value of $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS version 15.0.

RESULTS

Characteristics of patients

Among the 303 CHC patients, a total of 150 were excluded as they did not achieve a SVR. Those 153 patients with a SVR after treatment with PEG-IFN plus ribavirin (weight based) were included, with a mean age of 49 ± 9 years. There were 82 males (53.6%). Genotypes of HCV were distributed as follows: 116 genotype 1 (75.8%), one genotype 2 (0.6%), 32 genotype 3 (21%) and 4 patients with genotype 4 (2.6%). The baseline characteristics of patients with a SVR are shown in Table 1. One hundred and thirty patients (85%) were followed up for 5 or more after SVR. The median duration of follow-up was 76 ± 13 mo (range, 54-90) after the end of treatment, i.e., after achievement of a SVR was established.

Clinical outcomes

At the end of the follow-up, all patients were alive. Of 153 sustained responders, 5 patients had cirrhosis (F4) and 8 patients had F3 stage fibrosis before the start of the treatment, as determined by the METAVIR score. No

Table 1 Characteristics of 153 patients with a sustained virological response after peginterferon plus ribavirin combination treatment

	n (%)
Age (mean ± SD, yr)	47 ± 9
Sex	
Female	71 (46.4)
Male	82 (53.6)
Genotypes	
1	116 (75.8)
2	1 (0.6)
3	32 (21)
4	4 (2.6)
Stage of fibrosis (before therapy)	
F1-2	140 (91.6)
F3	8 (5.2)
F4	5 (3.2)
Fibrosis by FibroScan® (mean ± SD, kPa)	7 ± 4.3
Type of PEG-IFN	
α-2a	60 (39)
α-2b	93 (61)
Follow-up [range (mean ± SD), mo]	54-90 (76 ± 13)
Patients follow-up	
5 yr	130 (85)
4 yr	23 (15)

PEG-IFN: Peginterferon.

patient with a SVR developed signs of liver failure during the follow-up. These patients were hepatitis B surface antigen negative and HCV-RNA negative, and no other risk factors for liver disease were reported.

One patient, with cirrhosis on pre-treatment biopsy and genotype 1b, developed a HCC at 30 mo of follow-up. It was assessed by ultrasonography, AFP level and CT scan, was 3.5 cm in size and located sub-diaphragmatically at segment Ⅷ. The patient was still negative for serum HCV-RNA at the time of HCC diagnosis, and at last follow-up, HCV-RNA remained undetectable. The patient received an orthotropic liver transplant. Given that 5 patients had cirrhosis pre-treatment and one developed HCC, this represents a 20% risk of HCC after SVR in individuals with pre-treatment cirrhosis. The incidence of HCC in this cohort of 153 SVR patients after a mean of 76 ± 13 mo was 1/153 (0.65%).

Biochemical outcomes

All 153 SVR patients had at least 2 biochemical evaluations, and 123 (80.4%) had 5 or more years of laboratory data after achieving the SVR. There were significant reductions in ALT, AST, GGT and ALP levels between the samples collected pre-treatment and samples after the end of treatment, as shown in Table 2. However, there were no statistically significant differences ($P > 0.05$) between the first and last samples collected during the follow-up, in mean ALT (20 ± 9 IU/L), AST (20 ± 5 IU/L), AST/ALT ratio (1 ± 0.5), ALP (70 ± 19 IU/L), GGT (25 ± 20 IU/L), and AFP (3 ± 1 ng/mL) values.

Virological outcomes

Out of 153 patients, 138 (90.2%) had at least 4 serum HCV-RNA tests via RT-PCR. The mean number of samples tested per patient was 4 or 5 (range, 2-8). No patient had detectable HCV-RNA in serum *via* RT-PCR on any sample.

Table 2 Biochemical values pre-treatment and post-treatment (last sample of follow-up)

	Pre-treatment	Post-treatment	*P*
AST (IU/L)	73 ± 70	20 ± 5	< 0.001
ALT (IU/L)	138 ± 178	20 ± 9	< 0.001
ALP (IU/L)	70 ± 19	98 ± 55	< 0.001
GGT (IU/L)	51 ± 46	25 ± 20	< 0.001
AFP (ng/mL)	4.9 ± 4	3 ± 1	NS

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transpeptidase; AFP: α-fetoprotein; NS: Not significant.

Liver fibrosis analysis

Liver biopsy and transient elastography evaluation were obtained only in a limited number of patients. Fifty four patients (45%) had pre-treatment liver biopsies. Eighty of these (53%) had a Fibroscan® analysis at least once during the follow-up with a mean number of 4 (range, 2-8) explorations. Mean time between 2 Fibroscan® analyses was 4 ± 0.8 years. The technique was very well tolerated by all patients, without side effects. Results were obtained in all patients. The mean value of transient elastography after 4-5 years of follow-up was 7 ± 4.3 kPa. One patient (0.8%) had a decrease in fibrosis stage from liver biopsy F3 to F1 by transient elastography. No progression of fibrosis was seen in any patient.

DISCUSSION

We assessed the long-term clinical, biochemical and virological outcomes of 153 patients with CHC who achieved a SVR after PEG-IFN plus ribavirin combination therapy. This study showed that a SVR is associated with permanent undetectable HCV-RNA in serum during a long-term follow-up. Nevertheless, it is difficult to say whether the treatment *per se* is important or whether a SVR is important because no controls were included. A late relapse of at least 0.8% after 4-5 years of follow-up has been reported[7-11]; however, introduction of more sensitive PCR methods may contribute to reduce this late-relapse rate.

There are some studies of the long-term clinical outcome of CHC patients with a SVR[8,11-16,20-27] but the majority analyzed patients treated with recombinant IFN as monotherapy or in combination with ribavirin. At present, only 4 studies have enrolled patients treated with PEG-IFN plus ribavirin as shown in Table 3: in the study by Veldt *et al*[15], 83 patients were analyzed; Chavalitdhamrong *et al*[16] studied 78 patients; George *et al*[14] recently published the results of a long-term study of SVR patients including only 4 patients (3%) treated with PEG-IFN plus ribavirin; and Giannini *et al*[18] included 231 patients treated with PEG-IFN plus ribavirin, but only 33.3% were genotype 1.

Table 3 Comparative results of other studies analyzing long term outcomes in chronic hepatitis C patients who achieved a sustained virological response *n* (%)

Study	IFN-α2b alone or IFN-α2b + RBV	PEG-IFN + RBV	Genotype 1	Genotype non-1	No data of genotype
George *et al*[14]	146 (97)	4 (3)	75 (53)	66 (47)	9
Veldt *et al*[15]	55 (39)	83 (59)	56 (39)	86 (61)	-
Chavalitdhamrong *et al*[16]	93 (54.4)	78 (45.6)	48 (28.1)	113 (66.1)	10
Giannini *et al*[18]	0	231 (100)	77 (33.3)	154 (66.7)	-
The current study	0	153 (100)	116 (75.8)	37 (24.2)	-

PEG-IFN: Peginterferon; RBV: Ribavirin.

It is noteworthy that we included only patients treated with PEG-IFN plus ribavirin with a high proportion being genotype 1 (75.8%), in contrast to other studies (Chavalitdhamrong *et al*[16], where genotype 3 represented 62%; George *et al*[14], genotype 1 represented 47%; and Giannini *et al*[18] genotype 1 represented 66.6%).

Overall, our study showed that clinical events were rare in this population, indicating that SVR patients have an excellent prognosis, similar to previous studies[8,9,11,14-16,20,21,25-29]. No patient developed decompensated liver disease. There were 5 (4.2%) patients with cirrhosis pre-treatment in this study. None of the patients with advanced fibrosis (F3) pre-treatment progressed to cirrhosis. Similar findings have been reported with PEG-IFN[10,14,25]. In contrast, Pradat *et al*[27] found that cirrhosis developed in 2 of 87 patients who were followed for at least 5 years after a SVR.

One patient with pre-treatment cirrhosis developed a HCC that represented a rate of 0.8%. This patient had no other risk factors such as obesity, alcohol intake or diabetes. This is a similar rate of HCC as reported in other studies[12,15,20,21,23,24,26,30]. Veldt *et al*[21] reported that 3/142 patients (2%) with a SVR and F3-F4 stage pre-treatment developed HCC during follow-up. Nevertheless, Japanese authors[31,32] have reported a HCC rate of 0.02%-0.5% per year, slightly lower than our study. These data confirm that the risk of late development of HCC after a SVR is a real problem, and we must continue the follow-up of these patients for a long time. It is also important to take into account that HCV-RNA remains undetectable when HCC appears. Scientists speculate about the possibility of hepatocarcinogenesis, despite null replication of HCV, by other pathways[29,33,34].

It is well-known that most patients with a SVR normalize their serum ALT, AST and total bilirubin, unless another liver disease is present[8,9,11,24]. We found the same results in our study: 99% of patients had normal AST and ALT levels during the entire period of follow-up. The patient with HCC had persistently normal serum ALT values. Only one patient had elevated ALT and AST levels during follow-up period: a woman with fibromyalgia and relevant consumption of non-steroidal anti-inflammatory drugs. Nevertheless, ALP values were increased after treatment, but remained within the normal range (< 100 U/L). There is no explanation for this finding.

Limitations of our study are that not all patients had a period of follow-up greater than 5 years and, importantly, that analysis of outcomes of fibrosis (stability, improvement or progression) are of limited value as no paired pre-treatment and post-treatment biopsies were analyzed from each patient. However, a large European study[21] clearly demonstrated that the 5-year survival rate of patients achieving a SVR was similar to the overall population and that a SVR was associated with a decrease in fibrosis score; the authors speculated that excellent prognosis of sustained virological responders "is likely to hold true in the era of PEG-IFN and ribavirin". Our data confirm this important prognostic assumption. Moreover, extensive recent histological analyses have shown that most virological responders without cirrhosis had normalization of liver histology[13]; that is, up to 82% had improved fibrosis scores[14] and in addition to fibrosis stability/improvement in 88%, in 64% of patients (9 of 14) regression of cirrhosis was observed[35]. Taken all together[13,14,21,35], these data question the indication for a second liver biopsy in CHC patients with a SVR after antiviral combination therapy.

The long-term clinical outcome of patients with a SVR to PEG-IFN plus ribavirin is favorable. However, a risk of HCC development still remains, although it is very low, so we must clinically monitor SVR patients for a long time, even with undetectable HCV-RNA, normal ultrasonography, and normal aminotransferase and AFP levels after PEG-IFN plus ribavirin therapy.

COMMENTS

Background

The combination treatment of peginterferon (PEG-IFN) α plus ribavirin improved the sustained virological response (SVR) rate in chronic hepatitis C (CHC) patients. The long-term benefits of CHC combination therapy have been well established in several studies, but the results are limited by differing patient populations or treatment regimens and, importantly, a brief duration of follow-up.

Research frontiers

Occult hepatitis infection by hepatitis C virus (HCV) has been proposed and some cases of delayed relapses have been published.

Innovations and breakthroughs

The conclusions of long-term studies may be compromised by the small number of patients, and the fact that most studies used IFN monotherapy or IFN combined with ribavirin, with only 4 studies using PEG-IFN plus ribavirin combination therapy. This study analyzed patients with a SVR after antiviral combination therapy of PEG-IFN plus ribavirin with a mean follow-up greater than 5 years.

Applications

The study demonstrated that the long-term outcome of CHC patients who were sustained virological responders was good. It is important that evidence of a virological relapse must be assessed for a long time, as well as screening for hepatocellular carcinoma.

Terminology

A SVR is comparable with "clinical cure" in CHC patients. However, a minimal

percentage of patients present an activation of HCV replication, and are considered as "relapsers".

Peer review

The study has been well conducted and includes a large number of patients. Results have been described in a lucid and informative manner and are of clinical relevance.

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