see related editorial on page 2174

CME

Peginterferon Plus Ribavirin and Sustained Virological Response in HCV-Related Cirrhosis: Outcomes and Factors Predicting Response

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OBJECTIVES: **Patients with hepatitis C virus (HCV) cirrhosis are difficult to treat and have a high risk of liver decompensation or hepatocellular carcinoma. We sought to identify factors that could predict treatment response.**

METHODS: **Collaborating centers ($n=26$) provided data for patients ($n=568$) with HCV cirrhosis undergoing treatment with peginterferon-α plus ribavirin (RBV). Univariate and multivariate analyses were used to evaluate factors predicting treatment outcomes.**

RESULTS: **Sustained viral response (SVR) in naive patients was 30.7%, with no significant differences between centers. Median follow-up was 35 months (range: 1–81). Factors predicting SVR were: non-genotype 1 (odds ratio (OR)=4.183; 95% confidence interval (CI): 2.353–7.438) overall dose and ≥80% of the scheduled time of treatment (OR=3.177; 95% CI: 1.752–5.760); serum γ-glutamyl transpeptidase (GGT) <76 IU per ml (OR=4.092; 95% CI: 2.418–6.927); baseline viral load $<6\times10^5$ (OR=2.597; 95% CI: 1.583–4.262); absence of ultrasound signs of portal hypertension (OR=2.067; 95% CI: 1.26–3.39). No patient with a HCV-RNA decline <1 $\log_{10}$ at week 4 achieved SVR. Event-free survival at 5 years was 91% in patients with SVR vs. 59% in non-responders ($P<0.001$). Overall survival in patients with SVR was 98% vs. 86% in non-responders ($P=0.005$). Independent factors predicting events were absence of SVR (hazard ratio (HR)=2.66; 95% CI: 1.32–5.54), baseline serum albumin <3.9 g per 100 ml (HR=3.06; 95% CI: 1.81–5.15), presence of esophageal varices on endoscopy (HR=2.489; 95% CI: 1.546–4). Improved outcome was more evident in responders with less advanced disease at baseline.**

CONCLUSIONS: **SVR can be achieved in approximately one-third of patients with HCV-related cirrhosis. SVR independently reduces the likelihood of clinical decompensation and improves survival.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg.

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INTRODUCTION

Hepatitis C virus (HCV)-related cirrhosis is the leading cause of hepatocellular carcinoma and liver transplantation in the Western world (1). Once HCV cirrhosis is established, the risk of decompensation is about 5% per year (2–5). The therapeutic goals in this patient population should be the prevention of liver-related morbidity and mortality, and a reduction in the requirement for liver transplantation. A non-significant trend in the prevention of liver-related adverse outcomes was observed in patients with sustained virological response with interferon (INF)-α monotherapy (6). Two recent large-scale studies showed that patients with HCV-related cirrhosis achieving a sustained viral response (SVR) with IFN-α monotherapy had a significant reduction in liver-related mortality (7,8). Veldt *et al.* (9) showed that approximately one-

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third of HCV patients with advanced fibrosis achieved SVR, and that this response reduced the risk of complications.

Patients with HCV-related cirrhosis represent a population with poor therapeutic response, and reduced tolerance to the therapy (10,11). Information on the therapeutic efficacy in this population has been drawn mainly from subgroup analyses from pivotal trials; the data often containing confounding variables such as therapeutic heterogeneity (INF monotherapy, INF plus ribavirin (RBV), peginterferon plus RBV) or cirrhotic as well as non-cirrhotic patients with advanced hepatic fibrosis being included in the same study (7,9,12). In addition, although a positive effect on liver fibrosis has been described (13,14), the effects of SVR on clinically relevant end points are less well documented. Recently, Di Marco *et al.* (15) randomized 101 patients with HCV-related cirrhosis to receive either peginterferon-α-2b at a dose of 1 μg per Kg bodyweight per week alone or in combination with RBV at a dose of 800 mg per day for 52 weeks. The results indicated that patients with the combined treatment achieved a rate of SVR of 21.6% vs. 9.8% for those receiving monotherapy and that, using a composite end point, therapeutic benefit was achieved by the responders. However, there are few studies addressing the efficacy of treatment with full-dose peginterferon-α plus weight-adjusted RBV dose in a patient population with well-established cirrhosis. Nor have the effects of this treatment scheme been explored with respect to individual clinical end points such as development of liver failure, development of hepatocellular carcinoma (HCC), rate of esophageal variceal bleeding, and overall survival. Further, factors influencing SVR, or predicting survival in this population, have yet to be established.

We conducted this study in patients with HCV-related cirrhosis to assess the rate of SVR with full dose of peginterferon-α-2a or peginterferon-α-2b combined with bodyweight-adjusted dose of RBV, the effect of SVR on liver adverse events affecting survival (liver decompensation, portal hypertensive gastrointestinal (GI) bleeding, hepatocellular carcinoma), and overall survival. Secondary objectives were to identify factors predicting SVR, and to evaluate early HCV kinetics predictive of SVR.

METHODS

This is a multicentered, retrospective, cohort study of patients with HCV cirrhosis who, since 2001, had received treatment in 26 academic, or general, hospitals in Spain.

The study protocol was approved by the Ethics Committee of the Hospital Universitario Fundación Alcorcón on the understanding that all patient data were codified to guarantee anonymity. All procedures were within the guidelines of the Helsinki Declaration and of Good Clinical Practice.

Patient selection

Data were recorded for 568 patients (394 males and 174 females) with HCV-associated cirrhosis receiving treatment in 26 academic and community hospitals. Local principal investigators (see **Supplementary Appendix** online) identified eligible patients and entered data in a predefined database, which was periodically updated at each of the participating center. The treatment was with either peginterferon-α-2a (180 μg per week, s.c.; 315 patients) or peginterferon-α-2b per 1.5 μg per Kg bodyweight per week s.c.; 253 patients) plus RBV (800–1,200 mg per day). Patient treatment was assigned according to individual attending physician preference. Of the patients studied, 32.2% were treatment experienced, 11.1% were previous relapsers and non-completers, and 22.4% were non-responders to previous treatments.

Diagnosis of cirrhosis was biopsy proven in 429 cases (75.5%), by fibroscan in 9 cases (1.6%), and the remaining 130 cases (22.9%) met at least two of the following criteria: platelet count $< 100 \times 10^9$ per liter, ultrasound (US) scan signs of portal hypertension (spleen size >12 cm, portal vein enlargement >12 mm, repermeabilization of the umbilical vein, or presence of portal-systemic shunts), or presence of esophageal varices on endoscopy.

Patients with Child-Pugh-Turcotte's score (CPT) >6, HIV or hepatitis B surface antigen coinfection or with alcohol intake >40 g per day in males and 20 g per day in females were not included. In addition, the recommendations by the EASL International Consensus Conference on Hepatitis C (17) were followed in all participant centers: present or past psychosis or severe depression; neutropenia < 1,500 per ml and/or thrombocytopenia < 100,000 platelets per ml; organ transplantation; severe heart disease; uncontrolled seizures, uncontrolled diabetes; autoimmune disorders, end-stage renal failure; anemia; hemoglobinopathies; severe heart disease; pregnancy; no reliable method of contraception, uncontrolled arterial hypertension; and age older than 70 years. Serum analysis and US scan examination were carried out at each participating center and the local expert pathologist examined the liver biopsy specimens. Follow-up data were available for 509 patients.

Clinical assessment and definition of events

US scan was carried out in 559 patients (98.4%) at baseline and every 6 months thereafter. Patients showing focal lesions suggestive of hepatocellular carcinoma or ascites were not included. All patients in the study belonged to the CPT categories 5 or 6. Upper GI endoscopy was carried out in 495 patients before starting the therapy. Disease events were classified as hepatic decompensation (ascites, hepatic encephalopathy, or an increase ≥2 points on the CPT scale), upper GI bleeding secondary to rupture of esophageal or gastric varices, development of HCC, liver transplantation, and liver-related or liver-unrelated death. HCC was diagnosed according to the EASL guidelines (16). Ascites was confirmed by the abdominal US. The time of the initial adverse event was recorded in those patients who developed more than one event. Liver transplantation was recorded as a liver-related death event. Esophageal varices size was classified as small (Beppu F1) and large (Beppu F2 and F3) (17).

Virological determinations and definitions of response

HCV-RNA was determined in each participating center using the commercial polymerase chain reaction assays (Amplicor HCV or Amplicor HCV Monitor, Roche Diagnostics, Basel, Switzerland). Only patients with baseline and 24-week HCV-RNA determinations

were included in the statistical analyses. HCV-RNA determinations at week 4 and 12 were available for 215 and 393 patients, respectively. HCV genotyping was carried out in all but two cases. Rapid viral response was defined as undetectable HCV-RNA at week 4 of the therapy. Early viral response was defined as ≥2 $\log_{10}$ reduction of serum HCV-RNA at week 12 of the therapy. End-of-treatment response was defined as undetectable HCV-RNA at week 48 of the therapy in genotype 1 and at week 24 in genotypes 2 and 3. Sustained virological response (SVR) was defined as undetectable HCV-RNA (<50 IU per ml) 24 weeks after the end of the therapy.

Statistical analysis

Data were analyzed with SPSS software for Windows version 13.0 (Chicago, IL). Continuous variables are expressed as mean ± s.d. and categorical variables as absolute and relative frequencies. Mean differences were tested with the Student *t*-test and the Chi-square test for dichotomous and categorical variables. Survival rates were estimated by Kaplan–Meier analysis and Cox's adjusted proportional hazard analysis. Logistic regression analysis was used to identify factors independently associated with SVR. Receiver-operating curves were constructed to estimate the best cut-off value for quantitative variables. Results were analyzed on the intention-to-treat principle.

Those parameters, which were significant with univariate analysis were introduced into a Cox multivariate analysis to obtain a discriminant predictive model.

RESULTS

Baseline demographic and clinical features are summarized in **Table 1**. The age of the patients was 51±0.5 years, and 69.4% of patients were males. Baseline viral load was 2.7×10^6 IU per ml, and 70% of patients had genotype 1. All biopsy specimens showed an F4 grade on METAVIR. Hepatocellular steatosis >5% was present in 30.7% of liver specimens. The mean grade of inflammation (METAVIR) was 2.47±0.9. There were 146 patients with esophageal varices (29.5%). Varices were small in 120 cases and large in 26. Overall, there were 174 patients (30.6%) who achieved SVR. The end-of-treatment response was 52.8% and the relapse rate 42%. There were 160 patients (29.6%) requiring early discontinuation of treatment because of side effects. Reduction in peginterferon dose was required in 19.2% of patients and dose reduction of RBV in 17.4%. The proportion of patients who required dose reduction of either peginterferon or RBV was lower in responders than in non-responders (**Table 1**). There was information on 211 patients receiving growth factor support. Only 5.2% of patients of this subset received erythropoietin or filgrastim to treat cytopenias.

Factors associated with SVR (univariate analysis)

The main differences between responders and non-responders using univariate analysis are summarized in **Table 1**. There were no statistically significant differences between responders and non-responders with respect to age, gender, body mass index, hemoglobin, white blood cells, alanine transaminase, aspartate aminotransferase, prothrombin activity, glycemia, presence of diabetes mellitus, hepatocellular steatosis, or inflammation grade. Non-responders had lower platelet count, lower serum albumin and higher serum bilirubin, as well as higher serum levels of GGT, ferritin, α-fetoprotein, and baseline viral load. In addition, they showed US signs of portal hypertension more frequently. However, the prevalence of esophageal varices was similar in both the groups. There were no statistically significant differences between responders and non-responders with respect to steatosis or inflammation stage on METAVIR (**Table 1**). Discontinuation because of side effects was higher in non-responders. Further, more patients with SVR received full-dose peginterferon plus RBV in the first 12 weeks of treatment (**Table 1**) with more than two-thirds of patients (68.5%) receiving at least 80% of the therapeutic dose for >80% of the scheduled time. Therapeutic adherence was higher in patients who achieved SVR. Similarly, more patients with SVR received full-dose treatment in the first 12 weeks of therapy (**Table 1**). Treatment-experienced patients had a lower rate of SVR than treatment-naive patients. Previous non-responders had significantly worse SVR rate than naive patients (**Table 1**). There were no statistically significant differences in SVR rate between the centers (**Table 1**). The end-of-treatment response, SVR, and relapse rate were similar in patients treated either with peginterferonα-2a or peginterferon-α-2b, SVR was higher in patients infected with non-1 genotypes and low-baseline viral load. Non-responders patients to previous treatments reached significantly less SVR rate than naive patients (**Table 1**). Unexpectedly, the group of relapsers and previous non-completers patients achieved a SVR rate of 45.8%. Considering only naive patients, variables that reached significance at univariate analysis were the same as the whole cohort with the exception of serum bilirubin and glucose.

Factors associated with SVR (multivariate analysis)

All variables reaching statistical significance in the univariate analysis (**Table 1**) were introduced into a multivariate analysis. Variables independently associated with SVR in the multivariate analysis in both the whole cohort and in naive patients were: non-genotype 1 (OR = 4.183; 95% CI: 2.353–7.438), overall dose and time-of-treatment >80% (OR = 3.177; 95% CI: 1.752–5.760), serum GGT <76 IU per ml (OR = 4.092; 95% CI; 2.418–6.927), baseline viral load $<6\times10^5$ (OR = 2.597; 95% CI: 1.583–4.262), and absence of US signs of portal hypertension (OR = 2.067; 95% CI: 1.26–3.39) (**Figure 1**).

Early viral kinetics

The SVR rates for different RNA-HCV reductions at week 4 and 12 are summarized in **Table 2**. **Table 3** shows that the negative predictive values for <1 log decrease at week 4 and <2 log at week 12 were 100% and 98.4, respectively, whereas the positive predictive value for patients with rapid viral response was 83.9% and for patients with complete early virological response was 64.9%. The area under the curve Receiver-operating curves analysis for a cut-off of 1 log reduction of viral load at 4 weeks was 0.88 (95% CI: 0.827–0.939).

Table 1. Features associated with SVR and with non-response; univariate analysis

Variable	All patients, *n*=568	SVR, *n*=174	Non-SVR, *n*=394	*P*
Age (years)	51±0.5	50.81±0.45	51.64±0.48	0.311
Gender (M/F; %)	69.4/30.6	31.9/69.1	27/73	0.371
BMI (Kg/m^2)	26.44±3.78	26±0.3	26.6±0.23	0.28
Hb (g/dl)	14.9±1.44	14.88±1.39	14.95±0.09	0.67
Neutrophils (10^9/l)	3.045±1.27	2.99±1.37	3.065±7.5	0.306
Platelets (10^9/l)	129.3±4.9	137.5±3.9	125.7±2.48	0.013
Albumin (g/dl)	4.08±0.41	4.14±0.03	4.05±0.02	0.028
Prothrombin (%)	87.7±12.4	86.7±0.9	88±0.69	0.276
Bilirubin (mg/dl)	1.04±0.5	0.97±0.03	1.073±0.027	0.042
ALT (IU/l)	133±88	148±8.5	126±3.79	0.233
AST (IU/l)	108±65	109±5	108.6±5	0.560
GGT (IU/l)	94.84±79	71±4.5	105.5±4.5	0.0001
Glycemia (mg/ml)	109±4.5	104.5±3.3	106.1±1.79	0.09
Diabetes mellitus (Y/N; %)	15.3/84.7	30.5/69.5	32.5/67.5	0.789
Serum ferritin (ng/ml)	292±262	228±204	320±279	0.004
Serum α-fetoprotein (ng/ml)	8±39.7	7.59±8.3	22.4±41.47	0.001
Inflammation grade (METAVIR)	2.47±0.9	2.61±0.11	2.41±0.076	0.191
Liver steatosis (Y/N; %)	29/71	24.7/75.3	33.2/66.8	0.165
Baseline viral load <6×10^5 IU/ml	203/543	78/203	88/340	0.001
Baseline-HCV-RNA (10^6 IU/ml)	2.696±7.15	1.708±4.1	3.131±4	0.001
HCV genotype (%): type 1	70.1	24.4	75.6	0.001
Type non-1	29	54.9	45.1	
US signs of PHT (Y/N; %)	46.5/53.5	23.5/76.5	36.6/63.4	0.0001
Esophageal varices (Y/N; %)	29.5/70.5	21.5/79.5	26.9/73.1	0.222
Previous non-responders (Y/N; %)	22.2/77.8	16.2/83.8	24.8/75.2	0.001
Dose 80/80/80 (Y/N; %)	68.5/21.5	39.1/60.9	14.3/85.7	0.0001
Full-dose first 12 weeks (Y/N; %)	75.6/24.4	36.7/63.3	15.1/84.9	0.001
Peginterferon-α-2a	55.46%	30.79%	69.21%	0.131
Peginterferon-α-2b	44.54%	30.43%	69.57%	
Treatment discontinuation (Y/N; %)	29.6/70.4	10/90	39.4/60.6	0.0001
Recruitment per center				
≥50 Patients	31.9%	28.5%	71.5%	0.397
30–50 Patients	26.1%	43.3%	56.7%	
15–30 Patients	22.8%	31.6 %	68.4%	
<15 Patients	19.2%	30.8%	69.2%	

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; GGT, γ-glutamyl transpeptidase; Hb, hemoglobin; HCV, hepatitis C virus; PHT, portal hypertension; SVR, sustained viral response; US, ultrasound.

Occurrence of events

Complete follow-up data were available in 508 patients (89.6%). The median follow-up was 35 months (range: 1–81). As shown in **Table 4**, there were 89 adverse events and 29 deaths during follow-up. There were 59 cases of liver decompensation (ascites and/or hepatic encephalopathy and/or increase in CPT score ≥2 points), 31 cases of HCC, and 19 cases of upper GI hemorrhage secondary to ruptured esophageal varices.

Factors predicting adverse events

Unadjusted hazard ratio (HR) identified age, albumin <3.9 g per 100 ml, US signs of portal hypertension, absence of SVR,

platelet count, serum bilirubin, and prothrombin time as factors associated with the occurrence of adverse events (**Table 5**). Neither the presence of hepatocellular steatosis nor diabetes mellitus was associated with the occurrence of hepatocellular carcinoma. Cox's proportional adjusted hazard model identified the absence of SVR (HR = 2.66; 95% CI: 1.32–5.54), baseline serum albumin < 3.9 g per 100 ml (HR = 3.06; 95% CI: 1.81–5.15), and presence of esophageal varices on endoscopy (HR = 2.489; 95% CI: 1.546–4) as the variables independently associated with the occurrence of liver-related adverse events during follow-up (**Figure 2**).

Influence of SVR on clinical outcomes

The likelihood of event-free survival at 5 years in patients with SVR was 91% vs. 59% in non-responders ($P < 0.0001$) (**Figure 3**). The probability of remaining free of liver decompensation at 5 years was 97.3% in responders vs. 66.7% in non-responders (log rank $P < 0.001$) (**Figure 4**). However, there was no statistically significant reduction in the risk of developing HCC in responders compared with non-responders (16% vs. 4%; $P = 0.09$) (**Figure 5**). There was a reduction in the risk of GI bleeding from ruptured esophageal varices at 5 years of follow-up (97% vs. 88%; $P = 0.06$); the statistical significance being borderline (**Figure 6**). The overall survival was also higher in responders vs. non-responders (98% vs. 86%; $P = 0.005$) (**Figure 7**). The influence of SVR on event-free survival according to the severity of liver disease at baseline was assessed. Patients were arbitrarily segregated into two categories: patients with serum albumin >3.9 g per 100 ml and absence of esophageal varices on endoscopy ($n = 221$) were considered as having mild disease, whereas patients with serum albumin < 3.9 g per 100 ml with esophageal varices on endoscopy ($n = 47$) were considered as having more severe disease. On follow-up, in patients with mild disease there was 1 event in 74 patients who achieved SVR and 14 events in the 147 who did not achieve SVR. Conversely, among patients with severe disease, there were 2 events in 10 patients who achieved SVR and 20 events in 37 non-responders. The cumulative event-free survival was significantly better in sustained responders than in non-responders among patients with mild disease ($P = 0.019$) but not among those

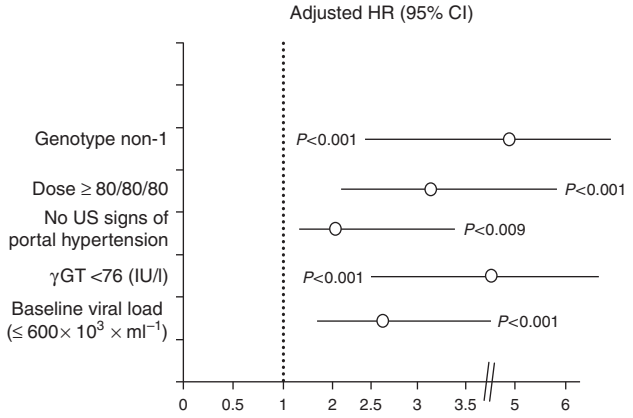

Figure 1. Factors independently predictive of sustained viral response. CI, confidence interval; γGT, γ-glutamyl transpeptidase; HR, hazard ratio; US, ultrasound.

Table 2. Mean decrease in viral load at weeks 4 and 12 in responders and non-responders

HCV-RNA	SVR	Non-SVR	*P*
Mean decrease of RNA-HCV $\log_{10}$ at week 4	4.5 ± 0.17	1.86 ± 0.14	0.0001
Mean decrease of RNA-HCV $\log_{10}$ at week 12	5.15 ± 0.13	2.45 ± 0.13	0.0001

HCV, hepatitis C virus; SVR, sustained viral response.

Table 3. Rates of SVR according to HCV-RNA reduction at weeks 4 and 12

HCV-RNA	SVR (%)	Non-SVR (%)	*P*
Reduction of <1 log at week 4	0	63 (100)	0.0001
Reduction of >1 log at week 4	73 (48)	79 (52)	
Reduction of <2 log at week 4	5 (5.5)	86 (94.5)	0.0001
Reduction of ≥2 log at week 4	53 (43.8)	68 (56.2)	
HCV-RNA positive at week 4	26 (15.1)	146 (84.9)	0.0001
HCV-RNA negative at week 4	47 (83.9)	9 (16.1)	
Reduction of <2 log at week 12	2 (1.6)	125 (98.4)	0.0001
Reduction of ≥2 log at week 12	132 (49.6)	134 (50.4)	
HCV-RNA positive at week 12	42 (21.5)	153 (78.5)	0.0001
HCV-RNA negative at week 12	104 (65.4)	55 (34.6)	

HCV, hepatitis C virus; SVR, sustained viral response.

Table 4. Adverse events segregated with respect to sustained virological response

Adverse event	All patients, *n*=508 (%)	SVR, *n*=156 (%)	NR, *n*=352 (%)	*P* log rank
Ascites/encephalopathy/CPT >2	59 (11.6)	4 (2.56)	55 (15.6)	0.0001
Variceal hemorrhage	19 (3.74)	2 (1.28)	17 (4.83)	0.067
Development of HCC	31 (6.1)	5 (3.2)	26 (7.38)	0.09
Any adverse event	89 (17.5)	11 (7)	78 (22.1)	0.0001
Liver-related mortality	29 (5.7)	2 (1.28)	27 (7.67)	0.005

CPT, carnitine palmitoyltransferase; HCC, hepatocellular carcinoma; NR, non-responders; SVR, sustained viral response.

Table 5. Factors independently predictive of adverse events; non-adjusted HR

	HR (95% CI)	P
Albumin <3.9 g/dl	2.99 (1.898–4.74)	0.001
Esophageal varices	2.920 (1.899–4.5)	0.001
US signs of portal hypertension	2.844 (1.815–4.458)	0.001
Age	1.097 (1.002–1.052)	0.031
No SVR	3.118 (1.657–5.866)	0.001
Platelets (10^9/l)	4.039 (2.14–7.6)	0.001
Bilirubin (mg/dl)	2.496 (1.762–3.536)	0.001
Prothrombin activity (%)	0.975 (0.957–0.993)	0.007

CI, confidence ratio; HR, hazard ratio; SVR, sustained viral response; US, ultrasound.

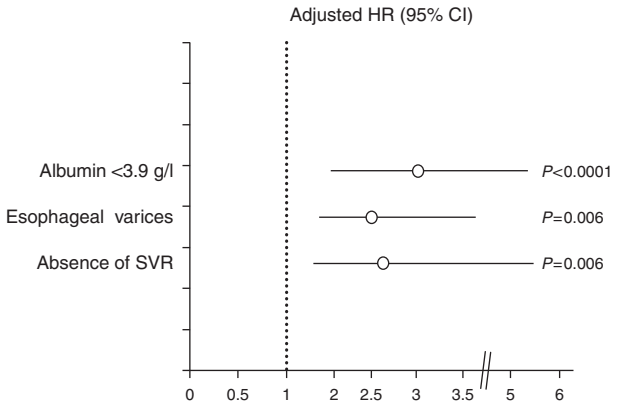

Figure 2. Factors independently predictive of liver-related adverse events. CI, confidence interval; HR, hazard ratio; SVR, sustained viral response.

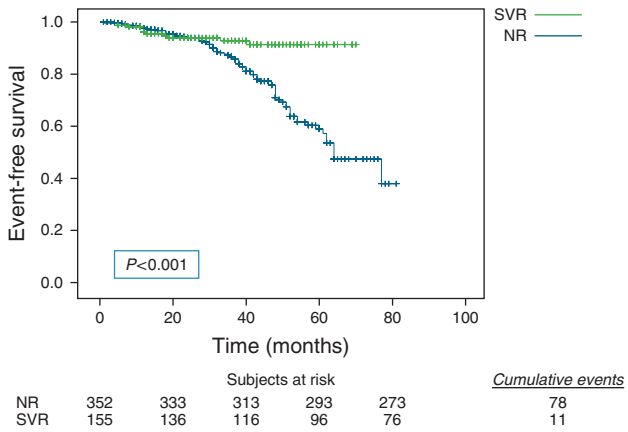

Figure 3. Liver-related event-free survival: 91% event-free survival at 5 years in patients with sustained viral response (SVR) vs. 59% in non-responders (NR).

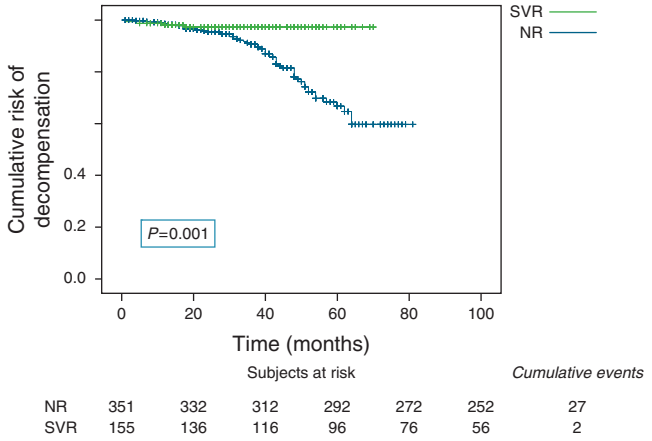

Figure 4. Risk of hepatic decompensation (ascites or encephalopathy or carnitine palmitoyltransferase ≥2 points); 97.3% in patients with sustained viral response (SVR) vs. 66.7% in non-responders (NR) at 5 years.

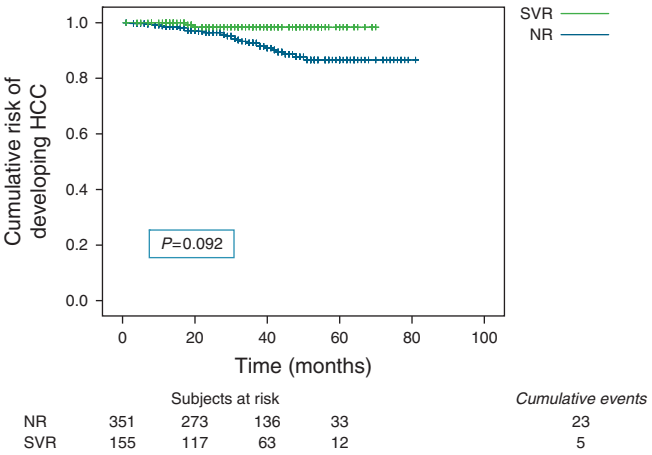

Figure 5. Risk of developing hepatocellular carcinoma (HCC); 96% in sustained viral response (SVR) vs. 83.5% in non-responders (NR) at 5 years.

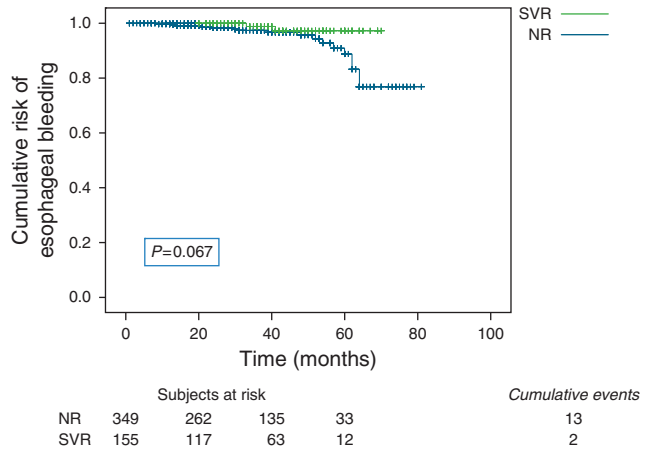

Figure 6. Risk of gastrointestinal bleeding secondary to gastro-esophageal varices rupture in patients with sustained viral response (SVR) vs. non-responders (NR); 97% in patients with SVR vs. 88% in non-responders at 5 years.

with more severe disease (**Figure 8a** and **b**). Patients with more advanced liver disease (presence of esophageal varices and serum albumin <3.9 g per 100 ml) who achieved SVR did not have better tolerance or compliance than those of this group who did not achieve SVR, as assessed by the 80/80/80 rule in the first 12 weeks of treatment (OR =0.60; 95% CI: 0.30–1.20; $P=0.14$).

The best-fit risk-predicting model was:

$(\beta 1X1 + \beta 2X2 + \beta 3X3 + ... + \beta nXn) = -0.979 \times RVS - 1.117 \times albumin + 0.912 \times varices$

SVR was 1, non-SVR was 0, presence or absence of esophageal varices were 1 and 0, respectively, serum albumin ≥3.9 g per 100 ml was 1 and <3.9 g per 100 ml was 0.

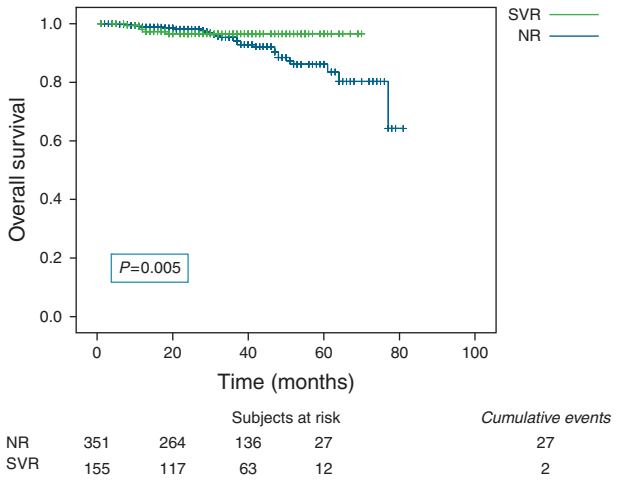

Figure 7. Overall survival at 5 years; 98% in patients with sustained viral response (SVR) vs. 86% in non-responders (NR).

The area under the curve for this model was 0.676 (95% CI: 0.604–0.748).

DISCUSSION

The main finding of this study was that, in patients with HCV-related cirrhosis, SVR to peginterferon plus RBV combination therapy is associated with a lower rate of liver-related adverse outcomes, and improved survival. However, SVR did not fully prevent the development of HCC.

In the intention-to-treat analysis, the rate of SVR was 30.6%, which was similar to that found in the *post-hoc* analysis of subgroups of patients with advanced fibrosis, or cirrhosis, treated with peginterferon plus RBV drawn from pivotal trials (18). As expected, patients with genotype other than one responded better than those infected with genotype 1.

The drop-out rate because of side effects was 29.6%. This is slightly lower than that reported in a recent prospective trial with a lower dose of peginterferon-α-2b (1 μg per Kg bodyweight per week) plus RBV (800 mg per day) (15). Thus, the use of standard doses of peginterferon and RBV seems adequate as initial therapy in patients with CPT A, clinically compensated, HCV-related cirrhosis.

The SVR rate was higher in patients receiving full-dose therapy in the first 12 weeks, or those who had better therapeutic compliance, or did not discontinue treatment. In the multivariate analysis, therapeutic compliance remained independently associated with SVR. These results reinforce the importance of treatment adherence in optimizing therapeutic success.

As expected, previous non-responder patients had a significantly lower SVR rate than naive patients. A surprising finding was the high SVR rate in relapsers and previous non-completers ($n=59$), these results were not due to an over-representation of

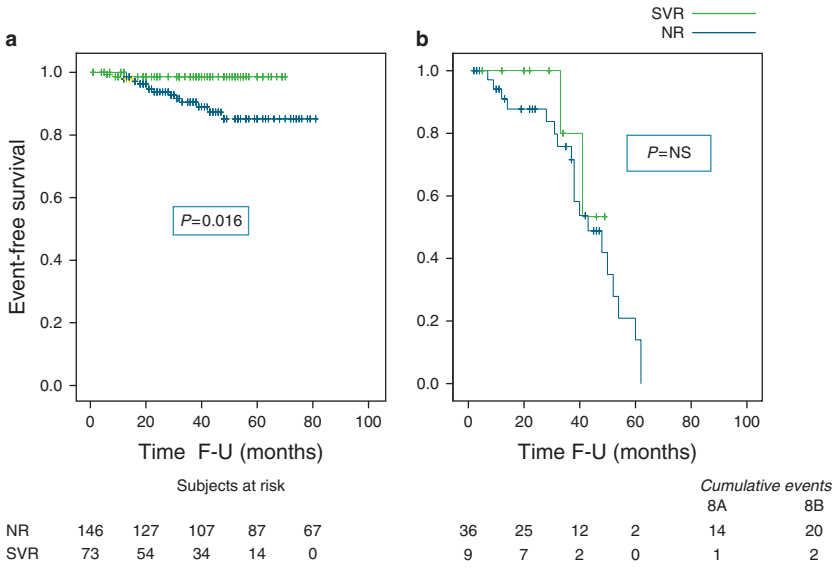

Figure 8. (**a**) Liver-related event-free survival in patients ($n=221$) with albumin >3.9 g per 100 ml and absence of esophageal varices regardless of the platelet count; 98% vs. 85% at 5 years. (**b**) Liver-related event-free survival in patients with albumin <3.9 g per 100 ml and presence of esophageal varices regardless of the platelet count; 53% vs. 13%. NR, non-responders; SVR, sustained viral response.

non-1 genotypes, and might be because of most of them being previously treated with INF monotherapy.

Data on the use of growth factors were available from 211 cases. Of these, only 5% of patients received support with erythropoietin or filgrastim. As severe cytopenia frequently causes dose reduction or discontinuation of the therapy, the use of growth factors, which may potentially improve therapeutic compliance and increase SVR rate needs to be evaluated prospectively.

SVR rate was lower in patients with abdominal US signs of portal hypertension. These are patients who, most likely, had more advanced disease and poorer liver function than patients in whom diagnosis of cirrhosis was based on histology.

Other factors such as steatosis, type of peginterferon, altered baseline serum glucose, presence of diabetes, or overweight did not influence the SVR rate.

An important observation in this study was that about 30% of patients were non-responders (<1 $\log_{10}$ reduction of HCV-RNA at week 4) and none of them achieved SVR. Thus, non-response at week 4 had negative predictive values of 100% with respect to SVR. Conversely, patients who cleared HCV-RNA at week 4 (who represented 20% of our patient population) had a high probability of achieving SVR (positive predictive value of 83.9%). In addition, 31.8% of patients without early viral response had a very low probability of SVR (negative predictive values 98.4%). Consequently, measurement of HCV-RNA decline at week 4 and at week 12 provides important on-treatment information concerning possible discontinuation of treatment to avoid unnecessary toxicity and cost in a subset of patients. Hence, individualization of therapy is feasible in a substantial part of this patient population.

The beneficial impact of SVR on the clinical outcome in cirrhotic patients documented in this survey is consistent with observations made in several recent reports (7,8,11,14,15). However, most of these cited studies included a significant proportion of patients with advanced fibrosis (rather than established cirrhosis) and used therapies that will no longer be used (such as non-pegylated INF-α monotherapy or in combination with RBV). In this study, all patients had well-established cirrhosis and received standard dose of peginterferon plus a weight-adjusted dose of RBV.

In this study, a decreased incidence of liver disease-related complications leading to an improved overall survival was documented in patients with SVR. These observations concur with those of Bruno *et al.* (8) who also showed a reduction in liver-related adverse events and mortality in responder patients from a large cohort of cirrhotic patients homogeneously treated with INF-α monotherapy. It may be argued that the improved outcome observed in responders may be related to the responders having less severe disease at baseline that, in turn, was associated with a higher rate of SVR. We carried out a multivariate analysis to resolve this potential confusion. The results indicated that, in addition to factors suggestive of less advanced disease at baseline, SVR remained a factor independently associated with event-free survival. Further, among patients with less advanced disease (serum albumin >3.9 g per 100 ml and absence of esophageal varices on endoscopy) SVR was significantly associated with improved event-free survival. Among patients with more advanced disease, the number of adverse events in patients achieving SVR was lower than in non-responders, albeit the difference did not reach statistical significance due, possibly, to small sample size. In addition, these differences were not because of better tolerance or better compliance, as assessed by the 80/80/80 rule in the first 12 weeks. Nevertheless, our data suggest that SVR is also beneficial in patients with more advanced disease.

Several reports suggest that the development of HCC in patients with HCV-related cirrhosis may be prevented by antiviral therapy (19,20), but this issue has been controversial (8,9,21). We did not observe a significant reduction in the overall incidence of HCC in responders relative to non-responders. However, all cases of HCC in responders, but not in non-responders, were recognized relatively soon during follow-up period, suggesting that long-lasting control of HCV replication, along with consistent remission of disease activity, may effectively block hepatic carcinogenesis in patients with HCV-related cirrhosis. In this regard, no cases of HCC were detected during follow-up of a small number of patients, in whom reversal of cirrhosis was documented after successful HCV eradication by antiviral therapy (21). Taken together, these data suggest that antiviral therapy has a beneficial effect on the development of HCC, particularly in responders. However, long-term follow-up studies involving a large number of sustained virological responders with previously documented HCV cirrhosis are necessary to confirm this hypothesis.

A trend toward a reduction in the incidence of bleeding from ruptured esophageal varices was observed in our patients with SVR. This observation is in accord with the reduction in portal pressure described in patients with HCV cirrhosis undergoing antiviral treatment (22). However, prevention of variceal bleeding in responder patients was not statistically proven in this study due, possibly, to the small number of patients at risk i.e. 26 patients (5% of the whole cohort) had large varices at baseline. Unfortunately, there were insufficient data to assess reliably the role of pharmacological or endoscopic measures as a primary prophylaxis of variceal bleeding. This could be a confounding factor in assessing the possible effect of antiviral therapy and SVR on variceal bleeding. The clinical benefit observed in patients achieving viral clearance may be related to the suppression of necroinflammation and reversal of fibrosis (21).

This study has some limitations. A selection bias cannot be excluded, considering the retrospective nature of the study. Missing values in a few variables exceeded 10% of the patient population, and this would reduce the accuracy of results. However, as patient inclusion criteria were less stringent than in formal drug-registration trials, the observations made in this study may add further valuable information in clinical decision making in daily medical practice.

In summary, nearly one-third of patients with compensated HCV-related cirrhosis and with CPT status A achieved SVR when treated with standard dose of peginterferon plus weight-adjusted dose of RBV. Genotype non-1, low baseline viral load, low serum GGT, absence of US signs of portal hypertension, and rapid virological response at week 4 predicted SVR. Determination of viral kinetics at weeks 4 and 12 provided important on-treatment information to guide further therapy. Patients who achieved SVR had significantly better clinical outcomes than non-responders, and this beneficial effect was more evident in patients with less advanced liver disease.

CONFLICT OF INTEREST

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Specific author contributions: Design, coordination of the study, gathering of data, and writing the final draft of the paper: Conrado M. Fernández-Rodríguez; design, analysis of data, and approved the final draft submitted: Sonia Alonso; recruitment of cases, discussion of data, and approved the final draft submitted: Stella M. Martinez; study design, discussion of data, and approved the final draft submitted: Xavier Forns; study design, discussion of data, and approved the final draft submitted: Jose M. Sanchez-Tapias; recruitment of cases, discussion of data, and approved the final draft submitted: Diego Rincón; study design, statistical analysis, and approved the final draft submitted: Gil Rodriguez-Caravaca; recruitment of cases, discussion of data, approved the final draft submitted: Rafael Bárcena; recruitment of cases, discussion of data, and approved the final draft submitted: Miguel A. Serra; recruitment of cases and discussion of data approved the final draft submitted: Manuel Romero-Gómez; recruitment of cases, discussion of data, and approved the final draft submitted: Inmaculada Fernandez; recruitment of cases, discussion of data, and approved the final draft submitted: Javier Garcia-Samaniego; recruitment of cases, discussion of data, and approved the final draft submitted: Javier Fuentes; recruitment of cases, discussion of data, and approved the final draft submitted: Ricard Solá; recruitment of cases, discussion of data, and approved the final draft submitted: Ricardo Moreno-Otero; recruitment of cases, discussion of data, and approved the final draft submitted: Ramón Planas.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Sustained virological response (SVR) improves liver-related survival outcomes in hepatitis C virus (HCV) cirrhosis.

WHAT IS NEW HERE

- ✓ SVR is achieved in nearly one-third of patients with HCV cirrhosis treated with full dose of peginterferon-α and weight-adjusted dose of ribavirin.
- ✓ SVR improves overall survival in patients with HCV cirrhosis.
- ✓ Genotype non-1, low-baseline viral load, low-serum γ-glutamyl transpeptidase, absence of ultrasound signs of portal hypertension were factors predictive of SVR.
- ✓ The main clinical benefits occur in less advanced liver disease.

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