BRIEF ARTICLE

Factors associated with early virological response to peginterferon-α-2a/ribavirin in chronic hepatitis C

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Abstract

AIM: To evaluate the impact of sociodemographic/clinical factors on early virological response (EVR) to peginterferon/ribavirin for chronic hepatitis C (CHC) in clinical practice.

METHODS: We conducted a multicenter, cross-sectional, observational study in Hepatology Units of 91 Spanish hospitals. CHC patients treated with peginterferon α-2a plus ribavirin were included. EVR was defined as undetectable hepatitis C virus (HCV)-ribonucleic acid (RNA) or ⩾ 2 log HCV-RNA decrease after 12 wk of treatment. A bivariate analysis of sociodemographic and clinical variables associated with EVR was carried out. Independent factors associated with an EVR were analyzed using a multiple regression analysis that included the following baseline demographic and clinical variables: age (⩽ 40 years *vs* > 40 years), gender, race, educational level, marital status and family status, weight, alcohol and tobacco consumption, source of HCV infection, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and gamma glutamyl transpeptidase (GGT) (⩽ 85 IU/mL *vs* > 85 IU/mL), serum ferritin, serum HCV-RNA concentration (< 400 000 *vs* ⩾ 400 000), genotype (1/4 *vs* 3/4), cirrhotic status and ribavirin dose (800/1000/1200 mg/d).

RESULTS: A total of 1014 patients were included in the study. Mean age of the patients was 44.3 ± 9.8 years, 70% were male, and 97% were Caucasian. The main sources of HCV infection were intravenous drug abuse (25%) and blood transfusion (23%). Seventy-eight percent were infected with HCV genotype 1/4 (68% had genotype 1) and 22% with genotypes 2/3. The HCV-RNA level was > 400 000 IU/mL in 74% of patients. The mean ALT and AST levels were 88.4 ± 69.7 IU/mL and 73.9 ± 64.4 IU/mL, respectively, and mean GGT level was 82 ± 91.6 IU/mL. The mean ferritin level was 266 ± 284.8 μg/L. Only 6.2% of patients presented with cirrhosis. All patients received 180 mg of peginterferon α-2a. The most frequently used ribavirin doses were 1000 mg/d (41%) and 1200 mg/d (41%). The planned treatment duration was 48 wk for 92% of patients with genotype 2/3 and 24 wk for 97% of those with genotype 1/4 (*P* < 0.001). Seven percent of patients experienced at least one reduction in ribavi-

rin or peginterferon α-2a dose, respectively. Only 2% of patients required a dose reduction of both drugs. Treatment was continued until week 12 in 99% of patients. Treatment compliance was ≥ 80% in 98% of patients. EVR was achieved in 87% of cases (96% *vs* 83% of patients with genotype 2/3 and 1/4, respectively; *P* < 0.001). The bivariate analysis showed that patients who failed to achieve EVR were older (*P* < 0.005), had higher ALT (*P* < 0.05), AST (*P* < 0.05), GGT (*P* < 0.001) and ferritin levels (*P* < 0.001), a diagnosis of cirrhosis (*P* < 0.001), and a higher baseline viral load (*P* < 0.05) than patients reaching an EVR. Age < 40 years [odds ratios (OR): 0.543, 95%CI: 0.373-0.790, *P* < 0.01], GGT < 85 IU/mL (OR: 3.301, 95%CI: 0.192-0.471, *P* < 0.001), low ferritin levels (OR: 0.999, 95%CI: 0.998-0.999, *P* < 0.01) and genotype other than 1/4 (OR: 4.716, 95%CI: 2.010-11.063, *P* < 0.001) were identified as independent predictors for EVR in the multivariate analysis.

CONCLUSION: CHC patients treated with peginterferon-α-2a/ribavirin in clinical practice show high EVR. Older age, genotype 1/4, and high GGT were associated with lack of EVR.

Key words: Antiviral therapy; Baseline factors; Early virological response; Peginterferon α-2a; Ribavirin

INTRODUCTION

Until recent approval of the first direct acting antivirals (DAAs) against hepatitis C virus (HCV)[1-4], the combination of pegylated interferon and ribavirin was the standard of care (SOC) for chronic hepatitis C (CHC)[5-8] with the goal of achieving a sustained viral response (SVR) [undetectable hepatitis C virus ribonucleic acid (HCV-RNA) at week 24]. However, the overall SVR rate with standard peginterferon and ribavirin combination does not exceed 56%-63%[5,9,10], and is even lower in some patient subgroups[10]. Indeed, pivotal studies showed that HCV genotype 1 patients achieve a SVR rate of 41%-56%, whereas in those infected with HCV genotype 2/3, a SVR is obtained in 74%-80%[5,9-11]. Variability in virological response depends on diverse patient factors as well as virological and histological factors. Genotype other than 1, low baseline viral load, age less than 40 years, body weight ≤ 75 kg and absence of advanced fibrosis and/or cirrhosis have been identified as predictive factors of SVR in the studies evaluating peginterferon α-2a plus ribavirin combination[9,12].

Pivotal studies have shown that early virological response (EVR) is highly predictive of SVR[9,13]. Accordingly, patients who do not achieve an EVR have an almost null probability of achieving a SVR[9,13-15]. The study conducted by Fried *et al*[9] showed that only 3% of patients who did not obtain an EVR with peginterferon α-2a plus ribavirin achieved a SVR. The high negative predictive value (PPV) of EVR has great clinical value as it allows us to decide whether to continue or discontinue treatment at week 12, therefore preventing or minimizing the adverse effects related to treatment continuation. Current treatment guidelines for hepatitis C include this decision criteria at week 12[5,7,8,16] and recommend discontinuation of treatment in patients who fail to achieve an EVR. In addition, the clinical utility of EVR has been demonstrated in the routine clinical practice setting, particularly in genotype 1-infected patients[17].

Limited data have been reported regarding the EVR predictive factors in patients receiving peginterferon α-2a plus ribavirin combination therapy. Correct identification of these factors could be a useful strategy to optimize treatment in CHC and improve SVR rates, particularly in patients with genotype 1. On the other hand, treatment adherence is key to achieve successful treatment. The occurrence of adverse effects associated with peginterferon and/or ribavirin is the main reason for dose reduction or treatment discontinuation. As a result, 15%-20% of patients participating in clinical trials and approximately 25% of those in routine clinical practice discontinue treatment[18]. Lack of adherence during the first 12 wk of treatment has been shown to have a particularly negative impact on EVR[13,19]. Thus, the PPV of EVR associated with good treatment compliance is very high, achieving a SVR in 75% of cases with EVR and good treatment adherence[9].

Given that sociodemographic and clinical factors associated with EVR are not well known and considering that treatment adherence is a variable closely related to EVR, characterization of viral and patient factors associated with treatment compliance, and hence EVR, has important clinical implications. The present study was designed to analyze baseline sociodemographic and clinical characteristics associated with EVR and antiviral treatment compliance in CHC patients treated with peginterferon α-2a in the routine clinical practice setting in Spain.

MATERIALS AND METHODS

Study design

This was a national, multicenter, cross-sectional, observational study. The study was carried out in the Hepatology Units of 91 Spanish hospitals. All participating patients gave their written informed consent, and the study was approved by the Clinical Research Ethics Committee of the Hospital Carlos Ⅲ of Madrid. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and their amendments.

The study included adult patients (over 18 years of age) diagnosed with CHC and treated with peginterferon α-2a plus ribavirin under routine clinical practice conditions. Patients with any contraindication to hepatitis C treatment according to the prescribing information and those with HBV and/or human immunodeficiency virus coinfection were excluded.

The main purpose of the study was to analyze EVR in relation to sociodemographic and clinical characteristics. For this purpose, the following variables were recorded at the start of treatment: age, sex, race, nationality, educational level, marital status, occupation and family status, weight, cigarette smoking, alcohol consumption, source of HCV infection, methadone replacement therapy, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT) and ferritin levels, cirrhotic status, viremia and HCV genotype. In addition, ribavirin dose and scheduled duration of treatment, dose reductions of peginterferon α-2a and/or ribavirin up to week 12, data on premature treatment discontinuation (week and reason for discontinuation) were also collected. Furthermore, data on HCV-RNA concentrations at week 12 were recorded and EVR was analyzed (complete/partial). HCV-RNA levels were measured using quantitative polymerase chain reaction assays, mostly the Amplicor HCV Monitor (Roche, Kenilworth NJ, United States), although other commercial tests were used in some centers. A lower limit of detection of 50 IU/mL was considered in all participating hospitals. The secondary objective of the study was to evaluate treatment adherence at week 12.

Virological response criteria
EVR was defined as undetectable levels of HCV-RNA at week 12 (complete EVR) or $\geq$ 2 log reduction in HCV viral load from baseline (partial EVR).

Treatment adherence criteria
To evaluate treatment adherence, compliance was recorded according to the 80/80/80 rule[20] and modified according to the study design. Treatment compliant or adherent patients were those receiving 80% or more of the total dose of peginterferon α-2a plus ribavirin during 80% of the time until week 12. Likewise, noncompliant patients included those who received < 80% of the prescribed dose of one or both drugs during < 80% of the expected duration (12 wk).

Statistical analysis
A descriptive statistical analysis was performed on the sociodemographic and clinical variables collected from the medical records at the start of treatment with peginterferon α-2a plus ribavirin. Quantitative variables were described using measures of central tendency and dispersion (mean, median, SD, minimum, maximum, first quartile and third quartile) and the results are expressed as mean ± SD or median (range). Qualitative variables are presented as absolute and relative frequencies. To characterize the population based on patient sex and the influence of sociodemographic and clinical characteristic on EVR, a bivariate analysis was carried out using Student's *t* test for quantitative variables and the chi-square test for the remaining sociodemographic and clinical qualitative independent variables. Similarly, a bivariate analysis of sociodemographic and clinical variables associated with EVR was carried out based on patient race. Variables with statistical significance or with $P < 0.10$ in the bivariate model were analyzed in a multivariate logistic regression model. Some factors that were not statistically significant were retained in the model based on previous clinical evidence. Odds ratios (OR) and 95%CI were calculated for the independent predictive factors of EVR. In the multivariate logistic regression analysis, only patients with available data for all the variables taken into account for the analysis were included. Significance level was set at $P < 0.05$. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, IL, United States).

RESULTS

Baseline patient characteristics
Baseline patient characteristics are shown in Table 1. A total of 1202 patients were included in the study. Thirty-six were excluded as they met at least one of the following criteria: peginterferon dose other than 180 mg (30 patients), negative HCV-RNA at baseline visit (1 patient), HCV-RNA level not available at week 12 when withdrawal had not occurred (8 patients). The number of evaluable patients was 1166, of which 1014 were analyzed and 152 were excluded for having a detectable viral load at week 12 without specifying the value and/or detection level.

Sociodemographic characteristics
Seven hundred and twelve (70%) patients were male. The vast majority of patients were Spanish (91%) and Caucasian (97%). Fifty percent of patients had completed compulsory education. Of the total number of patients, 580 (57%) were married and 898 (89%) patients lived with another person (Table 1).

The mean age was 43.3 ± 9.0 years in men and 46.6 ± 11.4 years in women ($P < 0.001$). No differences were found in race, educational level or family status based on gender. No significant differences were found in baseline sociodemographic characteristics based on race. The only differences noted were a greater proportion of women over 40 who were Caucasian ($P < 0.005$) and a higher educational level among Caucasian patients ($P < 0.01$).

Clinical characteristics
Alcohol consumption was reported in 154 (15%) patients and 514 (51%) were smokers. The most common source of HCV infection was intravenous drug use (25%) followed by transfusion (23%). Mean ALT and AST levels

Table 1 Patient baseline characteristics *n* (%)	
Characteristics	
Patient sociodemographics	
Sex	
Male	712 (70)
Female	302 (30)
Age (yr), mean ± SD	44.3 ± 9.8
Nationality	
Spanish	919 (91)
Other	93 (9)
Race	
Caucasian	980 (97)
Other	27 (3)
Educational level	
Did not complete compulsory education	125 (12)
Compulsory education	506 (50)
Professional training	243 (24)
University	131 (13)
Postgraduate/Master/PhD	7 (1)
Marital status	
Single	280 (28)
Married	580 (58)
Separated	138 (14)
Widowed	11 (1)
Family status	
Lives with another person	898 (89)
Lives alone	97 (10)
Prison inmate	16 (2)
Clinical characteristics	
Weight (kg), mean ± SD	75.7 ± 13.4
Alcohol consumption	154 (15)
Tobacco consumption	514 (51)
Source of HCV infection[1]	
IVDU	256 (25)
Transfusion	234 (23)
Other	55 (6)
Unknown	462 (46)
Methadone replacement therapy	65 (7)
ALT (IU/mL), mean ± SD	88.4 ± 69.7
AST (IU/mL), mean ± SD	73.9 ± 64.4
GGT (IU/mL), mean ± SD	82.0 ± 91.6
Ferritin (μg/L), mean ± SD	266.0 ± 284.8
Cirrhosis	62 (6.2)
HCV genotype	
1/4	784 (78)
2/3	223 (22)
HCV-RNA	
< 400 000 IU/mL	264 (26)
≥ 400 000 IU/mL	744 (73)

[1]One patient could have more than one presumed source of infection. Data are presented as number (percentage) of patients unless otherwise indicated. Proportions of patients are presented as valid percentages. Percentages may not add up to 100 due to rounding error. Values for age, weight and serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and ferritin are expressed as mean ± SD. IVDUs: Intravenous drug users; HCV RNA: Hepatitis C virus ribonucleic acid.

Table 2 Treatment *n* (%)	
Treatment data	
Peginterferon α-2a	
Dose: 180 mg	1014 (100)
At least one dose reduction of peginterferon	66 (7)[1]
At least one discontinuation of peginterferon	46 (81)
Ribavirin	
Dose	
800 mg/d	183 (18)
1000 mg/d	413 (41)
1200 mg/d	416 (41)
1400 mg/d	1 (0.1)
At least one dose reduction of ribavirin	66 (7)[1]
At least one discontinuation of ribavirin	56 (89)
Scheduled treatment duration	
24 wk	234 (23)
48 wk	773 (77)

[1]The percentage of patients with dose reduction of peginterferon α-2a and the frequency of patients with dose reduction of ribavirin coincide, but are not exactly the same patients. The frequencies presented correspond to valid percentages. Percentages may not add up to 100 due to rounding error.

with tobacco and alcohol consumption habit was greater in men ($P < 0.001$). The diagnosis of cirrhosis was also more common in men ($P < 0.05$). Intravenous drug abuse as the source of HCV infection was more frequent in men and transfusion was more frequent in women ($P < 0.001$). Among the clinical variables analyzed, there were no differences in baseline viral load level or HCV genotype according to gender, but men had higher ALT, AST and GGT values ($P < 0.001$) and higher levels of ferritin ($P < 0.001$). With regard to ribavirin dose, 800 mg/d and 1000 mg/d were the most common doses given to women, whereas men received the 1200 mg/d dose more frequently ($P < 0.001$).

Peginterferon α-2a plus ribavirin treatment
All patients received 180 μg of peginterferon α-2a. The most frequently used ribavirin doses were 1000 mg/d (41%) and 1200 mg/d (41%) (Table 2). In accordance with current treatment recommendations, the 1000 mg/d and 1200 mg/d doses of ribavirin were used more often for patients with genotype 1/4 (49% and 45% of patients received doses of 1200 and 1000 mg/d, respectively), whereas more than half of those with genotype 2/3 (58%) received 800 mg/d of ribavirin ($P < 0.001$).

In more than three-quarters of patients, the scheduled duration of treatment was 48 wk (Table 2). For 97% of patients with genotype 1/4, the planned treatment duration was 48 wk and in 92% of those with genotype 2/3 the scheduled duration was 24 wk ($P < 0.001$).

Treatment discontinuation and dose reduction
Sixty-six (7%) patients had their peginterferon α-2a dose reduced on at least one occasion. Of these, 46 (81%) patients had only one dose reduction. Similarly, 66 (7%) patients experienced at least one dose reduction of ribavirin. Of these, 56 (89%) patients had at least one dose

were 88.4 ± 69.7 and 73.9 ± 64.4 IU/mL, respectively, and the mean GGT level was 82 ± 91.6 IU/mL. The mean ferritin level was 266 ± 284.8 μg/L. Only 62 (6.2%) patients presented with cirrhosis.

Of the total number of patients, 784 (78%) had genotype 1/4, of which 694 (68%) had genotype 1. The HCV-RNA level was greater than 400 000 IU/mL in 744 (73.8%) patients (Table 1). The proportion of patients

Table 3 Sociodemographics, clinical and pathological characteristics of patients with early virological response and non-early virological response by bivariate analysis n (%)			
Factors	EVR	Non-EVR	P value[1]
Patient sociodemographics			
Age (yr), mean ± SD	43.9 ± 9.7	47.0 ± 10.0	< 0.005
Sex			
Male	602 (86)	101 (14)	NS
Female	264 (89)	33 (11)	
Origin			
Developed country	64 (93)	5 (7)	NS
Developing country	801 (86)	129 (14)	
Race			
Caucasian	836 (87)	130 (14)	NS
Other	24 (89)	3 (11)	
Educational level			
Equivalent to or less than high	537 (86)	85 (14)	NS
Professional training	209 (87)	31 (13)	
University or higher	119 (88)	17 (13)	
Marital status			
Single	235 (85)	41 (15)	NS
Married	491 (86)	81 (14)	
Separated/divorced/widowed	135 (92)	12 (8)	
Family status			
Lives alone	82 (85)	15 (16)	NS
Lives with another person	769 (87)	117 (13)	
Clinical characteristics			
Weight (kg), mean ± SD	75.6 ± 13.4	77.2 ± 13.5	NS
Alcohol consumption			
No	731 (86)	115 (14)	NS
Yes	133 (88)	19 (13)	
Tobacco consumption			
No	414 (85)	75 (15)	NS
Yes	450 (88)	59 (12)	
Source of HCV infection			
Injection drug use	221 (90)	26 (11)	NS
Transfusion	126 (89)	16 (11)	
IV route	79 (87)	12 (13)	
Other	435 (85)	78 (15)	
Methadone replacement therapy			
No	803 (86)	126 (14)	NS
Yes	57 (89)	7 (11)	
ALT (IU/mL), mean ± SD	86.3 ± 69.4	101.7 ± 71.5	< 0.05
AST (IU/mL), mean ± SD	72.1 ± 65.3	84.8 ± 58.5	< 0.05
GGT (IU/mL), mean ± SD	73.6 ± 85.2	134.0 ± 114.4	< 0.001
Ferritin (μg/L), mean ± SD	248.0 ± 268.8	388.8 ± 357.3	< 0.001
Cirrhosis			
No	817 (88)	112 (12)	< 0.001
Yes	41 (67)	20 (33)	
HCV genotype			
1/4	645 (84)	126 (16)	< 0.001
2/3	214 (96)	8 (4)	
HCV-RNA (IU/mL), mean ± SD	3 354 135.6 ± 5 978 359.9	3 781 940.0 ± 4 780 000.6	NS
Baseline viral load			
< 400 000 IU/mL	237 (91)	25 (10)	< 0.05
≥ 400 000 IU/mL	623 (85)	109 (15)	

Data are presented as number (percentage) of patients unless otherwise indicated. Proportions of patients are presented as valid percentages. Values for age, weight, and alanine aminotransferase/aspartate aminotransferase (ALT/AST), gamma glutamyl transferase (GGT) and ferritin are expressed as mean ± SD. [1]P value of bivariate analysis. EVR: early virological response; HCV-RNA: Hepatitis C virus ribonucleic acid; IV route: Intravenous route; NS: Not significant.

reduction before week 12. Only 15 (2%) patients required a dose reduction of both drugs (Table 2).

Early virological response

Of 1014 patients included in the analysis, 866 (87%) achieved an EVR. Of these patients, 699 (70%) had a complete EVR and 176 (18%) achieved a partial EVR. The results showed significant differences in EVR depending on genotype, and the percentage of patients with EVR at week 12 was higher in the group of patients with genotype 2/3 (96% vs 83% of patients with genotype 2/3 and genotype 1/4, respectively; P < 0.001).

Predictive factors of early virological response

Table 3 shows the sociodemographic and clinical characteristics of the early responders (EVR) and non-responders (non-EVR). According to the results obtained from the bivariate analysis, the only sociodemographic variable associated with EVR was age (P < 0.005). The clinical variables associated with EVR were ALT (P < 0.005), AST (P < 0.05) and GGT values (P < 0.001), ferritin levels (P < 0.001), presence of cirrhosis (P < 0.001), viral genotype (P < 0.001), and baseline viral load (P < 0.05).

In the multivariate analysis, the only sociodemographic factor identified as a predictor of EVR was age (OR: 0.543, 95%CI: 0.373-0.790, P < 0.01) and the clinical factors predictive of EVR were GGT level (OR: 3.301, 95%CI: 0.192-0.471, P < 0.001), ferritin level (OR: 0.999, 95%CI: 0.998-0.999, P < 0.01) and genotype (OR: 4.716, 95%CI: 2.010-11.063, P < 0.001). Age ≤ 40 years, GGT level ≤ 85 IU/mL, low ferritin levels and HCV genotype other than 1/4 were independent predictors of EVR (Figure 1).

Adherence to treatment and predictive factors associated with compliance

Treatment compliance was greater than 80% in 971 (97.8%) patients. No significant differences were found between patients with treatment adherence greater than 80% and those whose compliance was less than 80% with regard to their sociodemographic and clinical characteristics (data not shown).

DISCUSSION

The response to treatment with peginterferon plus ribavirin is heterogeneous and non-optimal in several HCV patients, as occurs in those infected with genotype 1, high viral load, advanced fibrosis, metabolic syndrome or non-CC polymorphisms of the interleukin 28b gene (IL28b)[12,13,15,21,22].

EVR is highly predictive of SVR[9,23] and provides hepatologists with a valuable tool to decide on continuation and duration of treatment, as well as providing patients with an additional motivation to adhere to treatment. The predictive value of EVR in patients infected with genotype 1 in the clinical practice setting in Spain[17] was previously shown to be comparable to that obtained in pivotal trials[9,23]. However, although identification of both viral and host factors associated with EVR may be very useful to predict SVR and therefore guide thera-
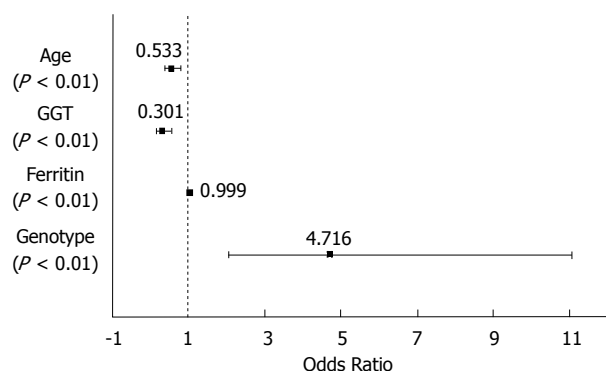
Figure 1 Independent factors associated with an early virologic response according to multiple logistic regression analysis. Baseline demographic factors used in the multiple regression analysis included age (≤ 40 years *vs* > 40 years), gender, race, educational level, marital status and family status. Clinical baseline factors included in the multiple regression analysis were weight, alcohol and tobacco consumption, source of hepatitis C virus (HCV) infection, alanine aminotransferase, aspartate aminotransferase and gamma glutamyl transpeptidase (GGT) levels (≤ 85 *vs* > 85), serum ferritin, serum HCV-RNA concentration (< 400 000 *vs* ≥ 400 000), genotype (1/4 *vs* 3/4), cirrhotic status and ribavirin dose (800/1000/1200 mg/d). An odds ratio equal to 1 (dashed lines) indicates no difference between the subgroups defined according to the given factors. Bars indicate 95%CI. The results demonstrated that age ≤ 40 years (*P* < 0.01), low levels of GGT (≤ 85 IU/L) (*P* < 0.001), low ferritin (*P* < 0.01) and genotype 1/4 (*P* < 0.001) were independent predictors of early virological response.

py[13], to date, there are limited data available addressing this issue.

To our knowledge, the present study is the largest series from a clinical setting to analyze factors associated with EVR in CHC patients treated with peginterferon plus ribavirin under routine clinical practice conditions. The data analysis showed that 87% of patients achieved EVR. This response rate is comparable or even higher than that reported in international pivotal trials with peginterferon α-2a plus ribavirin[9,23] and confirm the results reported in previous studies conducted in Spain, also under routine clinical practice conditions, but with a considerably lower number of patients[17,24]. A complete EVR was observed in 70% of our patients and again this rate was higher than that reported in other previous studies, which ranged from 34% to 64%[9,10,12,25,26].

As expected, the percentage of patients with EVR was higher in the group of patients with genotype 2/3 than in those with genotype 1/4 according to previous studies[9,10,27-29]. However, despite including a high percentage of patients with genotype 1 (the most difficult to cure), our study achieved response rates as high as those in the pivotal trials.

Patients who failed to achieve EVR were older, had higher ALT, AST, GGT and ferritin levels, a more frequent diagnosis of cirrhosis and a higher baseline viral load than patients achieving EVR. Most of the limited available studies on factors associated with EVR have shown that low baseline viral load, younger age, absence of overweight/obesity and lack of cirrhosis are independent factors associated with EVR[30-33]. In our study, age < 40 years, GGT levels < 85 IU/mL, low ferritin levels and

genotype non-1/4 were identified as independent predictive factors of EVR in the multivariate analysis.

Interestingly, a recent study has identified high GGT as a predictor of nonresponse to treatment with peginterferon in patients infected with genotype 1[34]. The precise mechanism whereby increased GGT levels may affect treatment response in CHC remains a matter of debate, although it may be related either to a more intense degree of necroinflammatory activity, more advanced fibrosis, or to hepatic steatosis[35,36]. In this regard, a positive correlation between serum GGT levels and the hepatic expression of proinflammatory tumor necrosis factor-α (TNF-α) mRNA in CHC has been suggested[37]. Indeed, hepatic levels of TNF-α mRNA have been found to be significantly higher in nonresponders to IFN-α-based therapy than in those with a SVR. On the other hand, although the multivariate analysis identified high levels of ferritin as an independent predictor of EVR, this association was clearly irrelevant (OR = 0.999). Therefore, ferritin level may lack clinical validity as a predictive factor of EVR in this setting.

Age was found to be an independent factor for EVR in our study, in agreement with previous series where it was shown that age greater than 40 years is an independent predictor of nonresponse to treatment[12,29,34]. Furthermore, older patients have been suggested to be more resistant to peginterferon-based therapies since they are more frequently infected by HCV genotype 1b, have a longer disease duration and exhibit greater liver damage than younger patients.

Consistent with most published studies[10,12,17,38], our findings show that the proportion of women with CHC treated with peginterferon plus ribavirin in routine practice in Spain is much lower in comparison to the proportion of men, in the absence of demographic variables justifying this difference, or known barriers of access to treatment for women. In addition, women are treated at an older age than men. We can speculate that the lower fibrosis severity as well as the higher rate of normal ALT levels in women with CHC can explain the relatively low proportion of female patients treated in our series. Although in some studies women have shown higher response rates than men[31,38], our data did not show differences in EVR based on gender despite the high proportion of male patients. In light of these results, new epidemiological studies on the prevalence of HCV infection, as well as clinical studies including a larger number of women are needed to determine if there is gender inequality in the prescription of antiviral therapy.

Baseline HCV viral load is a well-known independent predictive factor of treatment response[12,29-31,33]. In agreement with previous evidence, the patients in our study who achieved EVR were those who had lower baseline viral loads (< 400 000 IU/mL), although viral load did not constitute a predictive factor for EVR in the multiple logistic regression analysis.

Race has been identified as a predictive factor of EVR in previous studies[12]. The data from our study, despite its large sample size, does not allow us to conclude

that race plays a role in EVR because the vast majority of patients included in the study were Caucasian (97.3%). Furthermore, when the study was designed, genetic analysis of *IL28b* gene polymorphisms, which are related to race[21], was not available. Indeed, one limitation of our study is the lack of information on IL-28B genotype as it has been described as a relevant predictor of treatment response[39,40]. However, the impact of the imbalance of this genetic polymorphism between groups on treatment response was described just after the data from this study were collected.

Our study also revealed that Spanish CHC patients treated in routine clinical practice receive the correct doses of each drug according to current treatment guidelines, and this is critical since both dose optimization and treatment duration are essential to maximize response[17]. The treatment regimen is individualized, according to current guideline recommendations, based on the viral genotype, so that patients with genotype 1/4 are treated with ribavirin in weight-adjusted doses of 1000-1200 mg/d for 48 wk, whereas patients carrying genotypes 2/3 are treated in most cases with ribavirin at a dose of 800 mg/d for 24 wk.

Combination therapy frequently causes adverse effects. Most are mild and controlled by reducing the dose of each drug or with additional treatments including growth factors, but in some cases they require discontinuation of treatment. Various studies have shown that dose reductions and particularly treatment discontinuation are associated with a marked reduction in the EVR rate[20]. Other reports have noted that dose reductions of peginterferon and/or ribavirin are quite frequent during the first 12 wk of treatment[13]. However, in the current analysis, only 7% of patients required dose reduction of peginterferon or ribavirin. Moreover, it should be noted that only 7 patients of the total population analyzed discontinued treatment due to serious adverse effects in the first 12 wk. This percentage (less than 1%) is markedly lower than that reported in other studies[11,41].

Treatment compliance is a variable closely related to EVR[13,19,20]. It has been shown that lack of adherence during the first 12 wk of treatment has a negative impact on EVR. Previous studies have demonstrated that patients who met the 80/80/80 rule have a greater response than those receiving lower doses or for less time[20]. In our series, 98% of patients met the 80/80/80 rule up to week 12. Good treatment compliance is one of the factors explaining the high rate of EVR seen in our study. Treatment modifications and the motivation of patients may have had a significant impact on adherence to treatment. The low dose reductions required for both drugs could have encouraged patients to complete the prescribed course of treatment. Additionally, determination of EVR provides patients and physicians with an early goal and motivates them to adhere to treatment recommendations. Moreover, it is noteworthy that patients were treated by hepatologists belonging to units with wide experience in the care of CHC patients.

The main limitations of this study arise from the oc-currence of the major advance in CHC in the last years, the development of DAAs and the recent approval of the triple therapy as the new SOC for CHC. Nevertheless, despite the obvious change in treatment paradigm, therapy based on peginterferon plus ribavirin will continue to play an important role as SOC, especially for non-1 HCV patients, considering that protease inhibitors must be combined with peginterferon plus ribavirin in genotype 1 patients. In addition, while remarkably effective, the recently approved protease inhibitors are also accompanied by frequent serious toxicities and considerable costs. Therefore, some patients who cannot tolerate protease inhibitors will need to be treated with dual combination given that triple combination regimens have a higher side effect burden[3,42,43]. Additionally, the high cost of the DAAs will probably preclude the use of triple-combination therapies in health care systems constrained by rising costs and economically disadvantaged regions. It is well known that patients with rapid virological response to dual combination achieve SVR in higher rates, close to 90%, and therefore, despite the above limitations, our findings may be relevant and applicable at the onset of the DAAs era. Furthermore, our findings provide a meaningful assessment of factors associated with EVR regarding applicability to guide therapy of real-world patients given that our study population comprises a larger, more representative cohort of patients than those included in clinical trials evaluating predictive factors of EVR. However, further studies will be needed to validate whether the predictive factors of EVR to dual therapy remain a predictive tool in the context of new DAA agents in the routine clinical practice setting.

In summary, CHC patients treated with peginterferon α-2a plus ribavirin in routine clinical practice in Spain have high EVR rates, similar to those obtained in pivotal studies, and a high level of treatment compliance. Age > 40 years, genotype 1/4 and GGT $\geqslant$ 85 IU/mL were independent predictive factors of lack of EVR. In the new era of hepatitis C treatment where standard treatment is incorporated with DAAs, identification of predictive factors such as the new definitions of extended rapid viral response will be an essential tool to achieve maximum response rates.

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COMMENTS

Background

Peginterferon plus ribavirin is the standard therapy for chronic hepatitis C (CHC) world-wide. Early virological response (EVR) predicts sustained virological response (SVR) in CHC. Although identification of both viral and host factors associated with EVR may be very useful to predict SVR and therefore guide therapy, to date, there are limited data available addressing this issue in clinical practice.

Research frontiers

The high negative predictive value of EVR has remarkable value in clinical practice since it allows to decide whether to continue or discontinue treatment at week 12, therefore preventing or minimizing the adverse effects related to treatment continuation. Indeed, current treatment guidelines for hepatitis CHC include this decision criterion and recommend discontinuing treatment in patients who fail to achieve an EVR.

Innovations and breakthroughs

The present study is the largest series from a clinical setting to analyze predictive factors of EVR in CHC patients treated with peginterferon α-2a plus ribavirin in routine clinical practice. The remarkably high EVR rates obtained in our study were similar to those reported with this dual therapy in pivotal studies, and confirm the data from previous studies in clinical practice in Spain which included a significantly lower number of patients. Age > 40 years, genotype 1/4 and gamma glutamyl transpeptidase (GGT) $\geqslant$ 85 IU/mL were identified as independent predictive factors of lack of EVR.

Applications

The results from this study may be useful in guiding treatment decision making. In particular, early prediction of virological response to dual therapy can help to identify candidates who are unlikely to have a SVR before treatment initiation or in the early treatment phase.

Terminology

EVR indicates EVR which is defined as undetectable hepatitis C virus ribonucleic acid (HCV-RNA) or $\geqslant$ 2 log decrease in HCV-RNA after 12 wk of treatment.

Peer review

This study is well constructed and it is based in a big CHC patient cohort coming from 91 hospitals through all Spanish territory. This is an interesting and relevant study which confirms the results of previous studies with a notably lower number of Spanish cases. Moreover, this study consolidates some basal factors such a GGT levels, age or viral genotype as predictive factors of EVR. This study also highlights the higher rate of ERV in Spain compared with other regions.

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