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ORIGINAL ARTICLE

Safety and efficacy of triple therapy with peginterferon, ribavirin and boceprevir within an early access programme in Spanish patients with hepatitis C genotype 1 with severe fibrosis: SVRw12 analysis

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Abstract

Background & Aims: The addition of protease inhibitors (PIs) changed the hepatitis C virus (HCV) treatment standards and improved sustained viral response (SVR) rates in patients with genotype 1 HCV infection. *Methods:* Prospective, multicentre, national registry that includes naïve and treatment-experienced patients with HCV genotype 1 infection, who had bridging fibrosis or cirrhosis and were treated with triple therapy (peginterferon alfa-2a or alfa-2b, ribavirin and boceprevir) as compassionate use, and in accordance with the Summary of Product Characteristics. *Results:* Most of the patients (68.2%) were male, with a mean age of 53 years, 75% (n = 128) had HCV 1b genotype and baseline viral load of 6.2 log. According to prior treatment, 20% of patients were treatment-naïve and 80% had received prior treatment. Approximately 36.5% of patients (n = 62) reported at least one serious adverse events (SAEs) (total SAEs = 103). The most common SAEs were neutropenia (57.6%), anaemia (47.6%) and grade 3 thrombopenia (25.9%). Patients with albumin <3.5 g/dl and bilirubin >2 mg/dl had an increased relative risk (greater than one-fold) for SAEs, including infections and hepatic decompensation. In the intent-to-treat analysis (n = 170), the overall percentage of patients with SVRw12 was 46.5%. In patients with 1 log decrease at week 4 (lead-in phase), the overall SVRw12 rate was 67.0%. In the patients initiating triple therapy with boceprevir (n = 139), the global response rate was 56.4%. In a multivariate analysis, an increased probability of achieving SVR was associated with response to prior treatment (relapsers),

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>1 log decrease in viral load in the lead-in phase and baseline albumin >3.5 g/dl. *Conclusions:* Triple therapy in patients with severe fibrosis/cirrhosis is associated with a higher rate of SAE and a lower rate in comparison with patients with mild disease. However, for patients with intact liver function, it could be considered as a treatment option, when other alternatives would not be available.

The natural course of an untreated or unsuccessfully treated chronic hepatitis C virus (HCV) infection leads to the development of liver fibrosis, which may progress to cirrhosis, severe liver failure, hepatocellular carcinoma or death (1). The rate of progression to cirrhosis is variable, and is influenced by several factors, such as alcohol consumption, age at the time of HCV infection, degree of liver fibrosis, HCV genotype, coinfection with human immunodeficiency virus and hepatitis B virus and other comorbid conditions. Liver disease because of HCV infection and its complications are the most common indication for liver transplantation (1).

Prior to 2011, the standard of care treatment for HCV infection was the combination of pegylated interferon alfa and ribavirin (PegIFN/RBV). This combination is known to have limited efficacy in the treatment of genotype 1 HCV infection (with SVR rates as little as 5% in null responders and approximately 45%, in treatment naïve patients) and it is associated with considerable side effects [fatigue, influenza-like symptoms, gastrointestinal disturbances, neuropsychiatric symptoms and haematologic abnormalities (3)], which are burdensome for patients and may be treatment-limiting, require dose reduction or drug discontinuation.

The approval of the first generation protease inhibitors (PIs) in 2011, telaprevir and boceprevir, changed the standards of treatment for HCV genotype 1 infection from dual to triple therapy. Both PIs are inhibitors of the NS3/4A protease, a viral enzyme that has an important role in viral replication, and their addition to PegIFN/RBV, has resulted in an improvement in SVR rates, in comparison with published data for PegIFN/RBV (4). This improvement in SVR rates has been observed for treatment-naïve, as well as treatment-experienced patients with HCV genotype 1 infection, with a SVR rate gain ranging between 29% (in prior null responders) and 88% (in prior relapsers) (2, 5).

In terms of safety, the efficacy of the triple therapy is paired with an increased incidence of adverse events (AEs). PIs have been associated with skin rash [more frequently reported for telaprevir, up to 5% of which could be severe (6)], anaemia (reported for both first generation PIs) and gastrointestinal symptoms (7). This makes it necessary to conduct a more in-depth assessment and closer follow-up of the patients being treated. At the time of their initial authorization, the safety profile of the first generation PIs was considered reasonable in the selected population included in the clinical studies. As their use is increasingly wide spread, real clinical setting data will further confirm or disprove that fact.

The introduction of new drugs, from authorization into daily clinical practice, is a process that can be lengthy and it could delay the access to the new drugs for patients with an urgent need for treatment. In the light of a potential delay of the access to PIs treatment, the Spanish Medicine Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*), authorised an early access programme for boceprevir in patients with HCV infection and severe fibrosis (8). This compassionate use programme generated a safety registry to monitor the safety profile of boceprevir, as part of a triple therapy regimen. The analysis of the results obtained at 12 weeks after the planned end of treatment is presented in this article. Safety as well as efficacy results have been included.

Patient and methods

Patients

The Spanish compassionate registry is a prospective, multicentre, national registry which includes patients with HCV genotype 1 infection, both naïve and treatment-experienced, who had severe fibrosis (F3 bridging fibrosis – F4 cirrhosis) and were treated with PegIFN (alfa-2a or alfa-2b), ribavirin and boceprevir as part of the Spanish early access programme. In addition to these requirements, to be eligible for initiating triple therapy with boceprevir, patients had to have haemoglobin levels within the normal range (>12 g/dl for females, >13 g/dl for males) and compensated liver disease, with Child–Pugh class A.

The diagnosis of liver fibrosis was established by non-invasive test (Firbroscan®; Echosens, Paris, France) or liver biopsy, according to local clinical practice. For the majority of the patients, Fibroscan® (Echosens) was used. The cut-off values to establish de degree of fibrosis were the following: patients with Fibroscan <7.6 kPa were considered to have mild-moderate fibrosis; patients with Fibroscan between 7.6 and <9.5 kPa were considered to have significant fibrosis; and patients with a Fibroscan test ≥9.5 kPa were considered to have severe fibrosis.

For those few patients with a recent liver biopsy, available Pathology reports were used. Because of the observational nature of the registry, no tests out of the usual clinical practice were performed to establish the diagnosis of liver fibrosis.

As part of the early access programme and according to national normative, all patients were informed prior

to their inclusion in the safety registry and their oral consent was recorded in their clinical medical history. Authorization from the competent Research Ethics Committee was obtained to collect and analyse the data. All data were reviewed by a trained clinical monitor.

To determine the adequate course of treatment, the patients were also classified according to their treatment status into: treatment naïve (those who had not received any prior anti-HCV treatment) or patients previously treated with PegIFN/RBV, who were further classified into relapsers, partial responders or null responders. For those patients without information on their prior response ($n = 7$), the worst case scenario would be assumed, and null responder recommendations were applied to them, following the same criteria applied in the boceprevir pivotal trials.

Objectives

The aim of this registry is to report the safety and efficacy profiles of the triple therapy with boceprevir in combination with PegIFN/RBV in patients with genotype 1 HCV infection and severe fibrosis, in the context of the compassionate use programme and following clinical practice recommendations for the use of boceprevir.

Treatments

Treatment was prescribed according to the Summary of the Product Characteristics of each of the anti-HCV drugs, including boceprevir.

Safety assessments

Adverse events data were collected on all patients during their treatment period and during their follow-up until the 12th week after the planned end of treatment. These data included clinical and laboratory grade 3 or 4 AEs, serious adverse events (SAEs), and special interest events, such as grade 2 or higher anaemia events, infections, hepatic decompensation and other cytopenias.

Standard definitions for AEs and SAEs were used. A SAE was defined as an event that resulted in death, considered a life-threatening event, led to a hospital admission, prolonged an existing hospital stay or it was considered as a SAE at the treating physician′s discretion. Hepatic decompensation was defined as the presence of ascites, upper gastrointestinal haemorrhage (because of oesophageal varices) or liver encephalopathy.

The management of the anaemia events was left to the discretion of the investigators. Overall, these events were managed following local practice, either by reducing the dose of ribavirin or by the administration of haematopoietic growth factors (erythropoietin). The use of other growth factors needed to manage other cytopenias, such as neutropenia or thrombocytopenia, was also collected.

The following factors were assessed for a potential relationship with safety events: age (>65, >75), gender (female/male), baseline MELD score (>10), degree of fibrosis (F3/F4), oesophageal varices (presence/abscence), platelet count (<100 000/mm^3, <90 000/mm^3, <80 000/mm^3, <70 000/mm^3), serum albumin (<3.5 g/dl), bilirubin level (>1.2 mg/dl, >1.5 mg/dl, >2 mg/dl), haemoglobin level (abnormal,), type of pegIFN (alfa 2a/alfa2b) and HCV genotype (1a/1b). The continuous variables were considered in relation to their value in a continuum (numerical continuous scale).

HCV RNA monitoring

HCV RNA levels were measured following clinical practice recommendations at the following time points: baseline, weeks 4, 8, 12, 16, 24, 36 and week 48 of therapy, and 12 and 24 weeks after treatment completion. Validated real-time PCR-based assays were used, either $m2000_{SP}$/$m2000_{RT}$ (Abbott Molecular, Des Moines, IL, USA) with a lower limit of detection of 12 IU/ml; or COBAS AmpliPrep®/COBAS TaqMan (Roche Molecular Systems, Pleasanton, CA, USA) with a lower limit of detection of 15 IU/ml. Testing was performed at each site, following local practice.

The same factors assessed for a relationship with safety events, along with the following factors, were also assessed to evaluate the probability of achieving SVR12: response to prior treatment (relapse/naïve, relapser/partial responders, relapser/null responders), baseline HCV load (>800 000, count as a continuous variable), response to the lead-in phase (response/no response), IL28B polymorphism (CC/non-CC).

Statistical methods

Demographical and baseline characteristics for the patients included in the safety registry have been presented in a descriptive manner, including frequencies, number and percentages for the most relevant baseline characteristics.

To identify predicting factors for severe adverse events, logistic-regression models were used. For each tested covariate, such as infection (grade 3–4), hepatic decompensation (grade 3/4), anaemia (≥grade 2) and other cytopenias, a univariate model was estimated. The threshold values used for the laboratory parameters were based on clinically meaningful values. All covariates that reached statistical significance ($P < 0.05$) in the univariate analysis and a frequency ≥10% were selected to be included in the multivariate step-wise logistic-regression analysis model.

Efficacy analyses were performed on an intent-to-treat basis, using the Fisher's exact test or the Mann–Whitney test for comparisons between independent groups. Wilcox signed-rank test or Pearson's chi-square tests were used for within group comparisons. All the statistical analyses were performed using IBM® SPSS®

(Statistical Package for the Social Sciences) Statistics software, version 18 (IBM® Corporation, Somers, NY, USA).

Results

Patient characteristics

One hundred and seventy adult patients with chronic HCV infection from 35 centres were included in the safety registry. Baseline and demographical characteristics are shown in Table 1.

Over two-thirds (68.2%) of the patients were male, with a mean age of 53 (range 29–76) years, 75% (n = 128) of patients had HCV 1a/1b genotype and baseline viral load of 6.2 log (±0.7).

Overall, almost 80% of the patients had cirrhosis (F4 fibrosis) and 38.2% had oesophageal varices. At baseline, 17% of the patients had platelet levels <90 000 platelets/mm^3; the mean baseline platelet count was 157 722 (range 45 000–466 000). With regard to prior treatment experience, 20% of the patients were treatment-naive and 80% had undergone prior treatment with PegIFN/RBV. According to their response to the prior PegIFN/RBV treatment, 35.3% were prior relapsers, 26.5% were partial responders and 38.2% were null responders.

Table 1. Baseline and demographical characteristics

Patient characteristics (n = 170)	n (%) or mean (range)
Male gender	116 (68.2)
Age, years	53 (29–76)
HCV Genotype 1a/1b	42/128 (25/75)
F4	134 (78.8)
Oesophageal varices	65 (38.2)
Naïve	34 (20.0)
Non-responders	
Relapser	48 (35.3)
Partial responder	36 (26.5)
Null responder	52 (38.2)
IL28B*	
CC	13 (15.9)
CT	45 (54.9)
TT	24 (29.3)
Baseline RNA HCV (log_{10} IU/ml)	6.2 log (0.7)
>800 000	120 (70.6)
Neutrophil count ×1000/mm^3	3.2 (0.8–9.8)
Haemoglobin level g/dl	15.1 (19.5–10.0)
Platelets count/mm^3	157 722 (45 000–466 000)
<100 000 platelets	37 (22)
<90 000 platelets	29 (17)
<50 000 platelets	1 (0.6)
ALT IU/L (SD)	109 (74)
Total bilirubin mg/dl	0.94 (0.26–3.80)
>2 mg/dl	3%
Serum albumin g/dl	4.16 (3.20–5.30)
<3.5 g/dl	9.4%
INR ratio	1.06 (0.84–1.33)

*Baseline ILB28 data were only available for 82 patients (48.2% of the overall population).

ALT, alanine aminotransferase; HCV, hepatitis C virus; INR, international normalized ratio.

Adverse events

The overall safety profile for HCV triple therapy with boceprevir in our registry, up to 12 weeks after the planned end of treatment, is presented in Table 2.

Incidence of SAEs

Sixty-two patients (36.5%) developed at least one serious adverse event (total number of SAEs reported = 103). SAEs led to early treatment termination in 15 patients (8.8%), being the second most frequent reason for premature discontinuation, following virological failure (23.5%).

Deaths and severe events

Two (1.18%) deaths have been reported in the registry. Both deaths occurred in relation to severe infection, one patient died because of septic shock and the second patient died because of multi-organ failure, secondary to pneumonia. Also, both deaths occurred between weeks 4 and 8 of triple therapy. Data on the microbiological causal agents were not available on either case.

Other frequent severe events included infections (30%) and hepatic decompensations (5.9%). Grade 3–4 infections were reported in 17 (10%) patients.

Table 2. Frequency of serious adverse events (SAEs)

Patients n (% patients with at least one event)	Week 12 after the planned end of treatment (n = 170)
SAEs	62 (36.5%)
Premature discontinuation	62 (36.5%)
Because of SAEs	15 (8.8%)
Lost to follow-up	7 (4.1%)
Virological failure	40 (23.5%)
Dose modification (PegIFN)	40 (23.5%)
Infection/grade 3/4 infection	51 (30.0%)/17 (10.0%)
Hepatic decompensation (grade 3/4)	10 (5.9%)
Anaemia	
Hg < 10.0 g/dl	81 (47.6%)
Hb < 8.0 g/dl	8 (4.7%)
EPO use	46 (27.1%)
Blood transfusion	12 (7.6%)
Ribavirin dose adjustment	84 (49.4%)
Neutropenia	
N < 1000/mm^3	98 (57.6%)
N < 500/mm^3	12 (7.1%)
Use of G-CSF	6 (3.5%)
Thrombopenia/mm^3	
Platelets <50 000	44 (25.9%)
Platelets <25 000	7 (4.1%)
Death septic shock. Multi-organ failure secondary to pneumonia	2 (1.18%)

Fifteen severe events of hepatic decompensation were reported in 10 (5.9%) patients: 11 events of hydropic decompensation, three events of encephalopathy and one event of upper gastrointestinal haemorrhage.

Anaemia

The overall incidence of anaemia (Hb < 10.0 g/dl) was 47.6% ($n = 81$), and 4.7% ($n = 8$) of Hb < 8.5 g/dl. These events ($n = 84$) were mostly managed by adjusting the dose of RBV (49.4%), followed by the use of haematological growth factors (EPO) (27.1% of the events). Only 12 patients (7.6%) required a blood transfusion for the management of their anaemia. The mean number of blood transfusions used per patient was 3.6. Seven patients received >2 red blood cells concentrates.

The median treatment duration with haematological growth factors was 10 weeks (1–30 weeks), with an average dose of 40 000 IU once-weekly (10 000–60 000 IU) for epoetin alfa and 90 mcg once-weekly (30–150) for darbepoetin alfa. The use of haematological growth factors occurred more frequently in the first 12 weeks of treatment with triple therapy (60% of the use of EPO).

Regarding the dose adjustments for RBV, in 43% of patients, who required a reduction in RBV the dose decrease started in the first 12 weeks of treatment with triple therapy. For 16% of patients, the dose decrease was performed during the lead-in phase. In 15 patients the dose reductions reached until 400 mg/day.

Other cytopenias

Neutrophil counts <1000/mm^3 were reported in 98 (57.6%) patients, 12 (7.1%) of which had neutrophil levels <500/mm^3. Granulocyte growth factors were used in six (3.2%) patients to manage their neutropenia.

Grade 3 thrombopenia (platelet counts <50 000/mm^3) was reported in 44 patients (25.9%), while 4.1% of the patients ($n = 7$) had platelet levels <25 000/mm^3. Platelet growth factors were not used in any of the patients to manage their thrombopenia. Their management was done following local clinical practice, by adjusting PegIFN doses (23.5%, $n = 40$).

Factors associated with severe adverse events

The univariate and multivariate analyses for factors associated with SAEs are shown in Table 3.

In the univariate analysis, the presence of serum albumin levels <3.5 g/dl was identified as a predicting factor for SAEs (five-fold risk increase). When analysed as separate factors, similar figures were observed for serious infections (six-fold increase), hepatic decompensation (almost 10-fold increase) and grade 4–5 thrombopenia (four-fold increase). An increased risk (greater than three-fold) for SAEs, infections and hepatic decompensation, was also identified for the association of serum albumin <3.5 g/dl and/or bilirubin >2 mg/dl.

Regarding the development of cytopenias during treatment and their association with cytopenia-related SAEs, only the association of liver decompensation and on-treatment thrombocytopenia (<50 000/mm^3) reached statistical significance [OR: 4.82, 95% CI (1.29–17.96), $P = 0.03$].

An association between anaemia and the development of anaemia-related complications, such as haemodynamic or cardiovascular complications, was not observed.

For the multivariate step-wise logistic-regression analysis, statistically significant events with a frequency ≥10% were selected to be included. In this analysis, baseline serum albumin levels <3.5 g/dl was confirmed as a predicting factor for SAEs.

Efficacy

In the intent-to-treat analysis (ITT; $n = 170$), the overall percentage of patients with SVRw12 was 46.5%. Based on their prior treatment experience, SVR rates were: 41.2% for treatment-naïve patients, 75.0% for relapsers, 47.2% for partial responders and 23.1% for null responders (Fig. 1). The percentage of patients achieving undetectable viral load during the course of time is shown in Fig. 2.

For the patients who initiated triple therapy with boceprevir ($n = 139$), the global SVR was 56.4%. In this per-protocol (PP) analysis, response rates were: 43.8% for treatment-naïve patients ($n = 14$), 78.3% for relapsers ($n = 36$), 58.6% for partial responders ($n = 17$) and 36.4% for null responders ($n = 12$).

A total of 31 patients did not start triple therapy. The most common reason for not initiating triple therapy with boceprevir was lack of response to the lead-in phase ($n = 24$, 77.4%), followed by withdrawal because of an AE ($n = 5$, 16.1%) and patient's decision ($n = 2$, 6.5%).

According to the response to the lead-in phase (Fig. 3), in patients with 1 log decrease at week 4 [lead-in phase ($n = 100$)], the overall rate of SVRw12 was 67.0%; SVR rates in the different treatment subgroups were: 47.6% for treatment naïve patients, 85% for relapsers, 66.7% for partial responders and 52.4% for null responders.

Higher HCV RNA log decreases at week 4 were associated with increasingly higher SVRw12 rates: 79.3% (in 58 patients with 2-log decrease), 83.9% (in 31 patients with 3 log decrease) and up to 100% of patients with a 4 log decrease ($n = 15$) achieved SVRw12.

Of the patients with undetectable HCV RNA values at the end of the lead-in phase ($n = 12$), 91.7% achieved SVRw12, while only 51.2% of the patients with detectable HCV values ($n = 127$) achieved SVRw12.

A total of 39 patients did not achieve 1 log decrease at week 4 and initiated triple therapy. It needs to be

Table 3. Analyses of factors related to serious adverse events (SAEs)

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Factors related to SAEs $n = 62$ (36.5%)						
Age (years)						
Continuous variable		1.105–6.543	0.005			
Platelet count/mm^3						
Continuous variable		−44.81 to −2543.65	0.028			
Serum albumin (g/dl)						
<3.5	6.405	1.638–25.050	0.003	5.208	1.294–20.958	0.020
Continuous variable		−0.3654, −0.0443	0.013			
Haemoglobin level (g/dl) (abnormal)						
<12 (female) <13 (male)	2.862	2.326–3.522	0.008			
Factors related to infections grade 3/4 $n = 17$ (10.0%)						
Serum albumin (g/dl)						
<3.5	6.750	1.667–37.336	0.003	5.980	1.35–26.37	0.018
Continuous variable		0.502–0.544	0.019			
Bilirubin (mg/dl)						
>2	6.905	1.063.44.862	0.021	19.127	1.38–264.4	0.028
Haemoglobin level (g/dl)						
Continuous variable		0.018–1.501	0.045			
Factors related to hepatic decompensation $n = 10$ (5.9%)						
Oesophageal varices						
Presence	4.433	1.068–18.395	0.029			
Serum albumin (g/dl)						
<3.5	11.100	2.482–49.638	0.0001	7.558	1.53–37.19	0.013
Haemoglobin level (g/dl)						
Continuous variable		1.070–2.868	0.0001			
Haemoglobin level (g/dl) (abnormal)						
<12 (female) <13 (male)	0.051	0.006–0.407	0.0001			
Factors related to anaemia (haemoglobin level <10) $n = 81$ (47.6%)						
Age (years)						
Continuous variable		−7.707 to −2.522	0.0001	1.057	1.01–1.101	0.008
Gender						
Female/male	3.550	1.792–7.092	0.0001	2.558	1.23–5.306	0.012
Genotype						
1a/1b	2.924	1.375–6.216	0.004			
Platelet count/mm^3						
<80 000	0.279	0.098–0.795	0.012			
Bilirubin (mg/dl)						
>1.2	0.423	0.200–0.896	0.023			
Haemoglobin level (g/dl)						
Continuous variable		0.619–1.454	0.0001			
Haemoglobin level (g/dl) (abnormal)						
<12 (female) <13 (male)	2.156	1.831–2.539	0.034			

noted that the registry took place under 'real-life' conditions; therefore, initiation of treatment in these patients was done at their treating physicians' discretion.

In this subgroup of patients, nine (23.1%) had F3 fibrosis and 30 (76.9%) had F4-cirrhosis. According to their prior response to treatment, 10 (25.6%) were treatment naïve, 11 (28.2%) were partial responders, 12 (30.8%) were null responders and six (15.4%) were relapsers. Only 30.8% ($n = 12$) of these patients achieved SVRw12 (52.6% of patients with >0.5 < 1 log decrease achieved SVR and only 10% with < 0.5 log decrease achieved SVR).

When analysing SVR rates according to the response to the lead-in phase, the differences between the groups with ($n = 100$, SVR 67%) and without ($n = 36$, SVR12) a lead-in response were statistically significant [OR: 4.57, 95% CI (2.06–10.14), $P = 0.001$).

In patients with a good lead-in response, 86.4% (19/22) patients with F3-fibrosis and 61.5% (30/48) patients

with F4-cirrhosis achieved SVR. This difference was statistically significant [OR: 0.252, 95% CI (0.068–0.927), $P = 0.0287$].

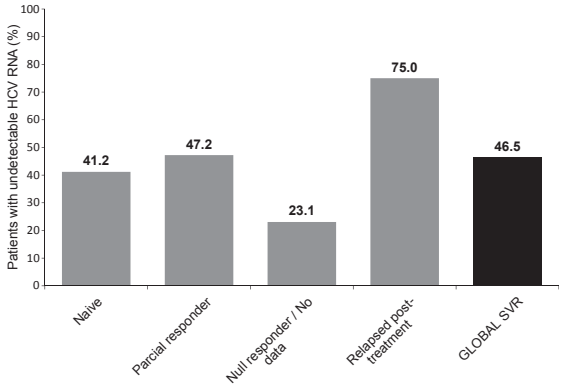

Fig. 1. SVRw12 intent-to-treat analysis ($n = 170$).

For patients with F4 fibrosis and a poor lead-in response and who initiated triple therapy ($n = 30$), the SVR rates were 13.3% for those with <0.5 log decrease and 53.3% for those with >0.5 and <1 log decrease. This difference was statistically significant [OR: 7.43, 95% CI (1.23–4501), $P = 0.0201$]. In this group, statistically significant differences according to the degree of fibrosis were not observed. Although the patient number was small, these findings are in line with those from the boceprevir pivotal trials.

SVR results based on HCV RNA values at week 8 (lead-in phase, plus 4 weeks of treatment) are shown in Fig. 4. The SVR rates in patients with undetectable viral load ($n = 70$) at week 8 was 72.3%. Among patients with a detectable viral load at week 8 ($n = 60$), the SVR for those who achieving a 3 log decrease ($n = 54$) was 41%%, will none of the subjects without a 3 log decline ($n = 6$) achieved SVR (0%).

The most frequent reasons for not achieving SVR in the ITT population (Fig. 5) were meeting a virological

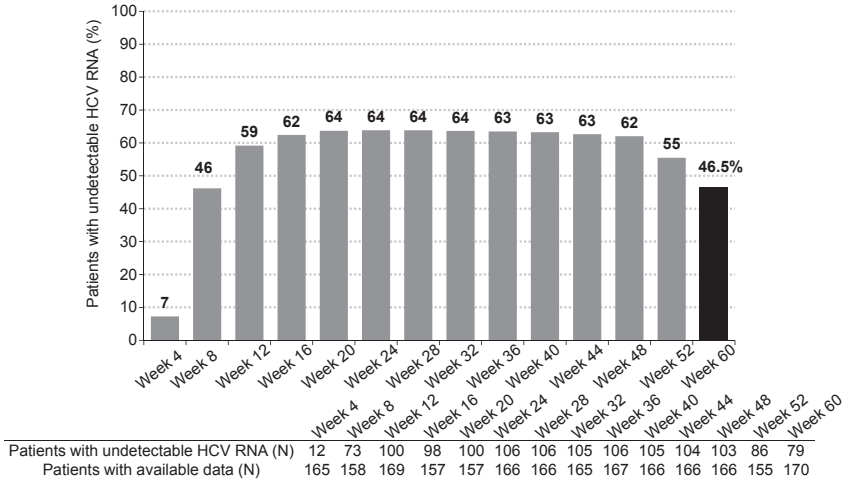

Fig. 2. Virological response across time ($n = 170$).

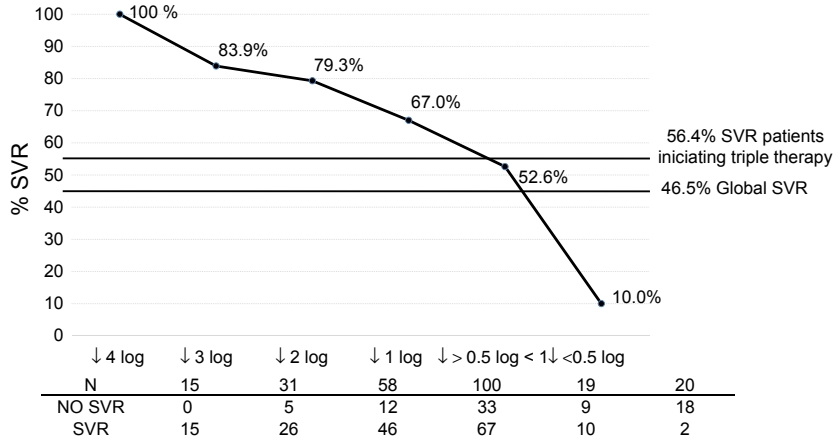

Fig. 3. SVR according to viral decline in the lead-in phase.

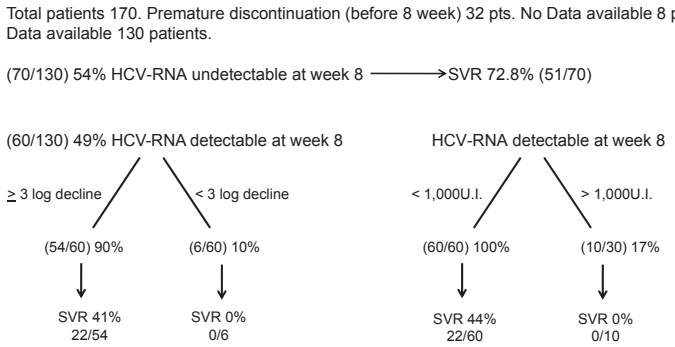

Fig. 4. SVR according to viral response at week 8 (n = 130).

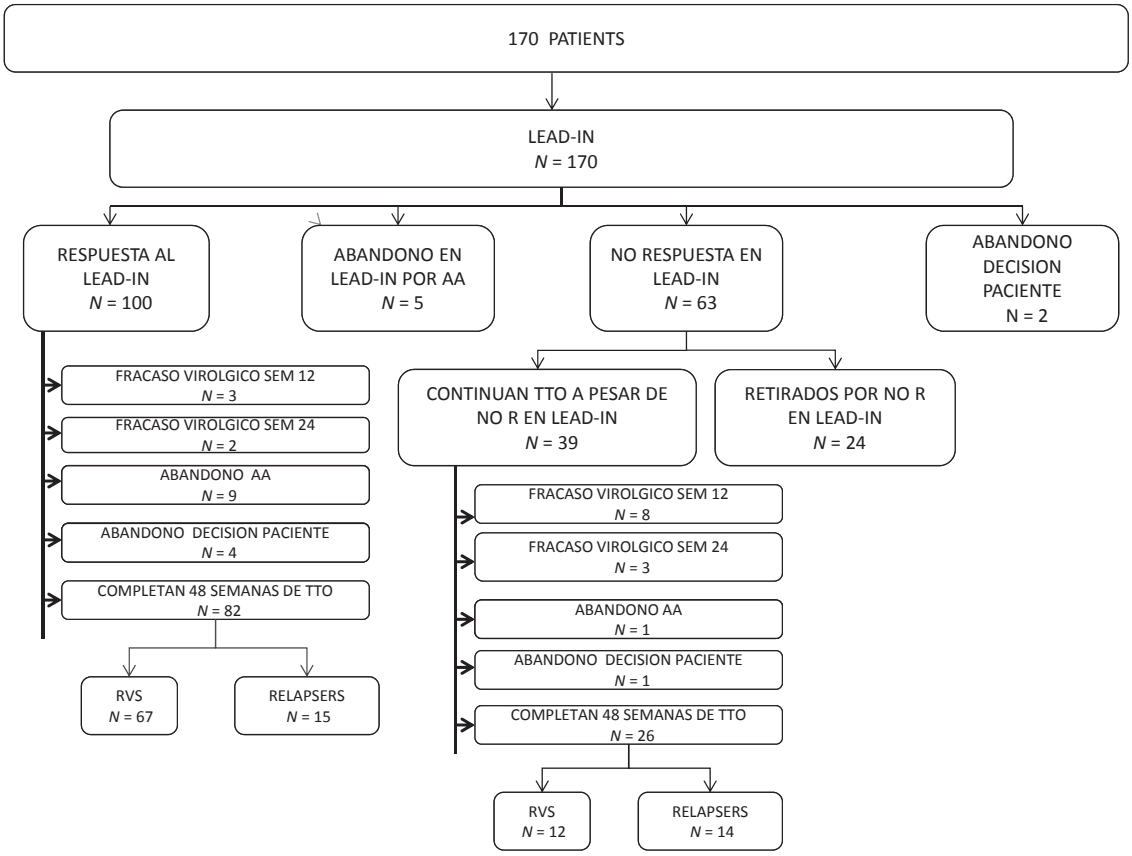

Fig. 5. Patient flow.

stopping rule (38.5%), virological relapse (31.9%), adverse event (16.5%), patient's decision (7.7%) and viral breakthrough (5.5%).

The univariate and multivariate analyses for factors related to SVR is shown in Table 4. The univariate analysis identified the following factors associated with SVR: age, response to lead-in phase, status based on prior response to treatment, platelet count bilirubin level, ILB28 subtype CC and serum albumin. The multivariate analysis further confirmed that the response to lead-in phase, status based on prior response to treatment and serum albumin were associated with SVR. The potential impact on SVR rates of RBV/PegIFN dose adjustments, history of previous decompensation and baseline Fibroscan results were also explored. Only RBV dose adjustments showed to have a statistically significant effect in SVR rates. A total of 84 (49.4%) patients required a RBV dose adjustment. Of these, 58.3% (n = 49) achieved SVR, compared with only 34.9% (30/86) of patient who did not require a RBV dose modifi-

Table 4. Analyses of factors related to sustained virological response (SVRw12)

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Factors related to SVR $n = 79$ (46.5%)						
Age (years)						
<70	1.919	1.658–2.222	0.05			
Response to prior treatments						
Relapse/naïve	4.282	1.660–11.021	0.001	13.264	3.70–47.51	0.0001
Relapse/partial response	3.353	1.331–8.453	0.006			
Relapse/null response	10.001	3.993–25.031	0.0001			
Response to LEAD-IN						
Response/no response	4.434	2.001–9.820	0.0001	4.907	0.03–0.715	0.018
ILB28						
CC/no CC	4.340	1.102–17.243	0.027			
Platelet count/mm^3						
<100 000	0.289	0.127–0.660	0.002			
<90 000	0.305	0.122–0.759	0.008			
<80 000	0.294	0.103–0.839	0.017			
Continuous variable		−45 094.6, −45 094	0.047			
Serum albumin (g/dl)						
<3.5	0.214	0.045–0.976	0.036	12.226	0.68–328.67	0.08
Continuous variable		9.419–44.519	0.003			
AST						
Continuous variable		9.419–44.519	0.003			

cation achieving SVR [OR: 2.613 (1.405–4.680) $P < 0.005$].

Discussion

In the rapidly evolving field of HCV therapeutics, treatment options are being added very fast. However, the availability date for the IFN-free regimens remains unknown and possible delays in the access to the new approved DAA are foreseen, even in some European countries.

Patients with HCV infection and advanced degree of fibrosis are an unmet medical need and are a patient population that often cannot wait for treatment. Bearing in mind that these patients are also more vulnerable to experiencing adverse events, our real-life conditions registry contributes with a clinically useful characterization of the safety and efficacy profiles of triple therapy with boceprevir.

With regard to safety, in our registry, serum albumin <3.5 g/dl and/or bilirubin >2 mg/dl were identified as predicting factors for SAEs. In general terms, the safety profile observed is less favourable than that previously reported in the RESPOND-2 and SPRINT-2 (2, 4, 5) pivotal studies, with over one-third of our patients reporting at least one SAE, in comparison with 10–12% in the pivotal studies. The incidence of infections/serious infections and hepatic decompensation was also higher in our registry. These findings are not unexpected and they could be explained by several differences noted between the selected population included in the pivotal studies and patients included in our registry.

One possible explanation for these differences is that our patients represent a population with more advanced liver fibrosis than those in the SPRINT-2 and RESPOND-2 studies. In addition to this, patients included in clinical trials must meet strict inclusion criteria and are not necessarily representative of all patients often encountered in clinical practice. For instance, 60% of the patients in our registry met at least one of the exclusion criterion implemented in the pivotal studies, such as baseline cytopenias or being a prior null responder.

In regard to the cirrhotic patients included in the pivotal studies, the safety profile observed was in line with that in patients without cirrhosis. However, these results need to be taken with caution, since data available are limited ($n = 112$).

Recently, results from the French early access programme, the CUPIC study (Compassionate Use of Protease Inhibitors in viral C Cirrhosis), have been published (9). This study included a larger cohort of treatment-experienced patients who did not respond to a prior course with PegIFN/RBV. In general, our safety results are similar to theirs, demonstrating a different safety profile for cirrhotic patients in the clinical setting. The authors identified low albumin levels (<3.5 g/dl) and platelet counts (≤100 000/mm^3) as predicting factors of SAEs. In our case, low serum albumin levels were also identified as a predictor of SAEs, grade 3/4 infections and hepatic decompensations, further supporting the CUPIC data.

In response to the CUPIC results, Carvalho-Filho *et al.* (10). questioned the CUPIC′s conclusions based

on a potential lack of statistical power for the safety analysis and the potential for bias because of multicollinearity of the variables tested in the multivariate models. Further analyses performed by the authors based on the CUPIC's data, confirmed that albumin levels <3.5 g/dl are good predictors for SAE (and deaths), especially in combination with platelet counts ≤100 000/mm^3. However, they concluded that triple therapy with PIs should remain a treatment option for cirrhotic patients below the cut-off when treated by experienced hepatologists. Our results further confirm their conclusions and support the use of triple therapy in patients with intact liver function and a high unmet medical need, but only when other treatment options are not available.

With regard to efficacy, several factors have been identified as predictors of higher SVR rates, such as serum albumin level (>3.5 g/dl), response to previous treatment (relapsers) and response to the lead-in phase. In comparison with the results from the pivotal studies, our SVR rates are lower, but they are generally in line with those from the CUPIC study and slightly higher than the result reported for the Department of Veterans Affair (VA) (11) study, both of them including a large number of cirrhotic patients.

One important difference between our registry and the CUPIC study is the representation of null responders. While 38% of patients in our registry were prior null responders, only 4.4% of these patients were included in the CUPIC study. Keeping in mind that patients with advanced degree of fibrosis/cirrhosis are a hard-to-treat population, the lower response rates in these patients are not unexpected and the implementation of a lead-in phase prior to starting triple therapy is considered an adequate method to identify those patients who may benefit the most from treatment with boceprevir and PegIFN/RBV.

Regarding the VA study, some differences in baseline characteristics with a higher representation of males and African American patients could account for the differences in efficacy results.

The limitations of our study come from the uncontrolled nature of a real practice cohort, since the observed SAE can also be seen in cirrhotic patients without antiviral treatment. However, our registry has allowed us to identify a subgroup of patients (those with serum albumin <3.5 g/dl and bilirubin >2 mg/dl, no response to lead-in phase and prior partial & null responders) who clearly do not benefit from triple therapy with first generation PI, as shown by their lower SVR rates and higher SAE incidence. Nevertheless, our results support the use of triple therapy in patients with intact liver function, when other treatment options are not available or in those locations where newer HCV therapies might not be readily available and a significant delay in the access to treatment could be expected.

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Conflict of interest: JL Calleja has served as a speaker and an advisory board member for MSD, Jannsen, Gilead; ABBvie and BMS. JM Pascasio has served as a speaker and a consultant for Gilead, Bristol-Myers Squibb and Janssen and a speaker for Merck Sharp Dohme and Roche. Belén Ruiz Antorán has served as a consultant for Novartis and Boehringer Ingelheim. F Gea, R Bárcena, Juan Ramón Larrubina, Ramón Pérez Álvarez, JM Sousa, M Romero Gómez, Juan de la Revilla, JM Navarro and JI Arenas declare no conflict of interest in this study. R Solà has served as a speaker, a consultant and an advisory board member for Roche Pharma, Bristol Myers Squibb, Gilead Sciences, Novartis, Roche/Genentech, Tibotec, Jansen and Schering-Plough/Merck. J Crespo has served as a speaker, a consultant and an advisory board member for Abvvie, BMS, Janssen, MSD and Roche. Manuel Delgado has served as a speaker for Merck, Sharp and Dome and Roche. CM Fernández Rodríguez has served as a speaker, a consultant and an advisory board member for MSD, BMS and Abbvie and has received research funding from MSD. Ramon Planas has served as a speaker, a consultant and an advisory board member for MSD, BMS, Roche-Farma, Janssen and Gilead. Maria Butti has served as a speaker and consultant for Janssen. MSD, BI and BMS. Xavier Forns has served as a consultant for Jansen, MSD, Gilead and Roche and has received research funding from Roche and MSD.

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Appendix 1
Participating Centres and the Principal Investigators Belonging to the Spanish Group for the Study of the use of Direct-Acting Drugs Hepatitis C with severe fibrosis

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