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Effectiveness and safety of elbasvir/grazoprevir therapy in patients with chronic HCV infection: Results from the Spanish HEPA-C real-world cohort

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Abbreviations: AE, adverse event; AEEH, Spanish Association for the Study of the Liver; CIBERehd, Networked Biomedical Research Centre for the Study of the Liver and Digestive Diseases in Spain; DAA, direct-acting antiviral; EBR, elbasvir; EMA, European Medicines Agency; EOT, end of treatment; GT, genotype; GZR, grazoprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; IFN, interferon; LDL-C, low-density lipoprotein cholesterol; MDRD-4, Modification of Diet in Renal Disease 4-variable equation; MELD, Model for End-Stage Liver Disease; PR, pegylated interferon plus RBV; RAS, resistance-associated substitution; RBV, ribavirin; SAE, serious adverse event; SVR12, sustained virologic response at 12 weeks post-treatment; TG, triglyceride.

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Summary

In randomized controlled trials of patients with chronic HCV infection, elbasvir/grazoprevir (EBR/GZR) demonstrated high cure rates and a good safety profile. This study assessed the effectiveness and safety of EBR/GZR, with and without ribavirin, in a real-world HCV patient cohort. HEPA-C is a collaborative, monitored national registry of HCV patients directed by the Spanish Association for the Study of the Liver and the Networked Biomedical Research Centre for Hepatic and Digestive Diseases. Patients entered into HEPA-C between December 2016 and May 2017, and treated with EBR/GZR with at least end-of-treatment response data, were included. Demographic, clinical and virologic data were analysed, and adverse events (AEs) recorded. A total of 804 patients were included in the study. The majority were male (57.9%), with a mean age of 60 (range, 19-92) years. Genotype (GT) distribution was GT 1, 86.8% (1a, 14.3%; 1b, 72.5%); GT 4, 13.2% and 176 patients (21.9%) were cirrhotic. Overall, among 588 patients with available data, 570 (96.9%) achieved sustained virologic response at 12 weeks post-treatment (SVR12). SVR12 rates by genotype were GT 1a, 97.7%; GT 1b, 98.6%; and GT 4, 98.1%. No significant differences in SVR12 according to fibrosis stage were observed. Eighty patients experienced an AE, resulting in treatment discontinuation in three. In this large cohort of patients with chronic HCV managed in a real-world setting in Spain, EBR/GZR achieved high rates of SVR12, comparable to those observed in randomized controlled trials, with a similarly good safety profile.

KEYWORDS
chronic hepatitis C, elbasvir/grazoprevir, real-world, Spain

1 | INTRODUCTION

Globally, an estimated 70 million people are chronically infected with the hepatitis C virus (HCV), with approximately 400 000 dying each year from the associated risks of infection, primarily cirrhosis and hepatocellular carcinoma (HCC).[1] Successful treatment results in a sustained virologic response (SVR), which equates with cure of HCV infection, and significantly reduces the risk of HCV-related complications, liver transplantation and death.[2,3] However, achievement of SVR with interferon (IFN)-free direct-acting antiviral (DAA) treatment regimens, as well as IFN-containing regimens, is associated with serum increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C) and plasma triglyceride (TG).[4] Although post-SVR changes in levels seem to be of the same magnitude regardless of the DAA used, significant differences in on-treatment lipid profiles have been observed.[5] The implications of changes in lipid profile on cardiovascular risk in patients infected with HCV are unknown.

In clinical trials, DAAs have achieved rates of SVR above 90%, in many cases above 95%, across all HCV genotypes.[6] Among these trials are those evaluating the efficacy and safety of a once-daily

fixed-dose combination of elbasvir (EBR; 50 mg), an NS5A inhibitor, and grazoprevir (GZR; 100 mg), an NS3/4A protease inhibitor,[7] with or without ribavirin (RBV), in both treatment-naïve[8] and treatment-experienced (±RBV)[9] patients with chronic HCV infection. Based on SVR12 rates of 92%-100%, 99%-100% and 60%-100% in patients infected with HCV genotypes (GTs) 1a, 1b and 4, respectively,[8,9] this treatment regimen was approved by the European Medicines Agency (EMA) for the treatment of HCV GTs 1 and 4 with and without compensated cirrhosis.

In Spain, as in other countries, a significant proportion of those chronically infected with HCV are aged >65 years and have concomitant morbidities, including renal impairment. No dose adjustment of EBR/GZR is required in patients with moderate or severe renal impairment, including those on dialysis. Consequently, EBR/GZR is a recommended DAA regimen in these patients according to both AASLD and EASL guidelines.[6,10]

Although clinical trials have demonstrated the efficacy and safety of EBR/GZR, their highly controlled environment and selected patient populations have the potential to limit the applicability of results to the management of patients in routine clinical practice. Therefore, the objective of this study was to evaluate the clinical effectiveness and safety of EBR/GZR in routine clinical practice in Spain.

2 | MATERIALS AND METHODS

This was a retrospective analysis of data collected prospectively in a collaborative, monitored national registry of HCV patients (HEPA-C) directed by the Spanish Association for the Study of the Liver (AEEH) and the Networked Biomedical Research Centre for the Study of the Liver and Digestive Diseases in Spain (CIBERehd). All registry participants provided written informed consent.

All data recorded between December 2016 and January 2018 in treatment-naïve and treatment-experienced patients chronically infected with HCV and treated with EBR/GZR in 30 Spanish centres were analysed. No other inclusion or exclusion criteria were specified. Depending on treatment duration, patient follow-up ranged from 20 to 28 weeks. The Research Ethics Committee of Hospital Universitario Puerta de Hierro of Majadahonda approved the study in advance [ClinicalTrials.gov Identifier: NCT03111966].

2.1 | Treatment

Treatment decisions relating to the administration of the once-daily fixed-dose combination of EBR (50 mg)/GZR (100 mg), including treatment duration and the use or not of concomitant RBV, were entirely at the discretion of the treating physician based on the clinical characteristics of individual patients.

2.2 | Measurements

Demographic, clinical, virologic and safety data were collected. HCV RNA levels were determined using either the COBAS AmpliPrep®/COBAS TaqMan® (Roche Molecular Systems, Pleasanton, CA, USA; lower limit of detection [LLOD] 15 IU/mL) or the m2000SP/m2000RT (Abbott Molecular, Des Moines, IL, USA; LLOD 12 IU/mL) real-time polymerase chain reaction (PCR)-based assays. Cirrhosis (Fibrosis [F] 4) was defined by a transient elastography score >14 kPa, liver biopsy or clinical evidence of previous liver decompensation. To address the effect of EBR/GZR and subsequent achievement of SVR on lipid metabolism, cholesterol (total cholesterol, high-density lipoprotein [HDL] and LDL) in plasma samples was quantified and the 10-year cardiovascular risk assessed using the Framingham score.[11]

2.3 | Outcomes

Virologic response was defined as undetectable HCV RNA and was determined at end of treatment (EOT) and at Week 12 (SVR12) post-treatment. Virologic failure was defined as detectable HCV RNA at any time during treatment (breakthrough) or post-treatment follow-up. Changes from baseline in markers of lipid metabolism were assessed at Week 12 after treatment. Details of all recorded adverse events (AEs) were collected from the time of first drug administration to Week 12 after the planned EOT. Serious adverse events (SAEs) were defined as any life-threatening event, an event that led to a hospital admission, prolonged an existing hospital stay or resulted in death, or those that were considered serious based on physician judgement. Incident hepatic decompensation was defined as the onset of variceal haemorrhage, ascites and/or portosystemic (hepatic) encephalopathy during treatment. Anaemia was defined as a haemoglobin level <10 g/dL.

2.4 | Statistical methods

Analyses were as described in previous studies from the HEPA-C registry on the effectiveness and safety of other oral DAA combination regimens in patients with HCV GT1[12] or GT 4[13] in routine clinical practice. Briefly, results were analysed using the intent-to-treat (ITT) approach. The chi-squared test, Student's *t* test or the Mann-Whitney test was used to compare efficacy and safety between independent groups, with the Wilcoxon signed-rank test or chi-squared test used for within-group comparisons. The Fisher's exact test was used with frequencies <5%. *P*-values <0.05 were considered statistically significant.

Multivariate stepwise logistic-regression analysis was used to identify any independent continuous and categorical baseline variables (Table 1) predictive of no response or development of AEs. Covariates with $P < 0.05$ in likelihood ratio testing in univariate analysis were included in a multivariate model; covariates with $P < 0.05$ following a backward elimination procedure were considered independent predictors of no response or development of AEs. Computation for the statistical tests was performed with IBM® SPSS® (Statistical Package for the Social Sciences) statistics software, version 23 (IBM® Corporation, Somers, NY, USA).

TABLE 1 Continuous and categorical variables evaluated

Continuous variables	Categorical variables
• Age • Baseline HCV RNA (log_{10} IU/mL) • Elastography score • Model for End-Stage Liver Disease (MELD) score • Haemoglobin • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Creatinine • Modification of Diet in Renal Disease 4-variable equation (MDRD-4) • Bilirubin • Platelet count • Serum albumin • International normalized ratio (INR)	• Age (>65 years) • Treatment group (12 weeks vs 24 weeks) • Ribavirin (yes/no) • HCV subtype (1b vs 1a) • Previous treatment status (naïve/experienced) • Sex (female/male) • Fibrosis stage (cirrhosis/no cirrhosis) • Child-Pugh score (A or B) • History of oesophageal varices (yes/no) • MELD score (>18) • History of previous therapy with proton pump inhibitors (yes/no) • Estimated glomerular filtration rate (eGFR) (<30 mL/min/1.73 m^2) • Bilirubin (>2 mg/dL) • Serum albumin (<3.5 g/dL) • Platelet count (≤70 000/mm^3) • Virologic response at post-treatment Week 4 (yes/no) for no response only

3 | RESULTS

3.1 | Patient population

Data from 804 patients treated with EBR/GZR were analysed. The majority had HCV GT 1b infection 583/804 (72.5%) and 222/804 (27.6%) were relapsers or non-responders to previous antiviral therapy (Table 2). The majority of patients did not have cirrhosis (F0-1, 46.4%; F2, 18.5%; F3, 13.2%). Among those with cirrhosis (F4, 29.1%), 174/176 (98.9%) were Child-Pugh A, 26 (14.6%) had oesophageal varices, nine (5.1%) had experienced decompensation previously, and mean Model for End-Stage Liver Disease (MELD) score was 9.2 (SD 4.2). Most patients received 12 weeks of therapy without concomitant administration of RBV. The majority of the 176 patients with cirrhosis who had available efficacy data received 12 weeks of treatment (93.2%) with 14 (8%) receiving concomitant RBV. Most patients who were non-responders or relapsers to previous therapy received 12 weeks of EBR/GZR (203/222 patients, 91.4%) with 28 patients receiving concomitant RBV (28/222, 12.6%).

3.2 | Clinical effectiveness

A total of 625 patients had 12-week post-treatment data available, of whom 570 (91.2%) achieved SVR12 in the ITT analysis and 570/588 (96.9%) in the modified ITT (mITT) analysis (Figures 1A and B), which excluded 37 patients lost to follow-up. Among those who received 16 weeks of therapy (of which 77.8% were GT 1a), the SVR12 rate was 100%, compared with 98.5% and 80% in those receiving 12 and 8 weeks (all non-cirrhotic), respectively ($P = 0.003$). HCV RNA was undetectable at EOT in 620/631 (98.3%).

SVR12 rates did not vary significantly between genotypes (GT 1a, 97.7%; GT 1b, 98.6%; GT 4, 98.1%) or fibrosis stage (F0-1, 98.7%; F2, 98.2%; F3, 97.4% and F4, 98.5%). In mITT analyses, rates of SVR12 were similar regardless of the presence (141/144; 97.9%) or absence (366/371; 98.7%) of cirrhosis ($P = 0.7$) and the co-administration or not of RBV (35/36 [97.2%] vs 535/545 [98.5%]; $P = 0.4$). SVR rates in treatment-experienced vs treatment-naïve patients were 169/173 (97.7%) vs 378/383 (98.7%); $P = 0.5$. The two Child-Pugh B patients included in the analysis achieved SVR12. Among patients who received 12 weeks of EBR/GZR without RBV, 98.7% (523/530) achieved SVR12 in the mITT analysis. In these patients, no significant difference in SVR12 was observed according to genotype (GT 1a, 96.7% [HCV RNA <800 000 IU/mL: 100% and >800 000 IU/mL: 93.3%], GT 1b, 98.7%; GT 4, 100%), presence (98.4%) or absence (98.8%) of cirrhosis or treatment experience (98.6% in both treatment-naïve and treatment-experienced patients).

Of the 55 patients (8.7%) who did not achieve SVR12, 37 patients (67.3%) were lost to follow-up. All these patients had undetectable viral load at EOT. Of the 18 patients (2.9%) with virologic failure, nine (50%) experienced relapse after completion of treatment, four (22.2%) discontinued treatment voluntarily, three (16.7%) withdrew from treatment due to an AE, and two (11.1%) experienced virologic breakthrough. Among the 11 patients who relapsed or experienced breakthrough, six patients were GT 1b, four patients were GT 1a and one patient was GT 4. Mean viral load was 6.82 (SD 6.75) log_{10} IU/mL and 2/11 patients (18.2%) had cirrhosis. All 11 patients were treated in accordance with the EASL guidelines; eight patients were treated with sofosbuvir/ledipasvir and three patients were treated with sofosbuvir/velpatasvir. All completed treatment. On univariate analysis, duration of treatment was significantly associated with treatment failure ($P < 0.05$) (Table 3). None of the seven patients who discontinued therapy early achieved SVR12 and none received RBV. Among these seven patients, two had Child-Pugh A cirrhosis, three were non-responders to previous therapy, and four were treated for 12 weeks. One patient experienced virologic breakthrough on therapy.

All treatment-experienced GT 4 patients and one-third of GT 1a patients were not treated in accordance with the current EASL clinical practice guideline recommendations.[6] However, cure rates were high

TABLE 2 Baseline characteristics of patients treated with EBR/GZR ± ribavirin

Characteristics	Without cirrhosis (N = 628)[a]	With cirrhosis (N = 176)[a]
Sex, male, n (%)	244 (38.9)	107 (60.8)
Age, years, M (SD)	60 (12.8)	65 (12.9)
HCV genotype, n (%)		
1a	93 (14.8)	22 (12.5)
1b	443 (70.5)	140 (79.5)
4	92 (14.6)	14 (8.0)
Baseline HCV RNA, $\log_{10}$ IU/mL, M (SD)	6.59 (6.84)	6.55 (6.80)
MDRD-4, M (SD)	88.1 (32.5)	89.5 (39.4)
Creatinine, mg/dL, M (SD)	1.4 (4.6)	1.2 (1.3)
Haemoglobin level, g/dL, M (SD)	14.5 (1.9)	13.9 (2.0)
ALT, IU/L, M (SD)	57.9 (44.9)	77.3 (56.9)
AST, IU/L, M (SD)	47.5 (32.1)	77.4 (51.3)
Bilirubin, mg/dL, M (SD)	0.8 (4.0)	0.8 (0.4)
Albumin, g/dL, M (SD)	4.3 (0.4)	4.1 (0.4)
Platelets, /mm^3, M (SD)	212.1 (71.2)	158.5 (63.4)
HDL-C, M (SD)	53.2 (16.4)	55.0 (17.0)
LDL-C, M (SD)	96.0 (30.7)	88.0 (35.1)
T-cholesterol, M (SD)	166.1 (37.1)	168.3 (38.1)
INR, M (SD)	1.1 (0.3)	1.1 (0.4)
HCV antiviral treatment history, n (%)		
Naïve	443 (70.5)	139 (79.0)
Previous treatment[b]	185 (29.5)	37 (21.0)
First generation of protease inhibitor	49 (7.8)	11 (6.3)
Treatment regimen, n (%)		
EBR/GZR for 8 weeks	7 (1.1)	1 (0.6)
EBR/GZR for 12 weeks	595 (94.7)	164 (93.2)
EBR/GZR for 16 weeks	25 (4.0)	11 (6.3)
RBV	32 (5.1)	14 (8.0)

[a]Not all patients had available data for all parameters.
[b]Includes PEG-IFN + RBV and older generation protease inhibitors.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBR, elbasvir; GZR, grazoprevir; HDL-C, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; MDRD-4, Modification of Diet in Renal Disease 4-variable equation; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; SD, standard deviation.

(Figure 2); in GT 1a patients, SVR12 was achieved in 100% and 98.3% of patients with or without cirrhosis, respectively. Corresponding SVR rates in GT 4 patients were 100% and 90%, respectively.

3.3 | Safety and tolerability

Eighty AEs were reported (Table 4), resulting in treatment discontinuation in three patients (psychiatric event, headache and rash). The most commonly reported SAEs were gastrointestinal symptoms and anaemia. The latter occurred only in patients receiving RBV. Four patients died during treatment or follow-up (two with liver cirrhosis) and one had incident hepatic decompensation (Table 4). No clinically relevant changes in serum levels of albumin or rates of creatinine clearance were observed. Anaemia was resolved by reducing dose of RBV.

In multivariate analyses, worse creatinine clearance as measured by the Modification of Diet in Renal Disease 4-variable equation (MDRD-4) was associated with a decreased probability of experiencing an AE (OR, 0.98; CI, 95% 0.98-0.99; $P = 0.002$).

3.4 | Patients with cirrhosis

Cirrhosis was present in 176 patients included in the analysis. Among the 146 of these with available data, 140 achieved SVR12 (95.9%). There was no significant difference in SVR12 according to genotype (GT 1a, 100%; GT 1b, 97.4%; GT 4, 100% [$P = 0.7$]). Univariate analyses assessing association with failure to achieve SVR and occurrence of AEs are shown in Table 5. No baseline factors were significantly associated with failure to achieve SVR12 on multivariate analysis.

In patients with cirrhosis at baseline, AEs were reported in 26/176 (14.8%). Of these, all were Child-Pugh A and six had oesophageal varices. AEs were reported in 6/26 (23.1%) who had received RBV. AEs reported included gastrointestinal symptoms (n = 3) and anaemia (n = 2 [only in patients receiving RBV]). One patient, with no previous history of decompensation, had incident hepatic decompensation. Two patients died during follow-up (pneumonia and cardiac failure). The patient who died of cardiac failure had experienced previous hepatic decompensation. No baseline factors were significantly associated with AEs on multivariate analysis.

3.5 | Lipid profile

Among patients with both baseline and Week 12 post-treatment data available (n = 201), the total cholesterol levels were higher in 143 patients (73%), the LDL-C levels were higher in 153 patients (76.3%), and the HDL/LDL cholesterol ratio was lower in 141 patients (74.6%). However, the Framingham score of 10-year cardiovascular risk was only impaired in 21.4% of patients (43 patients). In addition, the Framingham score of 10-year cardiovascular risk was better in eight patients (4%) and unchanged in 150 patients (74.6%).

4 | DISCUSSION

Our real-world study is one of the largest to date in patients with chronic HCV treated with EBR/GZR. Although randomized controlled trials have demonstrated high rates of SVR12 with EBR/GZR in both treatment-naïve[8] and treatment-experienced patients,[9] studies like ours are critical to confirm efficacy and safety in the management of a heterogeneous patient population in routine practice, especially those with significant comorbidities, who are often unrepresented in clinical trials.

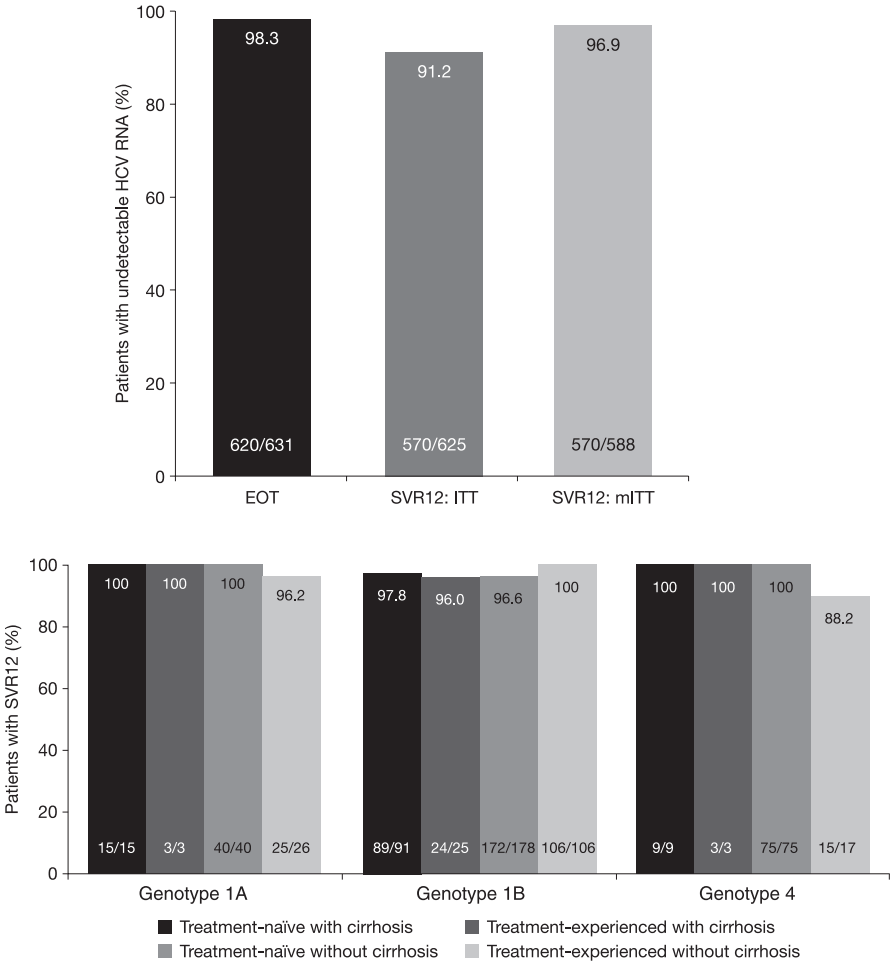

FIGURE 1 Rates of SVR with EBR/GZR ± RBV. (A) Patients with undetectable viral load at end of treatment; at post-treatment Week 12 in the ITT analysis; at post-treatment Week 12 in the mITT analysis. (B) Patients with undetectable viral load at post-treatment Week 12 in the mITT analysis by genotype, according to cirrhosis status and previous treatment. EOT, end of treatment; ITT, intent-to-treat; mITT, modified intent-to-treat; SVR12, sustained virologic response at Week 12 post-treatment

TABLE 3 Factors associated with failure to achieve SVR on univariate analysis

	SVR	No SVR	*P*-value
Treatment-experienced, n (%)	169/547 (30.9)	4/9 (44.4)	0.47
Sex, male, n (%)	334/570 (58.6)	4/9 (44.4)	0.5
Age, years, M (SD)	60.4 (12.6)	63.5 (10.2)	0.48
RBV, n (%)	35/570 (6.1)	1/9 (11.1)	0.44
Duration of treatment (8/12/16 weeks) %	0.7/94.9/4.4	11.1/88.9/0	0.003
AEs, n (%)	62/570 (10.9)	1/9 (11.1)	1
GT 1a, 1b, 4, %	14.9/71.9/13.2	22.2/66.7/11.1	0.89
Cirrhosis, n (%)	141/507 (27.8)	3/5 (37.5)	0.69
Albumin, g/dL, M (SD)	4.2 (0.4)	4.1 (0.5)	0.46

AE, adverse event; GT, genotype; RBV, ribavirin; SD, standard deviation; SVR, sustained virologic response.

In the current study, treatment with EBR/GZR resulted in high rates of SVR12 in the overall population (96.9%), as well as in treatment-naïve (98.7%) and treatment-experienced (97.7%) patients, with (98.7%) and without cirrhosis (97.9%). These results compare favourably with the limited experience from randomized controlled trials.[8,9,14,15]

EBR/GZR is approved for use in patients infected with HCV GTs 1 and 4.[6] Recent epidemiologic data suggest that these genotypes represent 80% of cases of HCV infection in the western world.[16] Cure rates reported here are at least as high as SVR12 rates in clinical trials of 92%, 99% and 100% in treatment-naïve patients[8] and 95%, 99% and 89% in treatment-experienced patients[9] infected with HCV GTs 1a, 1b and 4, respectively.

The presence of NS5A resistance-associated substitutions (RASs) can attenuate the efficacy of DAAs,[17] particularly in some genotypes, and subtyping of HCV genotypes has proven to be of

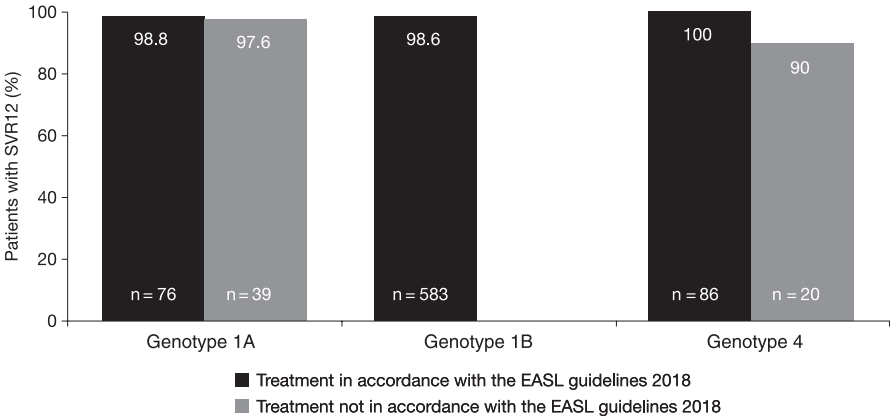

FIGURE 2 Rates of SVR with EBR/GZR ± RBV according to adherence to the EASL clinical practice guidelines 2018. SVR12, sustained virologic response at Week 12 post-treatment

value due to the lower barrier to resistance of GT 1a isolates compared with GT 1b for multiple classes of DAAs.[18] Of particular relevance, SVR12 rates in GT 1a patients found to be harbouring RASs to elbasvir can be markedly reduced.[8,9,15]

Low SVR12 rates with EBR/GZR among treatment-naïve (58%)[8] and treatment-experienced (52%)[9] GT 1a patients with NS5A RASs have been attributed to a >5-fold shift in resistance to elbasvir. However, SVR rates of >95% in treatment-experienced patients with HCV GT 1a infection and relevant NS5A RASs treated with EBR/GZR for 16 weeks with RBV[9] resulted in the recommendation to extend the duration of EBR/GZR treatment to 16 weeks, with the addition of RBV, in this specific population of patients.[19]

In Spain, as in most countries, routine resistance testing is not performed. As a consequence, information on the presence of resistance mutations at relapse is not available for our study. The US data sheet recommends performing baseline resistance testing in all patients with GT 1a, and this approach has been shown to be cost-effective compared with not testing prior to EBR/GZR treatment.[20] This recommendation is excluded from the EMA data sheet, so routine testing at baseline is not recommended in the latest EASL guidelines.[6] Indeed, it is likely that the European GT 1a differs from that present in the United States. In line with this, SVR12 rates in patients with HCV GT 1a infection were higher in our cohort (97.7%) than in the US patients (93%-95%).[8,9]

These observations could be due to the existence of two divergent clades (I and II) within GT 1a, as described recently.[21] These clades apparently have a distinct distribution; whereas clade I predominates in the United States, there is an equal distribution of the two clades in Europe. The clades also have different associations with the presence of naturally occurring resistance mutations to the NS3 protease inhibitors.[21,22] Although related to a different non-structural component of the HCV virus, this could potentially give some explanation as to the observed lower frequencies of relevant NS5A RASs to elbasvir among patients infected with HCV GT 1a in Spain (6.2%)[23] compared with those reported in clinical trials conducted in the United States (~12%).[17]

EBR/GZR with or without RBV has been shown to be a well-tolerated and highly effective treatment for chronic HCV infection in several clinical trials,[8,9,24,25] including those conducted in HCV patients with coexisting human immunodeficiency virus infection[26,27] or advanced renal disease,[28] as well as those failing to respond to previous therapy with pegylated interferon and RBV (PR)[29] or PR plus an earlier generation protease inhibitor.[14,30] In our study, only 5.7% of patients were treated with RBV, even in patients with GT 1a. Its use was not related to safety or to tolerability.

Impaired renal function is common among patients chronically infected with HCV and those with severe renal impairment have historically had fewer treatment options. Although our study did not include patients with severe renal disease, no renal concerns were

TABLE 4 AEs occurring during treatment or follow-up in patients treated with EBR/GZR ± RBV

Patients, n (%)	N = 80
Any SAE	8 (10)
AE leading to treatment discontinuation	3 (3.8)
Psychiatric event	1 (0.1)
Cutaneous disorder (rash)	1 (0.1)
Headache	1 (0.1)
AEs[a]	
Anaemia	7 (0.9)
Infection (herpes-zoster virus)	3 (0.4)
Psychiatric event	7 (0.9)
Elevated bilirubin	2 (0.2)
Gastrointestinal disease	12 (1.5)
AEs in patients with cirrhosis (n = 176)	26 (14.8)
Anaemia	2 (1.1)
Psychiatric disorders	3 (1.7)
Elevated bilirubin	1 (0.6)
Gastrointestinal disease	3 (1.7)
Hepatic decompensation	1 (0.6)
Acute liver failure	0
Deaths	4 (0.5)

[a]Most frequent adverse events listed.
AE, adverse event; EBR, elbasvir; GZR, grazoprevir; SAE, serious adverse event.

TABLE 5 Patients with cirrhosis (univariate analysis) SVR (A) and AEs (B)

(A)	SVR	No SVR	*P*-value
Sex, male, n (%)	109/175 (62.3)	0 (0)	0.06
Age, M (SD)	64.9 (13)	66 (10.1)	0.89
RBV, n (%)	14/175 (8)	0 (0)	0.44
Duration of treatment (8/12/16 weeks) %	0/93.7/6.3	33.3/66.7/0	<0.001
Genotype (1a/1b/4), %	100/97.4/100	0/2.6/0	0.74
AEs, n (%)	26/174 (14.9)	0/2 (0)	1
Child-Pugh A/B, %	98.9/1.1	100/0	0.98
Previous hepatic decompensation, %	2.9	0	1
Albumin, g/dL, M (SD)	4.1 (0.4)	3.9 (0.7)	0.62
Albumin <3.5 g/dL, n (%)	18/136 (13.2)	1/3 (33.3)	0.36
Platelets <100 000/mm^3, n (%)	27/139 (19.4)	1/3 (33.3)	0.49
(B)	**AEs**	**No AEs**	***P*-value**
Treatment-experienced, %	34.6	18.4	0.06
Oesophageal varices, %	24	13.7	0.19
MELD, M (SD)	10.4 (4.4)	8.9 (4.1)	0.15
RBV, %	23.1	5.3	0.002
Duration of treatment (16 vs 12), %	11.5	5.4	0.21
Child-Pugh A/B, %	100/0	98.7/1.3	0.98
Previous hepatic decompensation, %	34.6	18.4	0.06
Albumin, g/dL, M (SD)	3.9 (0.5)	4.1 (0.4)	0.03
Albumin <3.5 g/dL, n (%)	7/26 (26.9)	18/146 (12.3)	0.05
MDRD-4, M (SD)	65.6 (36)	93.9 (38.7)	0.003
Haemoglobin, g/dL, M (SD)	12.8 (2)	14.1 (2)	0.002
Platelets <100 000/mm^3, n (%)	8/26 (30.8)	25/151 (16.6)	0.09

AE, adverse event; MDRD-4, Modification of Diet in Renal Disease 4-variable equation; MELD, Model for End-Stage Liver Disease; RBV, ribavirin; SD, standard deviation; SVR, sustained virologic response.

raised with the use of EBR/GZR in our patients and, overall, safety and tolerability, including renal safety, were good.

The rate of AEs in our study was 10%. This rate is lower than reported in previous studies[8,9,25] and resulted in only three patients discontinuing treatment and one case of incident decompensation in a patient with cirrhosis.

An observation that has been made in previous studies is that SVR12, achieved with both IFN-based and all-oral DAA regimens, is associated with serum increases in total cholesterol, LDL-C and TG.[4,5] These findings are supported by our own observations of a reduced HDL/LDL cholesterol ratio and increased serum levels of total cholesterol in approximately three-quarters of patients. However, despite these findings the Framingham score of 10-year cardiovascular risk was unchanged in three-quarters of patients. Interestingly, and perhaps paradoxically, patients who achieve SVR12 have been shown to be at a significantly reduced risk of cardiovascular events (HR, 0.42; 95% CI, 0.25-0.69; $P = 0.001$)[31] compared with those who do not, but as is the case with HCC, the risk is not eliminated entirely and what these conflicting observations mean for cardiovascular risk surveillance in patients with chronic HCV infection warrants further investigation.

Limitations of our study, including potential physician prescribing tendencies, incomplete patient records, local practice discrepancies and data entry errors, are related to its observational, real-world design and to electronic data collection. Nevertheless, the large number of patients included gives an important insight into the effectiveness and safety of one of the latest DAA regimens to become widely used in routine clinical practice.

In summary, EBR/GZR achieved SVR12 in a comparable proportion of patients chronically infected with HCV in a real-world setting as reported in randomized controlled trials, irrespective of genotype or the presence of cirrhosis, with a similarly good safety profile. At the time of writing, there are few published data on the effectiveness of this DAA regimen for the routine management of patients chronically infected with HCV.

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AUTHORS' DECLARATION OF PERSONAL INTERESTS

CFR has served as an advisory board member and received lecture fees from AbbVie, Gilead and MSD. FG has served as a speaker for AbbVie, BMS and Gilead. IF has served as a speaker and consultant for AbbVie, Gilead, Janssen and MSD. JAC has served as a speaker and an advisory board member for AbbVie, Gilead and MSD. JC and JdlV have received personal and other fees from AbbVie, Gilead and MSD. JGS has received grant funding from Gilead and has served as a speaker and consultant for AbbVie, Gilead and MSD. JJSR has served as a speaker for AbbVie, Gilead and MSD and advisory board member for AbbVie. JLC has received personal fees from AbbVie, BMS, Gilead and MSD. JMP has served as a speaker and advisory board member for AbbVie, BMS, Janssen, Gilead and MSD. LGB has served as a consultant for AbbVie and Intercept, and as a speaker for Gilead and MSD. MD has received personal fees from AbbVie, BMS, Gilead, Janssen, MSD and Roche. RMM has served as a speaker, consultant and advisory board member for AbbVie, Gilead and MSD. AG, BF, BPA, CP, EB, FM, IC, JJMP, JLCU, JMMP, JMRZ, JS, MB, MDA, MFB, MHC, MRG, NGD, SL and SM declare no competing interests.

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