Research Article

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Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort

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Background & Aims: Clinical trials evaluating second-generation direct-acting antiviral agents (DAAs) have shown excellent rates of sustained virologic response (SVR) and good safety profiles in patients with chronic hepatitis C virus (HCV) genotype 1 infection. We aimed to investigate the effectiveness and safety of two oral DAA combination regimens, ombitasvir/paritaprevir/ritonavir plus dasabuvir (OMV/PTV/r + DSV) and ledipasvir/sofosbuvir (LDV/SOF), in a real-world clinical practice.

Methods: Data from HCV genotype 1 patients treated with either OMV/PTV/r + DSV ± ribavirin (RBV) (n = 1567) or LDV/SOF ± RBV (n = 1758) in 35 centers across Spain between April 1, 2015 and February 28, 2016 were recorded in a large national database. Demographic, clinical and virological data were analyzed. Details of serious adverse events (SAEs) were recorded.

Results: The two cohorts were not matched with respect to baseline characteristics and could not be compared directly. The SVR12 rate was 96.8% with OMV/PTVr/DSV ± RBV and 95.8% with LDV/SOF ± RBV. No significant differences were observed in SVR according to HCV subgenotype ($p = 0.321$ [OMV/PTV/r + DSV ± RBV] and $p = 0.174$ [LDV/SOF]) or degree of fibrosis (c0.548 [OMV/PTV/r/DSV ± RBV] and $p = 0.085$ [LDV/SOF]). Only baseline albumin level was significantly associated with failure to achieve SVR ($p < 0.05$) on multivariate analysis. Rates of SAEs and SAE-associated treatment discontinuation were 5.4% and 1.7%, in the OMV/PTV/r + DSV subcohort and 5.5% and 1.5% in the LDV/SOF subcohort, respectively. Hepatocellular carcinoma (HCC) recurred in 30% of patients with a complete response to therapy for previous HCC. Incident HCC was reported in 0.93%.

Conclusions: In this large cohort of patients managed in the real-world setting in Spain, OMV/PTV/r + DSV and LDV/SOF achieved high rates of SVR12, comparable to those observed in randomized controlled trials, with similarly good safety profiles.

Keywords: Hepatitis C, Chronic; Genotype 1; Ombitasvir; Paritaprevir; Ritonavir; Dasabuvir; Ledipasvir; Sofosbuvir; Real-world; Antiviral agents; Sustained virologic response; Randomized controlled trials.

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Lay summary: In clinical trials, second-generation direct-acting antiviral agents (DAAs) have been shown to cure over 90% of patients chronically infected with the genotype 1 hepatitis C virus and have been better tolerated than previous treatment regimens. However, patients enrolled in clinical trials do not reflect the real patient population encountered in routine practice. The current study, which includes almost 4,000 patients, demonstrates comparable rates of cure with two increasingly used DAA combinations as those observed in the clinical trial environment, confirming that clinical trial findings with DAAs translate into the real-world setting, where patient populations are more diverse and complex.

Introduction

An estimated 130–170 million people globally are chronically infected with the hepatitis C virus (HCV), and are at significant risk of liver disease, cirrhosis and hepatocellular carcinoma (HCC) [1]. Successful treatment leading to a sustained virologic response (SVR) effectively cures HCV infection, significantly reducing the risk of HCV-related complications, liver transplantation, and death [2,3]. Interferon (IFN)-based therapies were associated with treatment-limiting side effects and resulted in SVR rates of 40–50% in patients with HCV genotype 1 infection [4], the most prevalent genotype worldwide [5].

The advent of direct-acting antiviral agent (DAA) therapy has been widely acknowledged as a revolution in the field of HCV infection. In clinical trials, IFN-free regimens using second-generation DAA combinations yield SVR rates above 90% in genotype 1-infected patients. Ledipasvir and sofosbuvir (LDV/SOF) with or without ribavirin (RBV) resulted in SVR rates of 94–99% in treatment-naïve and treatment-experienced genotype 1-infected patients with and without cirrhosis [6–8], including those co-infected with HIV [9]. Similarly high SVR rates were obtained with the combination of ombitasvir plus paritaprevir and ritonavir (OMV/PTV/r) administered with dasabuvir (DSV) with or without RBV [10–16].

Based on data from these and other trials, both LDV/SOF and OMV/PTV/r + DSV regimens were approved by the European Medicines Agency (EMA) for the treatment of HCV genotype 1 infection. Both regimens were included in the National Hepatitis C Plan developed by the Spanish Ministry of Health, launched on April 1 2015, which allowed for increased access to DAAs in prioritized patients, including those with significant liver fibrosis (F2–F4).

Clinical trials include highly selected patient populations. Treatment is closely controlled and patients are well-supported. However, this potentially limits the applicability of results to routine clinical practice, where populations are more complex, more heterogeneous and not so tightly controlled. Real-world data are needed to confirm clinical trial findings and to guide treatment decisions. The objective of this study was to investigate the demographics and clinical characteristics and evaluate the clinical effectiveness and safety of OMV/PTV/r + DSV and LDV/SOF in two independent HCV genotype 1 patient cohorts.

Patients and methods

This was a retrospective, non-interventional, national, multicenter study evaluating antiviral treatment of HCV-infected patients in routine clinical practice. Data were collected through a National Registry (HEPA-C) under the auspices of 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). Informed consent was obtained in writing from all patients in the registry. The study recorded data from all patients chronically infected with HCV genotypes 1a or 1b undergoing treatment with OMV/PTV/r + DSV ± RBV or LDV/SOF ± RBV in 35 Spanish centers between April 1 and February 28, 2016. No other inclusion or exclusion criteria were specified. Patient follow-up ranged from 24 to 36 weeks depending on-treatment duration. The study was approved in advance by the Research Ethics Committee of Hospital Universitario Puerta de Hierro of Majadahonda (PI18-16; Madrid, Spain).

Treatment

The decision to treat and the choice of treatment, including treatment duration and the use or not of concomitant RBV, was entirely at the discretion of the treating physician. In accordance with the individual Summaries of Product Characteristics (SmPCs) issued by the EMA during the course of the study for each anti-HCV drug, recommended treatment duration and use of RBV was determined by clinical characteristics in individual patients.

Measurements

Demographic, clinical, adverse event and virologic data were collected throughout treatment and the post-treatment follow-up period. 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 PCR-based assays. Measurements were taken at baseline, weeks 4, 12 and 24 of therapy, and 4 and 12 weeks after treatment completion. Cirrhosis (F4) was defined by transient elastography score >14 kPa, or liver biopsy or clinical evidence of liver decompensation.

Outcomes

Virologic response, defined as undetectable HCV RNA, was assessed at week 4 of treatment (rapid viral response [RVR]), at end of treatment (EOT) and at week 4 (SVR4) and week 12 (SVR12) post-treatment. Virologic failure was defined as detectable HCV RNA at any time during treatment or post-treatment follow-up. Change in renal function was assessed at week 12 post-treatment. Details of all recorded serious adverse events (SAEs) were collected from the time of first drug administration to week 12 after the planned EOT. 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 the judgment of the treating physician. Incident hepatic decompensation was defined as the presence of variceal hemorrhage, ascites, and/or portosystemic (hepatic) encephalopathy. Anemia was defined as a hemoglobin level <10 g/dl.

Statistical methods

Frequencies, numbers and percentages are used for descriptive analysis of categorical variables. Quantitative variables are presented as mean, range and standard deviation (SD). Results were analyzed using the intent-to-treat approach. Efficacy and safety analyses were performed using the X^2 test, Student's t test or the Mann-Whitney U test for comparisons between independent groups. The Fisher's exact test was used when frequencies were less than 5%. Wilcoxon signed-rank test or χ^2 test were used for within group comparisons.

Logistic regression models were used to identify predictive factors for no response and adverse events. Multivariate stepwise logistic regression analysis was used to identify any independent baseline factors predictive of no response or development of adverse events. A range of continuous and categorical variables were tested in the model (Table S1). For each tested covariate, a univariate model was estimated. Covariates with p <0.05 in likelihood ratio testing in univariate analysis were included in a multivariate model, and selection of independent covariates was based on a backward elimination procedure, retaining covariates with p <0.05. Computation for the statistical tests was performed with IBM®

Research Article

SPSS® (Statistical Package for the Social Sciences) Statistics software, version 21 (IBM® Corporation, Somers, NY, USA). Statistical analyses were performed at a significance level of 0.05.

For further details regarding the materials used, please refer to the CTAT table.

Results

The decision to treat and the choice of treatment were entirely at the discretion of the physician. Randomization according to matched baseline characteristics was not possible meaning that effectiveness and safety of the two treatment regimens cannot be compared directly. Results for each treatment sub-cohort are therefore presented separately.

Subcohort of patients treated with ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin

Patient population

Data from 1,567 patients were included in the analysis. The majority had HCV genotype 1b infection (83.7%) and 45.7% were relapsers or non-responders to previous therapy (Table 1). Cirrhosis (F4) was present at baseline in 46.7%. The majority of patients with available data were Child-Pugh A (98.6%); mean model for end-stage liver disease (MELD) was 8 (6–34).

Clinical effectiveness

Week 12 follow-up data were available for 1,422 patients, among whom 1,376 (96.8%) achieved SVR12 (Fig. 1A). There was no significant difference in SVR12 according to HCV sub-genotype ($p = 0.321$) or fibrosis stage ($p = 0.548$) (Fig. 1B, C; Fig. S1). Rates of SVR12 were similar when data were analyzed by the presence or absence of cirrhosis (93.4–98.7%) and the co-administration or not of RBV (95.7–100%), irrespective of treatment duration (Table S2).

In patients without cirrhosis with available efficacy data (n = 749), the majority (98.4%) had received 12 weeks of treatment, with (30.3%) or without (68.1%) concomitant RBV. In cirrhotic patients with available data (n = 671), the majority (75.7%) had received treatment with OMV/PTV/r + DSV + RBV for 12 weeks. All treatment regimens resulted in high rates of SVR12 in both cirrhotic (92.9–100%) and non-cirrhotic (96.1–100%) patients (Fig. 1D). There was no significant difference in SVR12 between Child-Pugh A and B patients (96.6% *vs.* 94.1%; respectively; $p > 0.05$). Among 18 patients with Child-Pugh B cirrhosis, 16/17 (93.8%) who received OMV/PTV/r + DSV + RBV for 12 weeks achieved SVR12. The remaining patient received OMV/PTV/r + DSV + RBV for 24 weeks, and also achieved SVR12. In cirrhotic patients with genotype 1b infection (n = 631), 553 patients (87.0%) received 12 weeks of treatment with OMV/PTV/r + DSV + RBV and 98 patients OMV/PTV/r + DSV without RBV. There was no significant difference in SVR12 (97.0% *vs.* 93.0%; respectively; $p > 0.05$). Five patients who did not receive RBV failed to achieve SVR12; all five withdrew from treatment due to an adverse event. No virologic failure was observed in this specific subgroup.

Of those patients with available data, HCV RNA was undetectable at treatment week 4 in 93.1%, at EOT in 98.0%, and 98.0% achieved SVR4 (Fig. 1A). There was no significant difference in on-treatment or EOT response between non-cirrhotic and cirrhotic patients ($p > 0.05$). In cirrhotic patients, an RVR had an impact on attainment of SVR. Among 546 patients with RVR, 502 (95.4%) achieved SVR12 compared with 32/36 patients (88.9%) without RVR. Among 87 patients without an RVR, neither treatment duration nor exposure to RBV was associated with a significant difference in SVR12 compared with those in whom a RVR was observed.

Forty-six patients (2.9%) failed to achieve SVR12. Of these, 24 (52.2%) withdrew from treatment due to an adverse event, 18 (39.1%) experienced virological failure, and treatment was discontinued due to patient request in four patients (8.7%). Of those patients with virologic failure, 13/18 (72.3%) relapsed between post-treatment weeks 4 and 12 and 5/18 (27.7%) experienced on-treatment virologic breakthrough. None of the baseline variables analyzed were associated with the time of virologic failure.

On univariate analysis, treatment-naïve *vs.* treatment-experienced, lack of virologic response at week 4, baseline MELD score, baseline hemoglobin level, baseline bilirubin level, and baseline albumin (<3.5 g/dl and continuous) were significantly associated with treatment failure ($p < 0.05$) (Table S3). In multivariate analysis only baseline albumin was an independent predictor of treatment failure ($p = 0.04$).

Renal function

Both baseline and week 12 post-treatment glomerular filtration rate (eGFR) data were available for 659 patients, including 38 (5.8%) with abnormal baseline renal function (defined as eGFR <60 ml/min/1.73 m^2). For patients with normal baseline renal function, mean (SD) change in eGFR was −1.6 (12.4) ml/min/1.73 m^2. Among patients with abnormal baseline renal function, 19 (50%) showed an improvement in eGFR at week 12 post-treatment (mean [SD] change +3.19 [13.1] ml/min/1.73 m^2), including seven (18.4%) who showed >10 ml/min/1.73 m^2 improvement.

Safety and tolerability

A total of 33 patients (2.1%) discontinued treatment earlier than planned; 27 due to an adverse event (1.7%), five at patient request (0.3%), and one due to virologic breakthrough. Five out of the 33 patients with early treatment discontinuation achieved SVR12 (15.2%). Overall, 113 SAEs were reported in 84 patients (5.4%) (Table 2). The most commonly reported SAE was anemia (1.5%), which occurred only in patients receiving RBV. The majority of SAEs were reported at week 4 (43%) and week 12 (41%) of treatment. Incident hepatic decompensation occurred in eight patients (0.5%); all had cirrhosis at baseline, five with esophageal varices. Three of these patients were Child-Pugh B. Decompensation was associated with a significantly higher elastography value at baseline (46.16 *vs.* 15.56; $p < 0.001$), a higher MELD score (11 *vs.* 8; $p < 0.05$), a higher bilirubin level (1.6 *vs.* 0.89, $p < 0.001$) and a significantly lower baseline albumin level (3.3 *vs.* 4.2, $p < 0.001$). Eight deaths (0.5%) were reported during treatment or follow-up, three of which were directly related to liver failure (Table 2).

Age, sex, presence of cirrhosis (F4), baseline elastography values, Child–Pugh score, MELD score, a history of previous antiviral treatment, hemoglobin level, creatinine level, eGFR, bilirubin level, albumin level, platelet levels and international normalized ratio (INR) at baseline were all significantly related to the development of SAEs on univariate analysis (all $p < 0.05$) (Table S4). Of these, patient age ($p = 0.01$), elastography score ($p = 0.002$) and MELD score ($p = 0.001$) remained significant on multivariate analysis.

Table 1. Baseline characteristics of patients treated with ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin.

Characteristics	N = 1,567*
Sex, male, n (%)	842 (53.7)
Age, years, mean (range)	59.5 (21–87)
>65 years, n (%)	525 (33.5)
HCV genotype 1a/1b/1, n (%)	247/1,312/8 (15.8/83.7/0.5)
Baseline HCV RNA, log_{10} IU/ml, mean (SD)	6.1 (0.7)
Fibrosis stage, n (%)	
F0–1	185 (11.8)
F2	343 (21.9)
F3	303 (19.4)
F4	732 (46.7)
Missing	4 (0.2)
Transient elastography (FibroScan®), kPa, mean (SD), n = 1388	15.6 (11.2)
>20 kPa, n (%)	322 (23.2)
>25 kPa, n (%)	224 (16.1)
Esophageal varices, n (%)†	187 (25.5)
Child-Pugh score, n (%), n = 1283	
A	1265 (98.6)
B	18 (1.4)
C	0
MELD score, mean (range), n = 1439	8 (6–34)
MELD >18, n (%)	32 (2.2)
eGFR (CKD-EPI equation), ml/min/1.73 m^2, mean (SD), n = 1484	86.4 (22.4)
KDIGO CKD stage, n (%)‡	
G1 (>90 ml/min/1.73 m^2)	447 (67.8)
G2 (60–89 ml/min/1.73 m^2)	174 (26.4)
G3a (45–59 ml/min/1.73 m^2)	19 (2.9)
G3b (30–44 ml/min/1.73 m^2)	4 (0.6)
G4 (15–29 ml/min/1.73 m^2)	1 (0.2)
G5 (<15 ml/min/1.73 m^2)	14 (2.1)
Creatinine, (mg/dl), mean (SD), n = 1484	0.96 (0.90)
Hemoglobin level, g/dl, mean (SD), n = 1238	14.6 (1.6)
ALT, IU/L, mean (SD), n = 1157	75 (53)
AST, IU/L, mean (SD), n = 1255	83 (61)
Bilirubin, mg/dl, mean (SD), n = 1526	0.89 (0.42)
>2 mg/dl, n (%)	26 (1.7)
Albumin, g/dl, mean (SD), n = 1504	4.2 (0.44)
<3.5 g/dl, n (%)	83 (5.5)
Platelets, /mm^3, mean (range), n = 937	160,338 (17,000–704,000)
<70,000/mm^3, n (%)	71 (7.6)
INR, mean (range), n = 1442	1.06 (0.8–3.7)
HCV antiviral treatment history, n (%)	
Naïve	797 (50.9)
Non-responders	534 (34.1)
Relapsers	182 (11.6)
Unknown	54 (3.4)
Previous therapy with PPIs, n (%), n = 249	
Yes	49 (19.7)
No	200 (80.3)
Treatment prescribed	
OMV/PTV/r + DSV	683 (43.6)
OMV/PTV/r + DSV + RBV	884 (56.4)
Treatment duration	
12 weeks	1437 (91.7)
24 weeks	130 (8.3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI, chronic kidney disease epidemiology collaboration; DSV, dasabuvir; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; KDIGO, kidney disease: improving global outcomes; MELD, model for end-stage liver disease; OMV, ombitasvir; PPIs, proton pump inhibitors; PTV/r, paritaprevir/ritonavir; RBV, ribavirin; SD, standard deviation.

* Not all patients had available data for all parameters.

† Only in patients with cirrhosis (F4, n = 732).

‡ Only in patients with available data (n = 659).

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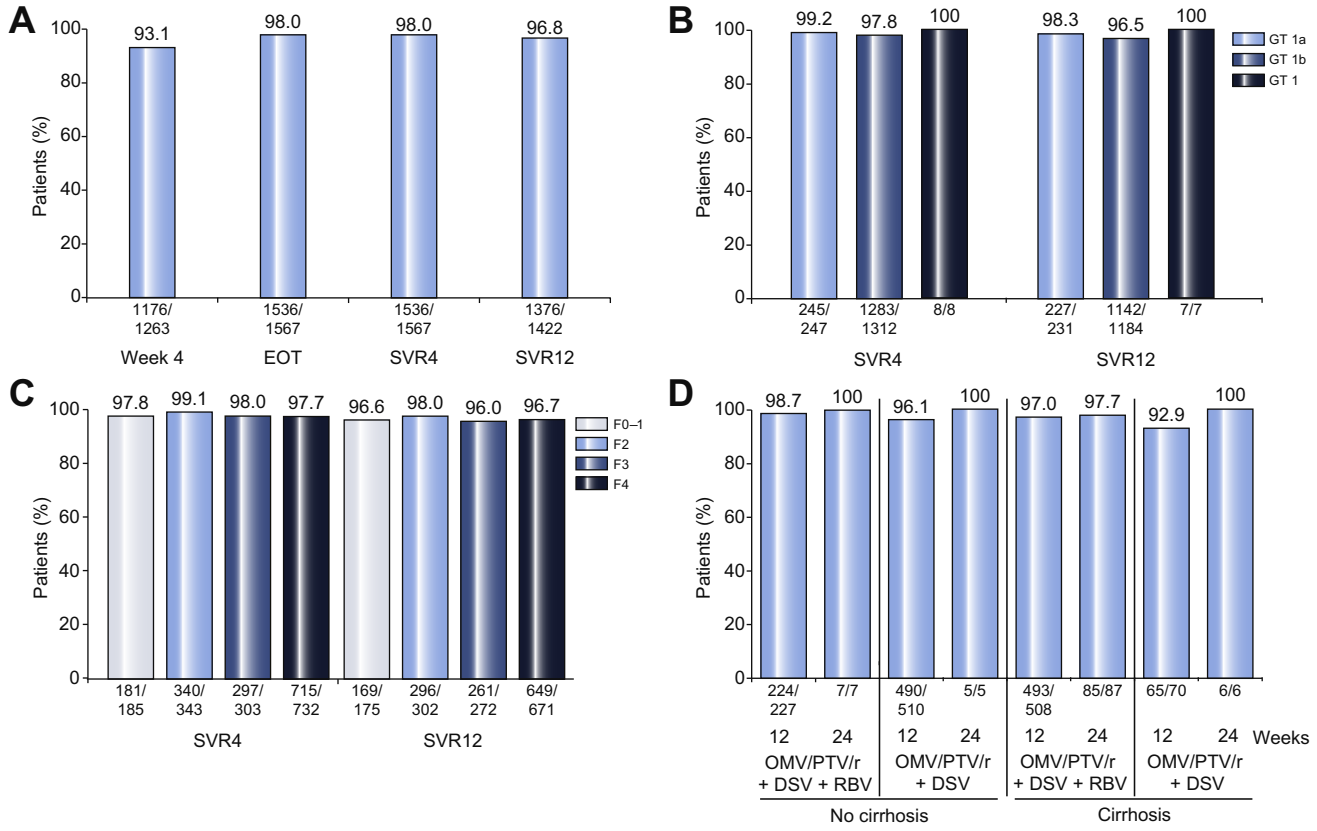

Fig. 1. Rates of virologic response to ombitasvir plus paritaprevir and ritonavir with dasabuvir ± ribavirin. Patients with undetectable viral load, during and post-treatment (A); At post-treatment week 4 and week 12 by sub-genotype (B); At post-treatment week 4 and week 12 by fibrosis stage (C); At post-treatment week 12 according to treatment regimen in patients with and without cirrhosis (D). No significant difference in SVR12 was observed according to HCV subgenotype, fibrosis stage, or treatment regimen in non-cirrhotic or cirrhotic patients (X^2 test). DSV, dasabuvir; EOT, end of treatment; GT, genotype; OMV, ombitasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SVR4/12, sustained virologic response at week 4/12 post-treatment.

Subcohort of patients treated with ledipasvir/sofosbuvir ± ribavirin

Patient population

Data from 1,758 patients were included in the analysis. Around one third of patients were infected with HCV genotype 1a (29.6%), 44.1% of patients had relapsed or were non-responders to previous therapy, and 12.5% of patients had previously received triple therapy (pegylated IFN [PegIFN] + RBV + protease inhibitor [PI]) (Table 3). More than half (57.4%) had cirrhosis (F4) and, of these, 34.2% had esophageal varices. Among 1,215 patients with available data, 1,097 patients (90.3%) were Child-Pugh A and 118 (9.7%) were Child-Pugh B or C. Mean MELD score was 8 (range 6–27).

Clinical effectiveness

Week 12 follow-up data were available for 1,745 patients (99.3%). Of these 1,672 (95.8%) achieved SVR12 (Fig. 2A). There was no significant difference in SVR12 according to HCV subgenotype ($p = 0.174$) or fibrosis stage ($p = 0.085$) (Fig. 2B, C; Fig. S2). Similar rates of SVR12 were obtained when data were analyzed by the presence of cirrhosis (93.7–98.1%) and co-administration of RBV (92.4–100%), irrespective of treatment duration (Table S5). In patients who had previously received triple therapy, SVR12 was 97.4%.

In non-cirrhotic patients with available data (n = 720), the majority received 12 weeks of treatment with LDV/SOF alone (65.6%) or with RBV (18.1%). All treatment regimens resulted in high rates of SVR12 (93.3–100%) (Fig. 2D). In cirrhotic patients with available data (n = 951), the majority (56.9%) received treatment with LDV/SOF + RBV for 12 weeks. High rates of SVR12 were observed for cirrhotic patients across all treatment regimens (91.7–96.3%), with the exception of patients treated for 8 weeks with LDV/SOF (78.6%; $p < 0.05$) (Fig. 2D). There was no significant difference in SVR12 between Child–Pugh A and B patients (96.0% *vs.* 92.4%; respectively; $p > 0.05$). Of the 118 patients with Child-Pugh B or C cirrhosis, 71 were treated with LDV/SOF + RBV for 12 weeks, 12 with LDV/SOF + RBV for 24 weeks, and 35 with LDV/SOF alone for 24 weeks, with no significant differences in SVR12 rates across the groups (94.4%, 83.3% and 91.4%, respectively; $p = 0.433$).

Overall, 305 patients (17.3%) were considered to be eligible for treatment with LDV/SOF for 8 weeks (treatment-naïve, no cirrhosis, baseline HCV RNA <6,000,000 IU/ml). Of these, only 70 received this regimen; 222 were treated for 12 weeks, and 13 for 24 weeks, achieving SVR12 rates of 95.7%, 98.2% and 92.3%, respectively (p = non-significant). Moreover, 25 additional patients were treated with LDV/SOF for 8 weeks, despite not fulfilling eligibility criteria (including 14 patients with cirrhosis,

Table 2. Serious adverse events occurring during treatment or follow-up in ≥1 patient treated with ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin.

Patients, n (%) (% patients with at least one event)/total patients	N = 1,567
Any serious adverse event	84 (5.4)
Adverse event leading to treatment discontinuation	27 (1.7)
Serious adverse events	
Anemia	24 (1.53)
Infection	8 (0.51)
Fatigue	3 (0.19)
Cardiovascular disease	6 (0.38)
Psychiatric disorders	3 (0.19)
Metabolic alteration	5 (0.32)
Neurologic disorders	0
Cutaneous disorders	11 (0.70)
Gastrointestinal disease	3 (0.19)
Renal failure	4 (0.26)
Neoplasia (not liver related)	3 (0.19)
Hepatic decompensation	8 (0.51)
Variceal bleeding	3 (0.19)
Hepatic encephalopathy	2 (0.13)
Ascites	3 (0.19)
Acute liver failure	1 (0.06)
Deaths	8 (0.5)
Non-liver-related deaths	
Severe cranioencephalic trauma	1 (0.06)
Hip fracture complications	1 (0.06)
Lung cancer	1 (0.06)
Acute leukemia	1 (0.06)
Acute pulmonary edema	1 (0.06)
Deaths directly related to liver failure	
Ascites	1 (0.06)
Acute liver failure	1 (0.06)
Lactic acidosis	1 (0.06)

nine previous non-responders, and four with baseline HCV RNA >6,000,000 IU/ml). SVR12 data were available for 24 of these patients of whom four failed to achieve SVR12, three following early withdrawal due to an adverse event and one on request (overall SVR12 83.3% *vs.* eligible patients 95.7%; p <0.05). No virologic breakthrough was observed.

In all patients with available virologic data, 81.9% had undetectable viral load at week 4, and 98.4% and 96.2% had a virologic response at EOT and at week 4 post-treatment, respectively (Fig. 2A). Response rates at week 4 of treatment were significantly lower in cirrhotic patients compared with those without cirrhosis (78.4% *vs.* 86.4%, respectively; p <0.001, odds ratio [OR]: 1.74, 95% confidence interval [CI]: 1.335–2.277). However, there was no significant difference in EOT response, or in SVR4 or SVR12 (p >0.05). In cirrhotic patients, RVR did not have a significant impact on SVR12. Among 739 patients with RVR, 710 (96.1%) achieved SVR12 compared with 192/204 patients (94.1%) without RVR. Among 300 patients without an RVR, neither treatment duration nor exposure to RBV was associated with a significant difference in SVR12 compared with those in whom a RVR was observed.

Seventy-three patients (4.2%) failed to achieve SVR12 (4.2%). Of these, 22 (30.1%) withdrew from treatment due to an adverse event, 36 (49.3%) experienced virologic failure, five (6.8%) requested early treatment discontinuation and 11 (15.1%) were lost to follow-up. Of the 36 patients with virologic failure, 25 (69.4%) relapsed between EOT and post-treatment week 4, five (13.9%) between post-treatment weeks 4 and 12, and six (16.7%) experienced virologic breakthrough. None of the baseline variable analyzed were associated with the time of virologic failure. On univariate analysis, a high baseline elastography value (>25 kPa), presence of cirrhosis (F4), bilirubin level and low albumin level (<3.5 g/dl) were significantly associated with treatment failure (Table S6). However, only baseline albumin levels remained significant in multivariate analysis (p <0.001).

Renal function

Both baseline and week 12 post-treatment eGFR data were available for 713 patients, including 36 (5.0%) with abnormal baseline renal function. For patients with normal baseline renal function, mean (SD) change in eGFR was −1.3 (11.3) ml/min/1.73 m^2. Of the 36 patients with abnormal baseline renal function, 22/36 (61.1%) showed an improvement in eGFR at week 12 post-treatment (mean [SD] change + 10.1 [19.6] ml/min/1.73 m^2), including 13 (36.1%) who showed >10 ml/min/1.73 m^2 improvement.

Safety and tolerability

A total of 37 patients (2.1%) discontinued treatment early, 26 due an adverse event (1.5%), four due to on-treatment virologic breakthrough, and seven on patient request. Eight of the 37 with early discontinuation achieved SVR12 (21.6%). Overall, 115 SAEs were reported in 97 patients (5.5%) (Table 4). The most commonly reported SAE was anemia, which predominantly developed in patients receiving RBV (91% of cases). The majority of SAEs were reported at week 4 (47%) and week 12 (35%) of treatment. Incident hepatic decompensation occurred in 16 patients (0.9%); all patients had cirrhosis at baseline, ten with esophageal varices. Decompensation was associated with a significantly higher baseline elastography (37.2 *vs.* 16.8; p <0.001), MELD score (11 *vs.* 8; p <0.001) and bilirubin level (1.7 *vs.* 0.98, p <0.001) and with a significantly lower albumin level at baseline (3.0 *vs.* 4.1, p <0.001). Eight deaths (0.5%) during treatment or follow-up were recorded, three of which were directly related to liver failure (Table 4).

On univariate analysis, patient age, presence of cirrhosis (F4), elastography score, MELD score, treatment with RBV, longer treatment duration, baseline HCV RNA level, aspartate aminotransferase level, hemoglobin level, bilirubin level, albumin level, platelet levels and presence of esophageal varices in patients with cirrhosis were significantly related to SAEs (all p <0.05) (Table S7). Of these, only MELD score (p = 0.008) and albumin level (p <0.001) remained significant on multivariate analysis.

Additional analyses

There were significant differences in baseline characteristics between the two treatment subcohorts. The LDV/SOF subcohort included significantly more patients with genotype 1a infection (15.8% *vs.* 29.6%), severe liver disease (cirrhosis [F4], 46.7% *vs.* 57.4%; esophageal varices, 25.5% *vs.* 34.2% of F4 patients; Child-Pugh B, 1.1% *vs.* 6.7%, respectively), bilirubin levels >2 mg/dl (1.7% *vs.* 6.3%, respectively), and albumin levels <3.5 g/dl (5.3% *vs.* 12.5%, respectively) compared with the OMV/PTV/r + DSV subcohort (p <0.001 for all comparisons).

The objective of our study was not to compare the efficacy of the two treatment regimens. However, a retrospective

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Table 3. Baseline characteristics of patients treated with ledipasvir/sofosbuvir ± ribavirin.

Patient characteristics	N = 1,758*
Sex, male, n (%)	979 (55.7)
Age, years, mean (range)	59.5 (18–90)
>65 years, n (%)	556 (31.6)
HCV genotype 1a/1b/1, n (%)	521/1167/70 (29.6/66.4/4.0)
Baseline HCV RNA, log_{10} IU/ml, mean (SD), n = 1747	6.1 (0.7)
Fibrosis stage, n (%)	
F0–1	110 (6.3)
F2	299 (17.0)
F3	311 (17.7)
F4	1,009 (57.4)
Missing	29 (1.6)
Transient elastography (FibroScan®), kPa, mean (SD), n = 1265	16.9 (12.1)
>20 kPa, n (%)	348 (27.5)
>25 kPa, n (%)	235 (18.6)
Esophageal varices n (%)†	345 (34.2)
Child–Pugh Score, n (%), n = 1215	
A	1097 (90.3)
B	118 (9.7)
C	0
MELD, mean (range), n = 1230	8 (6–27)
MELD >18, n (%)	21 (1.7)
eGFR, (CKD-EPI equation), ml/min/1.73 m^2, mean (SD), n = 1289	88.5 (19.9)
KDIGO CKD Stage, n (%)‡	
G1 (>90 ml/min/1.73 m^2)	458 (64.2)
G2 (60–89 ml/min/1.73 m^2)	219 (30.7)
G3a (45–59 ml/min/1.73 m^2)	23 (3.2)
G3b (30–44 ml/min/1.73 m^2)	12 (1.7)
G4 (15–29 ml/min/1.73 m^2)	1 (0.1)
G5 (<15 ml/min/1.73 m^2)	0
Creatinine, (mg/dl), mean (SD), n = 1290	0.84 (0.23)
Hemoglobin level, g/dl, mean (SD), n = 1661	14.4 (1.8)
ALT (IU/L), mean (SD), n = 1661	78 (58)
AST (IU/L), mean (SD), n = 1623	73 (53)
Bilirubin (mg/dl), mean (SD), n = 1742	0.99 (0.66)
>2 mg/dl, n (%)	110 (6.3)
Albumin (g/dl), mean (SD), n = 1721	4.0 (0.53)
<3.5 g/dl, n (%)	219 (12.7)
Platelets, /mm^3, mean (range), n = 999	151,664 (10,100–740,000)
$\leq$70,000/mm^3, n (%)	124 (12.4)
INR, mean (range), n = 1233	1.12 (0.6–5.3)
HCV antiviral treatment history	
Naïve, n (%)	835 (47.5)
Non-responders, n (%)	522 (29.7)
Relapsers, n (%)	253 (14.4)
Missing	148 (8.4)
Previous triple therapy (PegIFN + RBV + PI), n (%)	219 (12.5)
Previous therapy with PPIs, n (%), n = 819	
Yes	247 (30.1)
No	572 (69.9)
Treatment prescribed	
LDV/SOF	869 (49.4)
LDV/SOF + RBV	889 (50.6)
Treatment duration	
8 weeks	95 (5.4)
12 weeks	1329 (75.6)
24 weeks	334 (19.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; KDIGO, kidney disease: improving global outcomes; LDV/SOF, ledipasvir/sofosbuvir; MELD, model for end-stage liver disease; PI, protease inhibitor; PPIs, proton pump inhibitors; SD, standard deviation.

* Not all patients had available data for all parameters.

† Only in patients with cirrhosis (F4, n = 1,009).

‡ Only in patients with available data (n = 713).

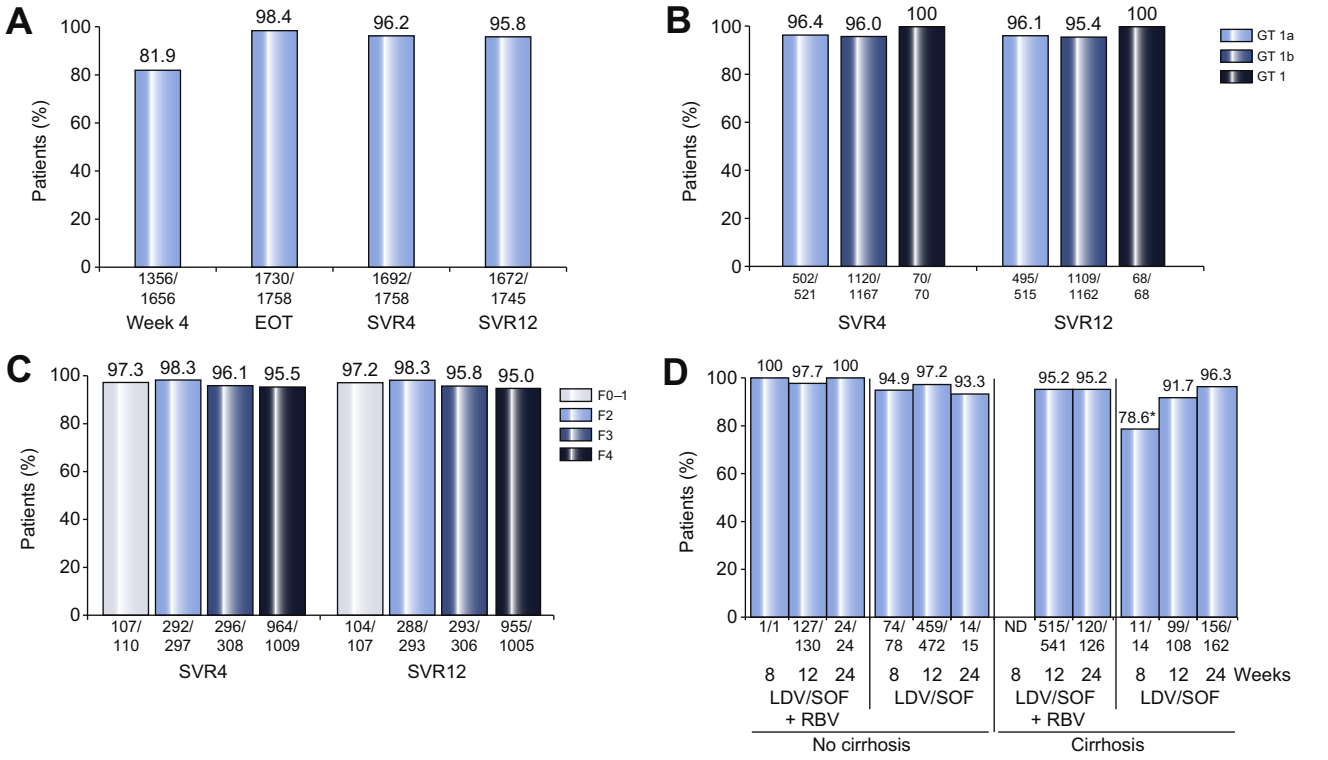

Fig. 2. Rates of virologic response to ledipasvir/sofosbuvir ± ribavirin. Patients with undetectable viral load, during and post-treatment (A); At post-treatment week 4 and week 12 by sub-genotype (B); At post-treatment week 4 and week 12 by fibrosis stage (C); At post-treatment week 12 according to treatment regimen in patients with and without cirrhosis (D). No significant difference in SVR12 was observed according to HCV sub-genotype, fibrosis stage or treatment regimen in non-cirrhotic patients (X^2 test). SVR12 rates were significantly lower among cirrhotic patients receiving 8 weeks of therapy with LDV/SOF ($^*p$ <0.05; X^2 test). EOT, end of treatment; GT, genotype; LDV/SOF, ledipasvir/sofosbuvir; ND, no data; RBV, ribavirin; SVR4/12, sustained virologic response at week 4/12 post-treatment.

sub-analysis was performed on a matched subgroup of patients who were non-cirrhotic, had a baseline albumin level >3.5 g/dl and who achieved an RVR (OMV/PTV/r + DSV, n = 693; LDV/SOF, n = 614). In this subgroup of patients there was no difference in rates of SVR12, which was achieved in 97.3% of patients treated with OMV/PTV/r + DSV and 97.9% of patients treated with LDV/SOF (OR 1.30; 95% CI, 0.638–2.661; $p = 0.466$). In addition, no significant difference was found between treatment groups with respect to time of virologic failure.

Recent studies have indicated that a major predictive factor of incident decompensation is a previous history of decompensation [17]. In our combined cohort, 14 out of 2,362 patients without prior decompensation at baseline experienced incident decompensation (0.6%) compared with 7/136 (5.1%) with a previous history of decompensation (OR, 9.1; 95% CI, 3.61–22.93; p <0.001).

Although evaluation of HCC was not an objective of this study, recent conflicting reports around the potential association of HCC with DAA-based therapy [18–20] prompted us to evaluate HCC recurrence and incidence in our combined cohort based on a review of patient records. Seventy patients had a prior diagnosis of HCC and had experienced a complete response prior to initiation of DAA therapy. Among these 70 patients HCC recurred in 21 (30%) within 12 months of starting DAA therapy (Table S8). Two patients subsequently died. Incident HCC was confirmed in 30/3,233 patients without a prior diagnosis within 18 months of starting DAA therapy. HCC was more common in patients with cirrhosis (p <0.001) but was not related to achievement of SVR ($p = 0.400$). At 14 months of follow-up post HCC diagnosis, four incident patients had died as a result of tumor progression, three as a result of liver failure and one from other causes. These observations should be interpreted with caution due to the absence of a specific surveillance protocol being adopted to follow patients in our cohorts.

Discussion

Ours is one of the largest real-world studies in patients treated with the second-generation DAAs OMV/PTV/r + DSV or LDV/SOF. Such studies are critical, since effectiveness and safety are often lower than in clinical trials In particular, safety concerns have been raised in cirrhotic patients [21,22]. Lower SVR rates have also been reported in early real-world studies of combination therapy including second-generation DAAs [23,24].

In the current study, both OMV/PTV/r + DSV and LDV/SOF resulted in high rates of SVR12, similar to those achieved in clinical trials, despite the inclusion of a high proportion of patients with cirrhosis and prior treatment failure. The SVR rates in our study were somewhat higher than those reported in a recent US study of 4,365 genotype 1 treatment-naïve veterans treated with LDV/SOF ± RBV [25]. This is likely to be related to differences in baseline characteristics; the US cohort included a high proportion of African-American patients, in whom SVR rates were significantly lower than in Caucasian patients (89.8% *vs.* 92.8%; $p = 0.003$) [25]. The higher response in our study may also reflect differences in patient management. In Spain, HCV patients are

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Table 4. Serious adverse events occurring during treatment or follow-up in ≥1 patient treated with ledipasvir/sofosbuvir ± ribavirin.

Patients, n (%)	N = 1,758
Any serious adverse events	97 (5.5)
Adverse event leading to treatment discontinuation	26 (1.5)
Serious adverse events	
Anemia	23 (1.31)
Infection	15 (0.85)
Fatigue	9 (0.51)
Cardiovascular disease	6 (0.34)
Psychiatric disorders	7 (0.40)
Metabolic alteration	2 (0.11)
Neurologic disorders	3 (0.17)
Cutaneous disorders	1 (0.06)
Gastrointestinal disease	3 (0.17)
Renal failure	3 (0.17)
Neoplasia (not liver-related)	5 (0.28)
Hepatic decompensation	16 (0.91)
Variceal bleeding	7 (0.40)
Hepatic encephalopathy	5 (0.28)
Ascites	4 (0.23)
Acute liver failure	3 (0.17)
Hepatocellular carcinoma	7 (0.40)
Deaths	8 (0.5)
Non-liver-related deaths	
Non-specific	3 (0.17)
Cardiac arrhythmia	1 (0.06)
Infection	1 (0.06)
Deaths directly related to liver failure	
Variceal bleeding	1 (0.06)
Acute liver failure	1 (0.06)
Hepatocellular carcinoma	1 (0.06)

managed by experienced clinicians in referral centers rather than in community-based practice, which may result in greater treatment adherence and consequently higher response rates [25,26].

The week 4 response with LDV/SOF in our study was lower than reported in clinical trials [6–8]. However, only up to 20% of patients in these studies were cirrhotic compared with almost 60% in our LDV/SOF cohort. Although the presence of cirrhosis had no impact on SVR12 in clinical trials, on-treatment data are not available to evaluate the effect of cirrhosis on early responses. In our study, patients with cirrhosis treated with LDV/SOF showed significantly lower on-treatment week 4 responses, compared with patients without cirrhosis. This was not the case in patients treated with OMV/PTV/r + DSV, possibly due to a higher proportion of patients with less advanced disease. Lower rates of week 4 response to LDV/SOF have been reported in other studies in advanced liver disease (83% in Child-Pugh B patients) [27]. Lack of response at week 4 was found to be related to significantly lower rates of SVR in the real-world study by Backus *et al.* [25]. However, lack of response at week 4 was not predictive of failure to achieve SVR in our cohort. In addition, despite a lower initial on-treatment response, the EOT and SVR12 rates in our patients treated with LDV/SOF were similar to those reported in pivotal clinical trials, and not significantly lower in cirrhotic patients. The exception to this was SVR12 following 8 weeks of LDV/SOF in 14 cirrhotic patients, a regimen which is not recommended in the product label. However, it is important to mention that failure to achieve SVR12 in these patients was mostly associated with treatment withdrawal and not with virologic failure.

Treatment for 8 *vs.* 12 weeks was associated with a significantly lower rate of SVR in the recent study by Backus and colleagues, including those who were eligible for this regimen according to treatment recommendations. However, although significant, the numerical difference in SVR rates was small (93.2% *vs.* 96.6%, respectively; $p = 0.001$). In the current study, patients who were eligible and treated with LDV/SOF for 8 weeks achieved an SVR12 rate of 95.7%, although they accounted for only 23% of those eligible for this regimen. Similarly, a substantial proportion of patients in the US Veteran study who would have been eligible for this regimen received 12 weeks instead [25], suggesting some reluctance to use the shorter regimen. However, data from our study should encourage confidence in this regimen in appropriate patients.

In patients with cirrhosis and a genotype 1b infection, treatment with OMV/PTV/r + DSV + RBV is recommended for 12 weeks [28], and was the most common regimen in our study. However, 98 patients with cirrhosis and a genotype 1b infection were treated with OMV/PTV/r + DSV without RBV for 12 weeks; of these, 93% achieved SVR12, a rate not significantly different to those receiving RBV (97%). These findings support data from the recently published TURQUOISE-III study (ClinicalTrials.gov identifier: NCT02219503) which showed an SVR in 100% with OMV/PTV/r + DSV without RBV for 12 weeks in 60 similar patients [16]. Taken together, these data confirm the effectiveness of OMV/PTV/r + DSV without RBV in cirrhotic patients with genotype 1b infection.

Overall in our cohort cirrhotic and non-cirrhotic patients achieved similarly high rates of SVR12 as did Child-Pugh A and B patients. Neither Child-Pugh B nor the presence of portal hypertension (esophageal varices) was associated with failure to achieve SVR. These results are particularly encouraging given the favorable safety profile in cirrhotic patients discussed below.

Rates of virologic failure were low, and similar to those reported in clinical trials. Resistance testing is not routinely performed in Spain and therefore data on the presence of resistance mutations at relapse to any of the DAAs used are not available. Relapse seemed to occur later in the OMV/PTV/r + DSV subcohort. Time of relapse is not available in phase 3 trials of OMV/PTV/r + DSV. However, in the phase 2b AVIATOR study (ClinicalTrials.gov identifier: NCT01464827) with OMV/PTV/r + DSV all relapses occurred before post-treatment week 4 [29]. The reason for, and relevance of, the later relapses with OMV/PTV/r + DSV seen in our cohort are unclear and long-term follow-up would be required to evaluate this. With LDV/SOF, the majority of patients who relapsed in the phase 3 ION-2 study did so between EOT and week 4 post-treatment [7], as in our cohort. In a recent analysis of 159 patients treated in National Institutes of Health studies followed for a period ranging from 1 to 116 weeks after achieving SVR12 with LDV/SOF, all patients maintained a virologic response with no evidence of late relapse [30].

It is important to reiterate that this study does not allow direct comparisons to be made between the two treatment regimens. Overall, the LDV/SOF subcohort included a significantly higher proportion of patients with traditionally harder to treat characteristics, such as genotype 1a infection and more advanced liver disease. This indicates differences in prescribing tendency for the two regimens. LDV/SOF may be perceived to be a more appropriate choice in patients with more advanced liver disease, as it is indicated in patients with decompensated cirrhosis, a

population in which OMV/PTV/r + DSV is contraindicated. Seventy-two percent of patients received treatment in line with guidance from the European Association for the Study of the Liver, with most deviations from this being related to the administration of RBV. Non-adherence to this guidance was not associated with any significant difference in SVR [4].

Safety and tolerability, including renal safety, with both regimens was good. However, despite the real-world nature of our cohort, few patients with markedly impaired renal function were included, thus precluding firm conclusions. Overall, reported rates of SAEs (5.5%) were only slightly higher or similar to those reported in the pivotal clinical trials (up to 5.5% for OMV/PTV/r + DSV and up to 3.8% for LDV/SOF) [6–15] although the rate of SAEs in cirrhotic patients was slightly higher in both subcohorts (OMV/PTV/r + DSV 8.1%; LDV/SOF 8.3%) than in clinical trials (5.5% with OMV/PTV/r + DSV; [12] 3.0% for LDV/SOF [31]). Liver-related SAEs were rare (<1.5%) and decompensation rates were low (<1%). Decompensation and liver failure have been reported in cirrhotic patients treated with OMV/PTV/r + DSV, which led to its contraindication in Child-Pugh B as well as Child-Pugh C patients in Spain [32] and recommendations for additional monitoring [33]. In the current study, only eight out of 732 patients with cirrhosis (0.5%) who were treated with OMV/PTV/r + DSV experienced decompensation. Although not significantly different, this rate was lower than observed with LDV/SOF (0.9%). Overall, the probability of incident decompensation was significantly higher in patients with a history of decompensation than in those without, which is consistent with recently published data [17]. Factors associated with poorer safety on univariate analysis were similar with both treatments and, as expected, were generally related to more advanced liver disease and dysfunction. As the primary baseline predictors of SVR12 by univariate analysis were also related to liver function, these data support treating patients earlier during disease. *Post hoc* analyses of recurrence and incidence of HCC in our combined cohort agreed with previous studies [18–20], but must be interpreted with caution given the lack of a routine surveillance monitoring protocol.

This study has the usual limitations related to its observational, real-world design and to electronic data collection, including potential physician prescribing bias, incomplete patient records, local practice discrepancies, and data entry errors. Nevertheless, the large number of patients included gives an important insight into the effectiveness and safety of two increasingly used treatment regimens in the diverse patient population managed in routine practice.

In summary, both OMV/PTV/r + DSV and LDV/SOF yielded similar or higher rates of SVR12 in the real-world setting compared with randomized clinical trials, with similarly good safety profiles. It is the authors' collective opinion that these results provide definitive evidence of the effectiveness of these regimens in the management of patients with chronic HCV genotype 1 infection in routine practice.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JLC, JC, BRA and CP contributed to the study concept and design. All authors contributed to the acquisition of data. JLC, JC and BRA contributed to the analysis and interpretation of data. JLC, JC and BRA drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. JLC, JC and BRA contributed to the statistical analysis. JLC and JC contributed to administrative, technical, or material support, and study supervision. All authors approved the final manuscript prior to submission.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2017.01.028.

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