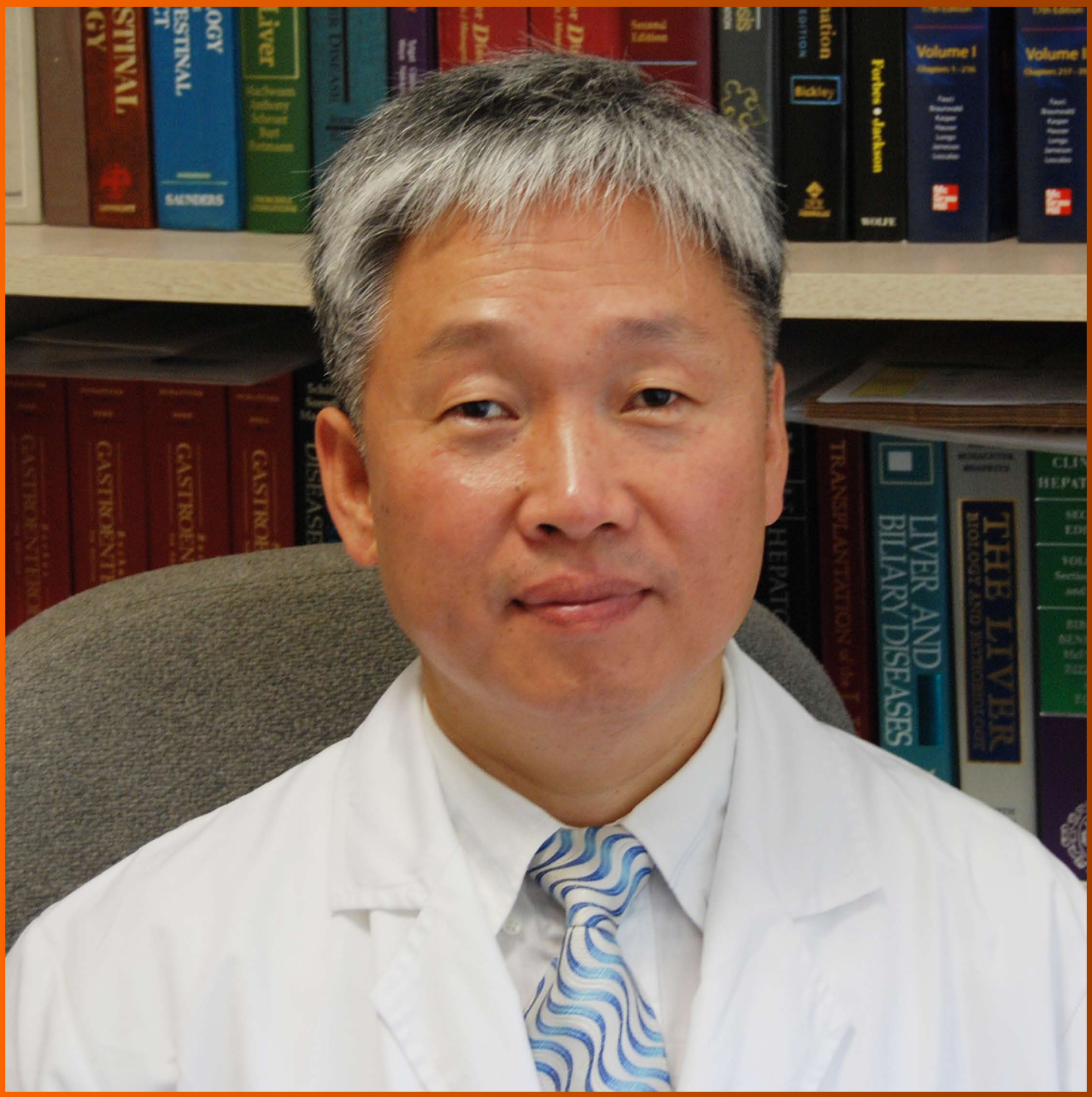
ISSN 2150-5349 (online)

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2017 May 6; 8(2): 90-154



Published by Baishideng Publishing Group Inc

WJGPT

World Journal of Gastrointestinal Pharmacology and Therapeutics

Contents

Quarterly Volume 8 Number 2 May 6, 2017

World Journal of Gastrointestinal Pharmacology and Therapeutics
Volume 8 Number 2 May 6, 2017

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN
ISSN 2150-5349 (online)

LAUNCH DATE
May 6, 2010

FREQUENCY
Quarterly

EDITORIAL OFFICE
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World Journal of Gastrointestinal Pharmacology and Therapeutics
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Help Desk: http://www.f6publishing.com/helpdesk
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Help Desk: http://www.f6publishing.com/helpdesk
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PUBLICATION DATE
May 6, 2017

World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Pharmacol Ther 2017 May 6; 8(2): 137-146

DOI: 10.4292/wjgpt.v8.i2.137

ISSN 2150-5349 (online)

ORIGINAL ARTICLE

Observational Study

Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting

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Supported by Fundación Burgos por la Investigación de la Salud and Gerencia Regional de Salud de Castilla y León, No. BUO/06/15.

Institutional review board statement: The study was reviewed and approved by the Comité Ético de Investigación Clínica de Burgos y Soria (Spain).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: November 4, 2016
Peer-review started: November 5, 2016
First decision: December 13, 2016
Revised: January 14, 2017
Accepted: February 8, 2017
Article in press: February 9, 2017
Published online: May 6, 2017

Abstract

AIM

To investigated the real-world effectiveness and safety of various regimens of interferon-free treatments in patients infected with hepatitis C virus (HCV).

METHODS

We performed an observational study to analyze different antiviral treatments administered to 462 HCV-infected patients, of which 56.7% had liver cirrhosis. HCV RNA after 4 wk of treatment and at 12 wk after treatment sustained virologic response (SVR) as well as serious adverse events (SAEs) was analyzed first for the whole cohort and then separately in patients who met or did not meet the inclusion criteria of a clinical trial (CT-met and CT-unmet, respectively).

RESULTS

The most frequently prescribed treatment was simeprevir/sofosbuvir (36.4%), followed by sofosbuvir/ledipasvir (24.9%) and ombitasvir/paritaprevir/ritonavir (r)/dasabuvir (19.9%). Ribavirin (RBV) was administered in 198 patients (42.9%). SVRs occurred in 437/462 patients (94.6%). The SVRs ranged between 93.3% and 100% for genotypes 1-4. SVRs were achieved in 96.2% patients in the CT-met group *vs* 91.9% patients in the CT-unmet group (P = 0.049). Undetectable HCV RNA at week 4 occurred in 72.9% of the patients. In the univariate analysis, the factors associated with SVRs were lower liver stiffness, absence of cirrhosis, higher platelet count, higher albumin levels, no RBV dose reduction, undetectable HCV RNA at week 4 and CT-met group. In the multivariate analysis, only albumin was an independent predictor of treatment failure (P = 0.04). Eleven patients (2.4%) developed SAEs; 5.2% and 0.7% of the patients in the CT-unmet and CT-met groups, respectively (P = 0.003).

CONCLUSION

A high proportion of patients with HCV infection achieved SVRs. For patients who did not meet the CT criteria, treatment regimens must be optimized.

Key words: Hepatitis C virus infection; Genotype 1-4; Real world treatment; Direct-acting antiviral agents

Core tip: Our study analyzes the hepatitis C virus (HCV) most common genotypes treatment and all the possible combinations with direct-acting antiviral agents which are nowadays available in our country. We have found sustained virological response rates up to 90%, even in genotypes 1 and 3. The current study analyzes HCV RNA after 4 wk of treatment and 12 and 24 wk after the end of the treatment, as well as the adverse events. We analyze, separately, the patients who meet or do not meet the inclusion criteria of a clinical trial, finding that in this last group the response is lower.

Ramos H, Linares P, Badia E, Martín I, Gómez J, Almohalla C, Jorquera F, Calvo S, García I, Conde P, Álvarez B, Karpman G, Lorenzo S, Gozalo V, Vásquez M, Joao D, de Benito M, Ruiz L, Jiménez F, Sáez-Royuela F; Asociación Castellano y Leonesa de Hepatología (ACyLHE). Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 137-146 Available from: URL: http://www.wjgnet.com/2150-5349/full/v8/i2/137.htm DOI: http://dx.doi.org/10.4292/wjgpt.v8.i2.137

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide, and its long-term impacts range from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma[1,2].

The objective of chronic HCV infection treatment is to achieve a sustained virological response (SVR). A SVR is stable over time, reduces morbidity and mortality, and is equivalent in most cases to curing the HCV infection[3-5].

In 2011, the association of pegylated-interferons (Peg-INFs) and ribavirin (RBV) with the first direct-acting antiviral agents (DAAs), telaprevir and boceprevir, increased the rate of SVRs in HCV genotype 1 from 30%-40% to 65%-75%[6,7]. However, all these treatments had limited efficacy and low tolerability[8-11].

Subsequently, next-generation DAAs which are produced with or without RBV, have been associated with improved efficacy (resulting in SVR rates greater than 90% in clinical trials), safety, tolerability, and shorter durations than first-generation protease inhibitor regimens[2,12,13].

However, information derived from HCV anti-viral clinical trials have limited applicability in clinical practice. Understanding the effectiveness of anti-viral regimens in real-world settings is essential to providing practical information and adopting better HCV treatment decisions[14,15].

The objective of this prospective study was to describe the clinical characteristics of real-world patients and evaluate the effectiveness and safety of different treatment regimens with different HCV genotypes according to real-world scenarios. We also aimed to investigate whether

patients who met or did not meet the usual inclusion criteria of clinical trials (CTs) have the same efficacy and safety profile when they are treated in real-world practice.

MATERIALS AND METHODS

Study design

This prospective, observational, intent-to-treat study analyzed different antiviral treatments for HCV-infected patients in routine clinical practice. The study was conducted in 9 (5 university and 4 non-university) hospitals in north-central Spain (Castilla y León).

Ethics statement

All study participants, or their legal guardian, provided informed written consent prior to study enrollment. The study protocol was performed according to the ethical guidelines of the 1975 Declaration of Helsinki and was approved in advance by the Research Ethics Committee of the Hospital Universitario de Burgos (Burgos, Spain).

Patient selection

The cohort consisted of all consecutively evaluated HCV patients of any genotype treated with INF-free treatments from December 1, 2014 to August 31, 2015. The patients were visited at baseline, at weeks 4, 12 and 24 (if necessary) during treatment, and at weeks 12 and 24 after completing treatment.

Inclusion criteria

Inclusion criteria were as follows: (1) underwent a complete clinical history and physical examination; (2) HCV documented by the presence of detectable serum RNA-HCV; (3) liver stiffness measurement was performed using transient elastography (FibroScan, Echosens, Paris France) in the six months before starting treatment and/or cirrhosis diagnosed either by liver biopsy and/or clinical plus ultrasound criteria; (4) absence of anti-HIV 1 and 2 antibodies; (5) absence of other causes of liver disease (autoimmune disorders, primary biliary cholangitis, Wilson's disease, α1-antitrypsine deficiency, and hemochromatosis); and (6) desire for and compliance with treatment.

Exclusion criteria

Exclusion criteria were as follows: (1) recipients of liver transplantation; (2) women who were pregnant or unable to adopt contraceptive measures; (3) hypersensitivity to therapy drugs; (4) previous treatment with another interferon-free combination; (5) coinfections (HBV, HDV, HIV); and (6) failure to establish the grade of fibrosis according to the criteria outlined. The presence of hepatocellular carcinoma was not considered an exclusion criterion.

Treatment

The decision to treat and the choice of treatment, including the treatment duration and the use or not of concomitant RBV, was entirely at the discretion of the treating physician in accordance, of the majority of the cases, with the product label, the European Association for the Study of the Liver clinical practice guidelines and the National Hepatitis C Plan developed by the Spanish Ministry of Health, giving priority to the treatment of patients with significant liver fibrosis (F2-F4)[2]. The availability of each DAA varied throughout the inclusion period of the patients (Supplementary material Table 1). The use of blood transfusion or erythropoietin in case of anemia was too entirely at the discretion of the treating physician.

Study variables

All data collection and analyses were performed anonymously. A range of continuous and categorical variables was tested (Supplementary material Table 2). The HCV RNA levels were determined using the COBAS AmpliPrep®/COBAS TaqMan® (Roche Molecular Systems, Pleasanton, CA, United States; lower limit of detection: 15 IU/mL). In previously treated patients, the last prescribed treatment and the type of prior response were registered. Cirrhosis (F4) was defined by a transient elastography score > 12.5 kPa, liver biopsy or data indicating clinical, analytical and ultrasound evidence of liver cirrhosis.

Virological response

The virological response, which is defined as undetectable HCV RNA, was assessed at week 4 of the treatment (undetectable HCV RNA at week 4), at week 12 after the EOT (SVR) and at week 24 after the EOT (SVR24). Virologic failure was defined as detectable HCV RNA at any time during treatment (with the exception of week 4 of treatment) or post-treatment follow-up.

Clinical trial inclusion criteria

Patients were arbitrarily divided into two groups based on the fulfillment or not of the more usual phase Ⅲ CT inclusion criteria: Age 18-70 years, HCV RNA > 10000 IU/mL, hemoglobin $\geqslant$ 11 g/dL in women and $\geqslant$ 12 g/dL in men, platelet count $\geqslant$ 50 × $10^3/\mu$L, ALT $\leqslant$ 200 UI/mL, total bilirubin $\leqslant$ 1.5 mg/dL, albumin $\geqslant$ 3.5 mg/dL, INR $\leqslant$ 1.5, Child-Pugh score A and MELD score < 12. Patients fulfilling all these criteria were classified as CT-met patients; however, if one or more criteria were unmet, they were considered CT-unmet patients.

Adverse events

Adverse events (AEs) were reported from the time of the initial drug administration to week 12 after the planned EOT. Serious adverse events (SAEs) were defined as any event that was life-threatening; an event that led to a hospital admission, prolonged an existing hospital stay or resulted in death; or an event that was considered serious based on the judgment of the treating physician. Incident hepatic decompensation was defined as the presence of variceal hemorrhage, ascites, and/or porto-

systemic (hepatic) encephalopathy. Anemia was defined as a hemoglobin levels < 10 g/dL.

End points

The primary efficacy end point was the SVR rate in all patients who received at least one dose of treatment. Secondary end points included the rate of undetectable HCV RNA at week 4, the rate of SVR in CT-met patients and CT-unmet patients and the rate of adverse events and treatment discontinuation because of adverse events.

Statistical analysis

The data analysis was performed with SPSS 19 statistical software (IBM Corp., Armonk, New York, United States) after collecting and organizing the data with Excel 2010 (Microsoft Corp., Redmond, Washington, United States). A descriptive analysis of the sample was conducted by determining the means (SD), medians (IQR), and frequencies (percentages) according to variable characteristics and distributions. Differences between variables were evaluated using the χ^2 or Fisher's tests for qualitative variables. For quantitative variables, Student's *t*-test (if normality conditions were met) or its corresponding nonparametric tests, including the Mann-Whitney *U*-test or the Kruskal-Wallis test (if data were not normally distributed), were used. Finally, a binary logistic regression was performed using the RVS as the dependent variable. The significance level was α = 0.05, and 95%CIs were calculated.

RESULTS

During the study period, 468 patients received an interferon-free treatment. Of these patients, 6 could not be reached or did not complete follow-up. Thus, 462 patients were included in the analysis.

Baseline characteristics

Of the 462 patients included in the study, 311 (67.3%) were male, and the median age was 54 years (range 15-87 years). Cirrhosis (F4) was present at baseline in 56.7% of the cohort. The majority of patients with cirrhosis (86.7%) were Child-Pugh A class (Table 1 and Supplementary material Table 1).

The most frequent treatment prescribed was SMV and SOF (36.4%), which was followed by SOF and LDV (24.9%) and OBV, PTV/r, and DSV (19.9%). A RBV occurred in 198 patients (42.9%; Table 1).

Clinical effectiveness

Overall, 437 of the 462 patients (94.6%) achieved a SVR (Figure 1A, Tables 2 and 3). The proportion of patients with HCV genotypes 1, 2, 3 and 4 who achieved a SVR was 94.5% (1a, 97.3%; 1b, 93.4), 100%, 93.3% and 95.5%, respectively. The SVR was above 91% in all genotypes and with all treatment combinations (Table 2 and Supplementary material Tables 3 and 4).

HCV RNA at week 4 data were available for 457/462 patients (98.9%), of which 333/457 (72.9%) showed an undetectable viral load at week 4 of treatment. Patients who presented an undetectable HCV RNA at week 4 achieved a SVR (96%) more frequently than patients who did not present it (90%, *P* = 0.004; Figure 1B and Supplementary Material Table 3).

Twenty-five patients (5.4%) failed to achieve a SVR. Two patients (0.4%) who had achieved a SVR experienced a relapse with RNA-HCV detectable at week 24 after EOT. Therefore, of the 437 patients with a SVR, 435 (99.6%) maintained SVR24 (positive predictive value of SVR for SVR24 of 99.5% and negative predictive value of 100%).

In the univariate analysis, the following factors were associated with a SVR: Liver stiffness (continuous, < 20 kPa *vs* ⩾ 20 kPa and < 25 kPa *vs* ⩾ 25 kPa), cirrhosis *vs* non-cirrhosis (Figure 1B), platelet count (⩾ 100000/mm³ *vs* < 100000/mm³), albumin (continuous), RBV dose reduction or not, undetectable HCV RNA at week 4 *vs* non-undetectable HCV RNA at week 4 and CT-met *vs* CT-unmet (Supplementary material Table 3 and 4). In the multivariate analysis, only baseline albumin (continuous) was an independent predictor of treatment failure (*P* = 0.04; Supplementary material Table 3 and 4).

Safety and tolerability

Four patients (0.9%) with genotype 1 discontinued treatment early, with three (0.6%) discontinuing because of a SAE and one discontinuing at the patient's request. Altogether, 321 patients (69.5%) experienced one or more AEs, and most of them (96.6%) were mild. The AEs that appeared with a frequency over 3% are described in Table 3. The most commonly reported AE was fatigue (22.5%), which was followed by headache (11.7%) and anemia (11.3%). Anemia was present in 47/198 (23.7%) of patients who received RBV, compared with 5/264 (1.9%) of patients who did not receive it (*P* = 0.000). In 21 patients (8.5%), the dose of RBV had to be modified. Two patients (0.4%) required a blood transfusion, and none required erythropoietin.

Eleven patients (2.4%) developed SAEs. Ten of these patients had liver cirrhosis (three Child-Pugh score A, 6 Child-Pugh score B and one Child-Pugh score C at baseline). Nine of the eleven patients who developed SAEs were also treated with RBV. SAEs were related to hepatic decompensation in seven patients with six of these patients experiencing ascites (one with hepatocellular carcinoma and another one with hepatic encephalopathy) and one patient developing only hepatic encephalopathy. Two patients developed severe anemia; both of these patients were cirrhotic and treated with RBV, and one patient developed suicidal ideation and the other developed hyperbilirubinemia. There were no deaths during treatment or follow up.

Subanalysis of patients with met or unmet clinical trials criteria

The predefined requirements to participate in a theoretical CT were not fulfilled by 173 patients. Regarding the

Table 1 Baseline characteristics of patients receiving direct-acting antiviral agents: Overall patients, patients subgroup clinical trial-met and clinical trial-unmet

Characteristics	Total *n* = 462	CT-met *n* = 289	CT-unmet *n* = 173	*P* value
Sex, male	311 (67.3)	196 (67.8)	115 (66.5)	0.765
Age, yr	54 (15-87)	53 (30-69)	59 (15-87)	[1]
BMI, kg/m^2, *n* = 368	26.4 (17.6-47)	26.2 (17.6-47)	26 (18.6-40.6)	0.132
IL28B genotype CC/CT/TT, *n* = 367	80/231/56	39/153/34	41/78/22	0.021
HCV genotype 1/2/3/4	78.4/2.4/9.7/9.5	76.1/2.1/10.4/11.4	82.1/2.9/8.7/6.4	0.549[2]
HCV genotype 1a/1b/1	31.2/66.6/2.2	40.1/58.6/2.7	16.2/78.9/1.4	0.000[3]
Baseline HCV RNA, log10 IU/mL	6.1 (3.0-7.8)	6.5 (4.2-7.6)	6.4 (3.0-7.8)	[1]
HCV antiviral treatment history				0.233
Naïve	186 (40.0)	112 (38.8)	74 (42.8)	
Non-responders	211 (45.7)	131 (45.6)	80 (46.2)	
Relapsers	64 (13.9)	46 (15.9)	18 (10.4)	
Fibrosis stage, *n* (%)				0
F0-1	26 (5.6)	21 (7.3)	5 (2.9)	
F2	100 (21.6)	83 (28.7)	17 (9.8)	
F3	77 (16.7)	59 (20.4)	15 (8.7)	
F4	259 (56.1)	126 (43.6)	136 (78.6)	
Transient elastography, kPa, *n* = 435	13.5 (2.8-65)	10.9 (2.8-75)	18.2 (3.5-75)	0
Cirrhosis				
No	200 (43.3)	163 (56.4)	37 (21.4)	0
Yes	262 (56.7)	126 (43.6)	136 (78.6)	
Child–Pugh Score, *n* = 209				[1]
A	180 (86.1)	116 (100)	64 (68.8)	
B	22 (10.5)	0 (0.0)	22 (23.7)	
C	7 (3.3)	0 (0.0)	7 (7.5)	
MELD score, *n* = 229	8.1 (6–29)	6.9 (6-11)	9.4 (6-29)	[1]
Hemoglobin level, g/dL,	15.3 (11-19.1)	14.3 (8-19.5)	15 (8-19.5)	[1]
Platelets, /mm^3, *n* = 446	158666 (23000-457000)	177301 (50000-457000)	124363 (23000-436000)	[1]
ALT, IU/L, *n* = 461	81 (64)	71.8 (43.9)	97.6 (79.8)	[1]
Bilirubin > 1 mg/dL, *n* = 243	94 (38.7)	19 (15.3)	75 (63.0)	[1]
Albumin < 3.5 g/dL, *n* = 239	25 (10.3)	0 (0.0)	25 (21.2)	[1]
INR	1.1 (0.7-2.9)	1.0 (0.7-1.3)	1.1 (0.9-2.9)	[1]
Treatment prescribed				0.024[4]
SMV and SOF	168 (36.4)	90 (31.1)	78 (45.1)	
SMV and DCV	7 (1.5)	1 (0.3)	6 (3.5)	
SOF and DCV	56 (12.1)	40 (13.8)	17 (9.8)	
SOF	11 (2.4)	9 (3.1)	2 (1.2)	
OMV and PTV/r	13 (2.8)	10 (3.5)	3 (1.7)	
OMV, PTV/r, and DSV	92 (19.9)	60 (20.8)	31 (17.9)	
SOF and LDV	115 (24.9)	79 (27.3)	36 (20.8)	
+ RBV	198 (42.9)	131 (45.3)	67 (38.7)	165
Treatment duration				0.973[5]
8 wk	12 (2.6)	9 (3.1)	3 (1.7)	
12 wk	407 (88.1)	253 (87.5)	154 (89.0)	
24 wk	43 (9.3)	27 (9.3)	16 (9.2)	
Treatment at University Hospital	395 (85.5)	259 (89.6)	136 (78.6)	0.001

[1]The *P* value was not calculated because the variable was part of inclusion criteria in the C-met group; [2]Genotype 3 *vs* the rest; [3]1a *vs* 1b; [4]To calculate the *P* value the SMV and DCV, SOF and OMV and PTV/r groups were excluded because of a low *n*; [5]8 plus 12 wk *vs* 24 wk. Continuous variables reported as median (range). Categorical variables reported as *n* and/or %. DDAs: Direct-acting antiviral agents; CT: Clinical trial; BMI: Body mass index; PEG: Pegylated interferon; PIs: Protease inhibitors; ALT: Alanine aminotransferase; SMV: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; OMV: Ombitasvir; PTV/r: Paritraprevir/ritonavir; DSV: Dasabuvir; RBV: Ribavirin.

basal characteristics and apart from the CT inclusion criteria, which were obviously different, the patients in the CT-unmet group presented the IL28B CC genotype more frequently, which is a genotype 1 subtype, and more advanced fibrosis, and they were more frequently treated in a non-university hospital (Table 1). These CT-unmet patients had a globally lower SVR than the CT-met patients (91.9% *vs* 96.2%, *P* = 0.049; Figure 1C, Supplementary material Table 3). However, the undetectable HCV RNA at week 4 was similar in both groups [75.0% in the CT-unmet group and 71.6% in the CT-met group (*P* = 0.426)] (Figure 1C). The frequency of AEs was significantly higher in the CT-unmet group (52.2% *vs* 32.9%, *P* = 0.000). However, there were no differences regarding the development of anemia and the need for RBV dose reductions between the two groups. Importantly, SAEs (including hepatic decompensation) appeared more commonly in the CT-unmet group (5.2% *vs* 0.69%, *P* = 0.003 and 3.47% *vs* 0.35%, *P* = 0.013, respectively).

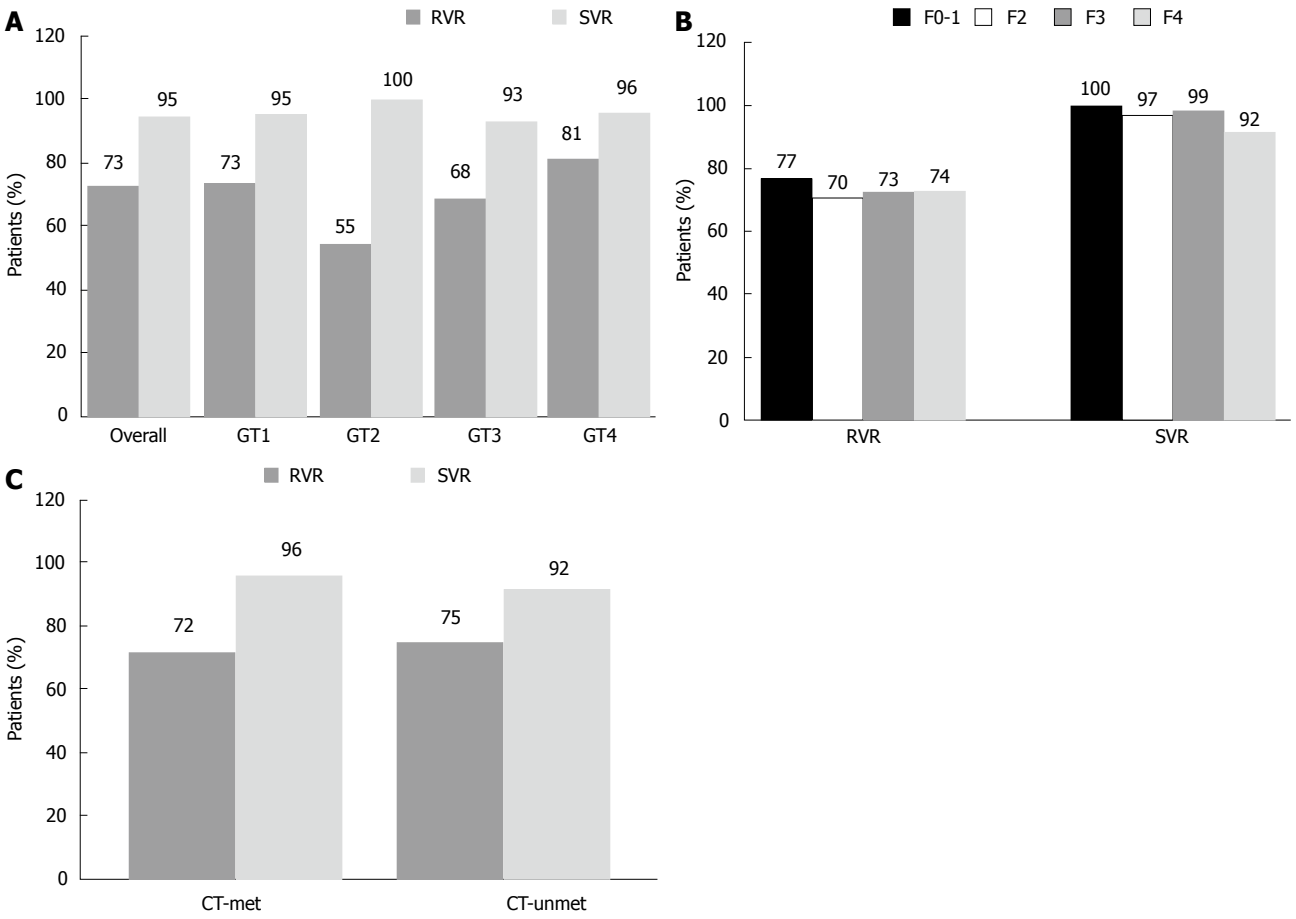

Figure 1 Rates of virological response. Patients with undetectable viral loads during and post treatment. A: At treatment week 4 and post-treatment week 12 (sustained virological response) by genotype; B: At treatment week 4 and post-treatment week 12 (sustained virological response) by fibrosis stage; C: At treatment week 4 and post-treatment week 12 (sustained virological response) by CT-met and CT-unmet. Data for 5 patients were lost: genotype 1, data from three patients were lost; genotype 3 and 4, a patient data in each genotype were lost. Data for 4 patients were lost. Data for 1 patient were lost. GT: Genotype; RVR: Undetectable HCV RNA at week 4; SVR: Sustained virological response; CT: Clinical trial.

Three of four patients who stopped treatment and 9 of 11 patients with SAEs were included in the CT-unmet group. In 6 of the 7 patients with a liver cirrhosis decompensation, a SAE was included in the CT-unmet group.

DISCUSSION

Our real-world study is representative of monoinfected, non-transplanted patients and the treatment regimens available in Spain in 2015. Because the decision to treat and the choice of treatment were entirely at the discretion of the treating physician and randomization was not possible, this study could not directly compare the effectiveness and safety of the treatment regimens.

In the general cohort, the global efficacy was high (94.6% SVR) and the results were similar to those achieved in the CTs, although almost 60% of the patients had received previous HCV antiviral treatment and more than half had liver cirrhosis.

We found that 0.4% of the subjects who achieved a SVR at week 12 subsequently relapsed at week 24 (did not achieve SVR24), and this percentage was a similar to or even lower than those found in other studies[16,17]. Therefore, this finding confirmed previous results in a real-world setting and showed good concordance between SVRs at week 12 and week 24 based on different new AAD-based regimens, including those with shorter durations and/or with drugs with lower barriers to resistance. However, in our opinion, to definitively determine a "cure" in every patient in clinical practice, a SVR must be confirmed at week 24.

Until now, few real-world setting studies have included results that consider the most frequent genotypes (1 to 4). The most significant study is the US retrospective analysis of data from 17487 patients with genotypes 1 to 4 from the Veterans Affairs (VA) National Healthcare System[18], in which a global SVR of 90.7% was found, which was lower than that in our study. This difference may be linked to early discontinuation of treatment in 4.4% of patients with available SVR data[18].

In our study, albumin was the only independent predictor of a SVR. Other studies[14,18] have also shown that albumin and other variables associated with cirrhosis or worse liver function were related to a lower SVR, thus confirming these findings in a real-world setting and with

Table 2 Sustained virological response by genotype and treatment regimen

Treatment regimen	Patients in each	SVR
Genotype 1		
SMV and SOF	149 (41.2)	139 (93.3)
SMV and DCV	7 (1.9)	7 (100)
SOF and DCV	15 (4.1)	15 (100)
OMV, PTV/r, and DSV	91 (25.1)	86 (94.5)
SOF and LDV	100 (27.6)	95 (95.0)
Total	362 (100)	342 (94.5)
Genotype 2		
SOF and DCV	5 (45.5)	5 (100)
SOF	5 (45.5)	5 (100)
SOF and LDV	1 (9.1)	1 (100)
Total	11 (100)	11 (100)
Genotype 3		
SOF and DCV	37 (82.2)	34 (91.9)
SOF	5 (11.1)	5 (100)
SOF and LDV	3 (6.7)	3 (100)
Total	45 (100)	42 (93.3)
Genotype 4		
SMV and SOF	19 (43.2)	18 (94.7)
SOF	1 (2.3)	1 (100)
OMV and PTV/r	13 (29.5)	12 (92.3)
SOF and LDV	11 (25.0)	11 (100)
Total	44 (100)	42 (95.5)

SVR: Sustained virological response; SMV: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; OMV: Ombitasvir; PTV/r: Paritraprevir/ritonavir; DSV: Dasabuvir.

Table 3 Safety profile *n* (%)

Patients	*n* = 462
Severe AEs	
Any AE[1]	11 (2.4)
AEs	321 (69.5)
Fatigue	104 (22.5)
Headache	55 (11.7)
Anemia	52 (11.3)
Insomnia	23 (5.0)
Infection	20 (4.3)
Arthralgia, myalgia	19 (4.1)
Dyspepsia	15 (3.2)
Rash	14 (3.0)
Deaths	0 (0.0)

[1]Adverse events (AEs) occurring during treatment or follow-up in ⩾ 3% patients.

a wide number of patients and supporting the results of CTs in which patients with a more advanced liver disease have a worse response to treatment.

Most real-world studies reported results in genotype 1 HCV patients[14,19,20]. The SVR rate in our study, which included 362 genotype 1 patients, was 94.5% of the overall genotype 1 patients, which was somewhat higher than previously reported rates (SVRs over 91%), although limited differences were observed among the different DAA combinations, treatment durations and use of RBV. SMV and SOF with or without RBV was the most used treatment in our genotype 1 patients, which was likely because it was the best combination available at the beginning of the study. This treatment was used in 149 of the total genotype 1 patients. Most of these patients had liver cirrhosis and were included in the CT-unmet group because the most severe patients were prioritized. However, these patients achieved a SVR of 93.3%. In other studies with thousands of patients with genotype 1 HCV treated with this regimen, the SVR rates were lower at between 75% and 84%[14,15,21]. The main cause of the differences between our cohort and the others was likely the lower rate of subtype 1a (31.2%) and Q80K variants in our genotype 1 patients. Although these variants were not analyzed in the current study, they appeared in only 2.7% of Spanish genotype 1 patients[22].

Other treatment combinations also showed high rates of SVR in our study; *i.e.*, 95.0% with SOF/LDV and 94.5% with OBV/PTV/r/DSV. These rates were similar to the 92.9% or 92% SVR rates derived from the first regimen presented in two US VA National Healthcare System studies[18,19] and the 94.9% or 95.1% SVR rates achieved with the second regimen in other studies in clinical practice[18,20].

In our cohort, only eleven genotype 2 patients were treated, and all of them achieved a SVR regardless of the treatment regimen used. High rates of SVR with the combination SOF + RBV were more similar to those described in Asian CTs[23] than the SVR of 79.0% or 86.2% achieved in clinical practice in the two VA studies[14,18] or the SVR of 88.2% from the recent analysis of 321 genotype 2 HCV infected HCV-TARGET participants[24]. However, the low number of genotype 2 patients in our study indicate that several of the currently recommended combinations in clinical guidelines, such as SOF and DCV[25] should be favored because they presented 100% SVR rates in all patients.

Patients with HCV genotype 3 are at a higher risk of liver disease progression and hepatocellular carcinoma development[26,27]. However, compared with other HCV genotypes, DAA combinations have lower efficacy against genotype 3 in patients with liver cirrhosis in CTs.

In the current study, the global SVR in patients with genotype 3 HCV infection was 93.3%. In our cohort, 82.2% of patients with this genotype were treated with SOF and DCV, with a global SRV rate of 90.3%-91.9% in patients with liver cirrhosis and 100% without. In others studies in real-world settings, a global SVR of 60%-70% was achieved in genotype 3 infection with SOF plus RBV[18,28]. All these studies had remarkably low rates, which was likely related to the use of combinations that are currently not recommended because of their low efficacy[25].

Patients with HCV genotype 4 infection are poorly represented in pivotal CTs of second-generation DAAs[25] and in most real-world studies. In the VA study, a SVR of 87.6% with SOF and LDV and 96.4% with OBV and PTV/r was achieved in patients with this genotype[18]. In the current study, 44 patients who were HCV genotype 4-infected were treated and the SVR rate was 95% (100% with SOF and LDV, 92.3% with OBV and PTV/r

and 94.7% with SMV and SOF).

The week 4 response data were available for almost all patients in the current study. We found that 72.9% of patients had an undetectable HCV RNA at week 4, similar to another analysis[19,29]. In this last real-world setting study, significant SVR rate reductions of 7.1% to 10.5% according to the addition of RBV or not, respectively, were observed in patients who did not have an undetectable HCV RNA at week 4 compared with those with undetectable HCV RNA at week 4, which was similar to the 6% observed in the current study[19]. The clinical implications of this finding on treatment decisions, such as potentially adding RBV or extending the treatment duration based on 4 wk of on-treatment HCV RNA, warrants further study.

Despite the real-world nature of our cohort, which included a higher proportion of elderly patients and many patients with liver cirrhosis, the safety and tolerability of all regimens were good. Discontinuation rates were low (< 1%), which is similar to that of CTs, and there were no deaths during treatment or follow up. In Backus *et al*[20] higher early discontinuation rates of 5.3% to 15.2% according to the treatment combination were found. In contrast, of the 802 patients in the genotype 1 group from the HCV-TARGET cohort treated with SMV and SOF, the rate of discontinuation for adverse events was only 2%[15].

In patients from the genotype 1 and genotype 3 groups from the HCV-TARGET cohort, the most commonly reported AEs were fatigue and headache, which is consistent with the results presented here[15,28]. However, anemia associated with RBV was less frequent in our study.

Overall, the reported rates of SAEs (2.4%) were similar to those reported in the pivotal CTs and lower than the 5.3% or the 7.3% described in other studies in "real-world"[15,28]. Again, in the three studies, the most frequent SAEs were the same decompensating events. However, in the current study, only seven of 262 cirrhotic patients experienced decompensation.

Because the real-world population is heterogeneous, it is important to investigate the treatment outcomes in patients excluded from CTs. Thus, we divided patients into two groups: Patients who met the requirements to take part in a CT and patients who did not meet these requirements. We found that the CT-unmet patients had lower rates of SVR and higher rates of SAEs, liver decompensation and treatment interruptions than the CT-met patients. Thus, in this group of patients, it might be advisable to conduct a more rigorous follow-up investigation to closely monitor tolerability and optimize treatment regimens.

This study has the usual limitations related to its observational, real-world design and electronic data collection. Resistance testing was not performed; thus, we were unable to assess the impact of this factor. The lack of randomization limited the ability to directly compare treatment groups, which is further compounded by the small number of patients in certain subgroups.

In conclusion, our study confirmed the efficacy and safety data reported in CTs in a cohort of patients with genotypes 1-4 and a wide range of basal characteristics, including a high proportion of patients with advanced fibrosis and treatment experience. Our results confirmed and occasionally improved upon the efficacy and safety results reported in other recently published real-world setting studies with a large number of patients[8,19], and these results are in sharp contrast to the lower SVR rates reported in certain early real-world studies on interferon-free therapy with second generation DAAs[14,15]. Moreover, our results indicate that treatment regimens should be optimized in patients that do not fulfill classical CT inclusion criteria because of their lower rates of SVR and higher rates of SAEs.

COMMENTS

Background

New direct-acting antiviral agents (DAAs) have shown higher efficacy (with sustained virological response, SVR, over 90%), safety, tolerability and shorter durations than previous antiviral agents used in the treatment of hepatitis C. However, information derived from hepatitis C virus (HCV) anti-viral clinical trials has limited applicability in clinical practice. Understanding the effectiveness of anti-viral regimes in real-world settings is essential to provide practical information in order to adopt better HCV treatment decisions.

Research frontiers

The research hotspot is to check whether the results of HCV anti-viral clinical trials can be extrapolated to the real world HCV population.

Innovations and breakthroughs

This study analyzes the efficacy and safety of all possible combinations of DAAs available in the authors' country in multiple HCV genotypes, in contrast to other studies where just one DAA treatment regimens and usually one genotype is analyzed. In this real world cohort, which includes a high proportion of elderly patients and patients with cirrhosis, the efficacy, safety and tolerability of all DAA regimens are good, and similar to the clinical trials results. However, patients who do not meet the requirements to participate in a theoretical clinical trial, have lower SVR rates and a higher proportion of adverse and serious adverse events, including liver disease decompensation, and more treatment interruptions.

Applications

The authors found that 0.4% of patients who achieved SVR at week 12 subsequently relapsed at week 24 so, in the authors' opinion, to definitively determine the infection cure in clinical practice, SVR should be confirmed at week 24. Moreover, as patients who do not meet clinical trial requirements have lower SVR and more adverse events, it might be advisable to conduct a more rigorous follow-up and to optimize treatment regimens in this population.

Terminology

DAAs: Direct-acting antiviral agents are molecules that target specific nonstructural proteins of the virus and result in disruption of HCV replication. There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. The four classes are nonstructural proteins 3/4A (NS3/4A), protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors. SVR: sustained virological response, is defined as undetectable HCV RNA at week 12 after the end of HCVtreatment. It is equivalent to the virological curie of the infection, and the goal of HCV treatment, although it does not mean the disease resolution in patients with advanced fibrosis.

Peer-review

This real-world prospective multi-center study was conducted at 9 centers in

Spain on a fair number of patients, the study is well designed and the paper is well written.

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