**Observational Study**

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

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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[3-5].

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...

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
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 ≥ 11 g/dL in women and ≥ 12 g/dL in men, platelet count ≥ 50 × 10\(^3\)/μL, ALT ≤ 200 UI/mL, total bilirubin ≤ 1.5 mg/dL, albumin ≥ 3.5 mg/dL, INR ≤ 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 analysis 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 Tables 3 and 4). In the multivariate analysis, only baseline albumin (continuous) was an independent predictor of treatment failure (P = 0.04; Supplementary material Tables 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
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).

### 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                                    |                |                 |                   |           |
| Age, yr                                      |                |                 |                   |           |
| BMI, kg/m$^2$, $n = 368$                     |                |                 |                   |           |
| IL28B genotype CC/CT/TT, $n = 367$           |                |                 |                   |           |
| HCV genotype 1/2/3/4                         |                |                 |                   |           |
| HCV genotype 1a/1b/1                         |                |                 |                   |           |
| Baseline HCV RNA, log10 IU/mL                |                |                 |                   |           |
| Child−Pugh Score, $n = 209$                  |                |                 |                   |           |
| A                                            |                |                 |                   |           |
| B                                            |                |                 |                   |           |
| C                                            |                |                 |                   |           |
| MELD score, $n = 229$                        |                |                 |                   |           |
| Hemoglobin level, g/dL, $n = 446$            |                |                 |                   |           |
| plateslets, /mm$^3$, $n = 446$               |                |                 |                   |           |
| ALT, IU/L, $n = 461$                         |                |                 |                   |           |
| Bilirubin > 1 mg/dL, $n = 243$               |                |                 |                   |           |
| Albumin < 3.5 g/dL, $n = 239$                |                |                 |                   |           |
| INR                                          |                |                 |                   |           |
| Treatment prescribed                         |                |                 |                   | 0.024$^4$|
| SMV and SOF                                  |                |                 |                   |           |
| SMV and DCV                                  |                |                 |                   |           |
| SOF and DCV                                  |                |                 |                   |           |
| SMV and PTV/r                                |                |                 |                   |           |
| SMV, PTV/r, and DSV                         |                |                 |                   |           |
| SOF and LDV                                  |                |                 |                   |           |
| + RBV                                        |                |                 |                   | 0.973$^3$|
| Treatment duration                           |                |                 |                   |           |
| wk                                           |                |                 |                   |           |
| 8 wk                                         |                |                 |                   |           |
| 12 wk                                        |                |                 |                   |           |
| 24 wk                                        |                |                 |                   |           |
| Treatment at University Hospital             |                |                 |                   | 0.001$^1$|

$^1$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 $n$; $^8$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; PI: Protease inhibitors; ALT: Alanine aminotransferase; SMV: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; OMV: Ombitasvir; PTV/r: Paritaprevir/ritonavir; DSV: Dasabuvir; RBV: Ribavirin.
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 17,487 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 to or even lower than those found in other studies[16,17].

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

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.

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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
the first regimen presented in two US VA National Healthcare System studies\textsuperscript{18,19} and the 94.9% or 95.1% SVR rates achieved with the second regimen in other studies in clinical practice\textsuperscript{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\textsuperscript{23} than the SVR of 79.0% or 86.2% achieved in clinical practice in the two VA studies\textsuperscript{14,18} or the SVR of 88.2% from the recent analysis of 321 genotype 2 HCV infected HCV-TARGET participants\textsuperscript{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\textsuperscript{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\textsuperscript{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 other studies in real-world settings, a global SVR of 60%–70% was achieved in genotype 3 infection with SOF plus RBV\textsuperscript{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\textsuperscript{28}.

Patients with HCV genotype 4 infection are poorly represented in pivotal CTs of second-generation DAA\textsuperscript{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\textsuperscript{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

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) |

Table 3 Safety profile a (%)

| Patients | n = 462 |
|----------|---------|
| Severe AEs |         |
| Any AE\textsuperscript{3} | 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) |

\textsuperscript{1}Adverse events (AEs) occurring during treatment or follow-up in ≥ 3% patients.

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

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\textsuperscript{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%\textsuperscript{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\textsuperscript{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
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[19,20]. 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%[19].

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 regimen 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 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 NSSA inhibitors. SVR: sustained virological response, is defined as undetectable HCV RNA at week 12 after the end of HCV treatment. It is equivalent to the virological cure 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.

REFERENCES

1 Thomas DL. Global control of hepatitis C: where challenge meets opportunity. Nat Med 2013; 19: 850-858 [PMID: 23836235 DOI: 10.1038/nm.3184]

2 European Association for Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015; 63: 193-236 [PMID: 25911336 DOI: 10.1016/j.jhep.2015.03.025]

3 Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010; 8: 280-288, 288.e1 [PMID: 19948249 DOI: 10.1016/j.cgh.2009.11.018]

4 Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011; 9: 509-516.e1 [PMID: 21397729 DOI: 10.1016/j.jgh.2011.03.004]

5 van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Kegt RJ, Hansen BE, Jansen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012; 308: 2584-2593 [PMID: 22368517 DOI: 10.1001/jama.2012.144878]

6 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011; 55: 245-264 [PMID: 21371579 DOI: 10.1016/j.jhep.2011.02.023]

7 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçalves FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982 [PMID: 12324553 DOI: 10.1056/NEJMoa020047]

8 Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011; 54: 1433-1444 [PMID: 21889493 DOI: 10.1002/hep.24641]

9 Jacobson IM, McHutchison JG, Dusheiko GS, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, McHutchison JG, Dusheiko G, Di Bisceglie AM, Jacobson IM. Comparative effectiveness of ledipasvir/sofosbuvir ± ribavirin vs. obitavir/paritaprevir/ritonavir/ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C. In the Veterans Affairs National Health Care System. Hepatology 2016; 51: 457-471.e5 [PMID: 27267053 DOI: 10.1001/jama.2016.05.049]

10 Backus LI, Belperio PS, Shahouman TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. Hepatology 2016; 64: 405-414 [PMID: 27115523 DOI: 10.1002/hep.28625]

11 Backus LI, Belperio PS, Shahouman TA, Loomis TP, Mole LA. Comparative effectiveness of ledipasvir/sofosbuvir ± ribavirin vs. obitavir/paritaprevir/ritonavir + dasabuvir ± ribavirin in 6961 genotype 1 patients treated in routine medical practice. Aliment Pharmacol Ther 2016; 44: 400-410 [PMID: 27291852 DOI: 10.1111/apt.13696]

12 Yee BE, Nguyen NH, Jin M, Lutchman G, Lim JK, Nguyen MH. Lower response to simprevir and sofosbuvir in HCV genotype 1 in routine practice compared with clinical trials. BMJ Open 2016; 6: e000056 [PMID: 26966547 DOI: 10.1136/bmjopen-2015-000506]

13 Sarrazin C, Lathouwers E, Peeters M, Daems B, Buelens A, Witte SK, Weykmans Y, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Earlier sustained virologic response with ledipasvir/sofosbuvir plus ribavirin in treatment-naive patients with chronic hepatitis C genotype 1. Hepatol 2016; 64: 10-16 [PMID: 25614456 DOI: 10.1002/hep.28625]

14 Sáez-Royuela F, Basave D, Suárez JP, Ordóñez S, Latorre R, Añó-Coll A, García-Rodríguez R, Camps M, Béjar J, Pérez-Pérez G, Carmona J, Ferrer S, Bataller R, Tous N, Soriano V, de la Torre J. Early response in the treatment of patients with genotype 1 HCV infection: history of a success? Liver Int 2016; 36: 1093-1095 [PMID: 27059163 DOI: 10.1111/liv.13138]

15 Welz TM, Nelson DR, Morelli G, Di Bisceglie A, Reddy RK, Kuo A, Lim JK, Darling JM, Pockros P, Galati JS, Frazier LM, Alqahtani S, Sulkowski MS, Vainorius M, Akushevich L, Fried MW, Zeuzem S. Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: results of the real-world, clinical practice HCVP-TARGET study. Gut 2016; 65: ahead of print [PMID: 27481632 DOI: 10.1136/gutjnl-2016-311669]

16 Bochud PY, Angulo P, Matthaei S, Zerbe P, Green PK, James E. New hepatitis C therapies: the toolbox, strategies, opportunities. BMJ Open 2016; Epub ahead of print [PMID: 27349997]

17 Ramos H et al. Treatments in HCV genotype 1-4
and Safety of Sofosbuvir-Based Regimens for Chronic HCV Genotype 3 Infection: Results of the HCV-TARGET Study. Clin Infect Dis 2016; 63: 776-783 [PMID: 27325691 DOI: 10.1093/cid/ciw387]

Thornton K, Deming P, Manch RA, Kuo A, Nelson DR, Di Bisceglie AM, Manns MP, Sherman K, Frazier LM, Sterling R, Mailliard M, Schmidt M, Akushevich L, Vainorius M, Fried MW. Is response guided therapy dead? Low cure rates in patients with detectable hepatitis C virus at week 4 of treatment. Hepatol Int 2016; 10: 624-631 [PMID: 27098355]

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