LIBYAN JOURNAL OF MEDICINE
2021, VOL. 16, 1949797
https://doi.org/10.1080/19932820.2021.1949797

Taylor & Francis
Taylor & Francis Group

Effectiveness of direct-acting antiviral drugs against hepatitis C virus: predictive factors of response to the treatment

María E. Cárdaba-García [a,b], Encarnación Abad-Lecha[b] and Miguel Á. Calleja-Hernández [a,c]

[a]Faculty of Pharmacy, University of Granada, Campus Universitario de Cartuja, Granada, Spain; [b]Hospital Pharmacy, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [c]Hospital Pharmacy, Virgen Macarena University Hospital, Sevilla, Spain

ABSTRACT

Background/Aims. Despite the high efficacy and safety of direct-acting antivirals against hepatitis C virus shown in clinical trials, treatment failures continue to occur. Our aim was to establish the effectiveness of these drugs in routine clinical practice, as well as to determine factors that could influence the response to the treatment.

Matherials/methods. Single-center, observational, retrospective study. Clinical, virological and pharmacotherapeutic variables were registered at baseline. Adverse drug reactions that occurred were recorded until week 24 of follow-up. Achievement of sustained virologic response was also recorded. Univariate and multivariate analysis were done to determine factors of response.

Results. A total of 333 treatment regimens corresponding to 330 different patients were evaluated. Sustained virologic response rate was 94.6% [95%CI: 91.6–96.6%]. 67.9% of the patients experienced adverse drugs reactions (92.2% were grade 1). The univariate analysis identified a higher baseline of platelets, albumin and total cholesterol as predictive factors of sustained virologic response ($p < 0.05$). Presence of diabetes and complications related to liver disease (splenomegaly, portal hypertension, portal hypertensive gastropathy), body mass index ≥30, greater liver fibrosis, receiving simeprevir and higher baseline levels of glucose, aspartate-aminotransferase, alanine-aminotransferase and alkaline-phosphatase, have been identified as predictive factors of non-response ($p < 0.05$). The multivariate analysis detected the following independent factors of non-response: body mass index ≥30 and presence of complications related to liver disease.

Conclusion. The effectiveness and safety of direct-acting antivirals against hepatitis C virus have been maintained in routine clinical practice. Further research on predictive factors of response is required in order to develop more reliable and reproducible predictive models.

ARTICLE HISTORY
Received 29 April 2021
Accepted 27 June 2021

KEYWORDS
hepatitis C virus; chronic hepatitis C; sustained virologic response; antiviral agents; predictive factors of response

1. Introduction

Hepatitis C virus (HCV) infection is a worldwide problem. It is estimated that 115 million people have antibodies to HCV and that 75 million have chronic infection due to this virus, according to the latest data published by the World Health Organization [1,2].

The goal of antiviral therapy used on patients with chronic HCV (cHCV) is to cure the infection in order to prevent hepatic and extrahepatic complications related to the disease, improve the quality of life, and avoid the transmission of HCV[3]. The objective of the treatment is to achieve sustained virologic response (SVR): 12 to 24 weeks after finalizing antiviral therapy the RNA of the HCV should remain undetectable. 99% of the patients who achieve SVR cure the infection[3].

The initial treatment for cHCV consisted of the combination of alpha-interferon with ribavirin (RBV). SVR rates ranging between 23%-50% were achieved through this dual therapy. Following the marketing of boceprevir and telaprevir in 2011, the percentage of SVR in genotype 1 patients increased to 61%-75% [4,5]. However, the revolution in the treatment of cHCV came about in 2014 with the marketing of the new generation direct-acting antiviral agents (DAAs) which target different HCV proteins: polymerase NS5B, NS3/4A serine protease, and the protein NS5A. The DAAs inhibitors of the polymerase NS5B are sofosbuvir (SOF) and dasabuvir (DSV). Daclatasvir (DCV), elbasvir, ledipasvir (LDV), ombitasvir (OMV), pibrentasvir, and velpatasvir are NS5A protein inhibitors. Glecaprevir, grazoprevir, paritaprevir (PTV), simeprevir (SMV), and voxilaprevir are inhibitors of the NS3/4A serine protease. The different combinations of these drugs make it possible to reach SVR rates that are higher than 90%, with few and mild associated adverse drug reactions (ADRs)[6].

The efficacy of regimens that incorporate new DAAs has been demonstrated in numerous clinical trials, with 'ideal' patients whose characteristics differ from patients using these drugs in routine clinical practice. That is why it is important to establish the

CONTACT María E. Cárdaba-García marielcg90@gmail.com Hospital Pharmacy, Hospital Universitario del Tajo, Amazonas Central Avenue, Aranjuez, Madrid 28300, Spain

effectiveness of these drugs in real-life conditions, in order to prove that high SVR rates reached in clinical trials are maintained in this scenario.

On the other hand, despite the high SVR rates achieved with the new DAAs, treatment failures continue to occur. Although at the present moment, the fact that antiviral therapy failures does not take away the possibilities of treating a patient, it would be convenient to know the different factors that could influence the achievement of SVR, as well as to assess their influence, with the goal of selecting the most appropriate treatment.

The aim of this study was to establish the effectiveness and safety of the DAAs in routine clinical practice, as well as to determine the factors that could influence the success or failure of antiviral therapy.

2. Materials and methods

2.1. Study design and population

A single-center, observational, retrospective study was carried out. All patients over age 18 diagnosed with cHCV who began treatment against HCV in the Clinical University Hospital of Valladolid, with regimens that incorporated DAAs (DCV, DSV, SOF, LDV, SMV, OMV, PTV) between August 1st, 2014, and February 28th, 2017, were included in the study. If any of these patients did not reach the therapeutic objective and was treated with a different regimen that incorporated DAAs, the new scenario was studied as if it were a new patient. Those patients who received DAAs in combination with alpha-interferon were excluded.

Although all those patients who met the inclusion criteria were part of the study, it is important to mention that in the most recent studies of DAAs used in routine clinical practice, the SVR rate exceeds 80%. Therefore, taking this into account and considering an error of 8%, with a confidence interval of 95% (95%CI) and 10% of possible losses, a sample of 107 patients would have been sufficient.

There was a monthly follow-up of all the patients included in the study during the antiviral treatment period, and after its completion at weeks 12 and/or 24.

To evaluate the treatment effectiveness, the SVR rate achieved was evaluated for each therapeutic regimen, for each viral genotype and for each degree of hepatic fibrosis. The safety of these drugs has been analyzed taking into account the type and severity of ADRs registered in the clinical and pharmacotherapeutic history. To establish the predictive and non-predictive factors of SVR, the influence on the achieved result of the baseline demographic, anthropometric and epidemiological variables, the baseline biochemical, hematological, histological and viral parameters, as well as the pharmacotherapeutic variables, was analyzed.

2.2. Variables

Before beginning the antiviral treatment, the following variables were collected:

-demographic, anthropometric, and epidemiological: sex, age, body mass index (BMI), human immunodeficiency virus or hepatitis B virus co-infection, presence of diabetes mellitus.

-histological and other pathologies related to liver disease: degree of liver fibrosis (measured by transition electrographic image, FibroScan®), presence of cirrhosis, complications related to liver disease and extrahepatic manifestations.

-laboratory tests: leukocytes, haemoglobin, platelets, glucose, creatinine, albumin, total cholesterol, aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline-phosphatase (ALP), total bilirubin.

-virological: HCV viral load (HCV-RNA amplification was carried out with COBAS-AmpliPrep equipment and the polymerase chain reaction with COBAS-Taqman), HCV genotype.

-pharmacotherapeutics: prescribed pharmacotherapeutics regimen (drugs and duration).

During treatment and until week 24 post-treatment, ADRs that occurred were recorded. In the 12 or 24 week post-treatment, achievement of SVR was recorded.

2.3. Ethical considerations

The protocol of the study and its development were approved by the Research Commission of the Clinical University Hospital of Valladolid.

To ensure compliance with the Personal Data Protection Law and Guarantee of Digital Rights[7], as well as to ensure proper use of the data, it was collected in a database Access® Microsoft Office 2010 (designed for that purpose by the Research Department of the Clinical University Hospital of Valladolid), and it was integrated into the Data Management System of said center.

2.4. Statistical analysis

The statistical analysis was carried out using the SPSS program (Statistical Package for the Social Science) 20.0 version for Windows®. The analysis of the results was described by taking $\alpha = 5\%$ with a 95%CI. The values of $p < 0.05$ have been considered statistically significant.

A descriptive study of the qualitative variables was carried out, collected with their frequency distribution and then expressed as a percentage. The quantitative variables were expressed using the mean and its standard deviation (SD) or the median and interquartile range (IQ) in the case of asymmetry. Prior to applying the hypothesis testing, the normality of the quantitative variables was tested with the Kolmogórov-Smirnov ($n \geq 30$) and Saphiro-Wilk ($n < 30$) test and the application assumptions of each one of the tests used.

In order to compare the groups, the Student T-Test and the non-parametric Mann-Whitney test were used in the case of the quantitative variables; in the case of categorical variables the Chi-Square distribution test with continuity correction was applied and Fisher´s Exact test was used in the case of non-compliance with the application assumptions (frequency ≥5).

To carry out the multivariate analysis, using those variables that turned out to be statistically significant in the univariate analysis at level 0.1, adjusting for confounding variables, the forward stepwise method was used (likelihood ratio) with probability criteria to enter 0.05 and probability to exit at 0.10. The strength of the association has been estimated with the Nagelkerke-R^2 test.

3. Results

A total of 333 treatment regimens corresponding to 330 different patients were evaluated. The fact that the number of treatments indicated was higher than the number of patients treated is due to the fact that some subjects presented a recurrence of the infection or had ADRs that forced the suspension of antiviral therapy and then they were treated again in a different way.

The mean age of the patients who received antiviral therapy was 53.8 ± 11 years old, with the percentage of men treated being higher (64%). The baseline characteristics of the subjects included in the study are summarized in Table 1. The average values of the hemogram and biochemistry tests were within the normal range, with the exception of liver enzymes (AST, ALT, GGT and ALP), whose baseline was above the upper normal limit.

11 different therapeutic regimens were prescribed, varying the duration of treatment between 8 and 24 weeks (Table 2). The uneven distribution of treatments can be explained by the staggered marketing of different drugs and by the adjustment of the treatments as described in the clinical guidelines, considering the individual characteristics of each patient.

In the intention-to-treat analysis, the SVR rate was 94.6% [95%CI: 91.6–96.6%] (315/333 patients achieved SVR). 4.2% (14/333) of the patients did not achieve SVR: 2.1% (7/333) registered viral reactivation, 0.9% (3/333) died without knowing the response to the therapy (none of the deaths were related to the antiviral treatment), 0.6% (2/333) discontinued treatment prematurely due to ADRs, 0.6% (2/333) were patients co-infected with two different HCV genotypes that eliminated only one viral genotype. Follow-up was lost on 1.2% (4/333) of the patients.

With these global response rates, the response per treatment received was analyzed, in order to assess its effectiveness, remaining higher than 80% in all regimens (Figure 1). Regarding the viral genotype among the patients who reached SVR, the distribution by genotypes was similar, higher than 90% in all cases: 90% (9/10) genotype 1, 98.6% (69/70) genotype 1a, 94.8% (110/116) genotype 1b, 100% genotype 2 (3/3), 95.5% (64/67) genotype 3, 100% (31/31) genotype 4,

Table 1. Clinical, sociodemographic, epidemiological, histological and virological characteristics of the study population.

Patients characteristics (N = 333)[a]	Mean ± standard deviation or median ± interquartile range [Q1-Q3] or n(%)
Gender	
• Male	213 (64%)
• Female	120 (36%)
Age (years)	53.8 ± 11
BMI	
• <30	253 (76%)
• ≥ 30	36 (10.8%)
• Unknown	44 (13.2%)
Diabetes mellitus	45 (13.5%)
HIV co-infection	98 (29.4%)
HBV co-infection	
• Chronic HBV infection	4 (1.2%)
• Inactive carrier or occult HBV infection	127 (38.1%)
Other comorbidities	231 (69.4%)
FibroScan® (kPa)	14.9 ± 11.8
Cirrhosis	142 (42.6%)
Complications related to liver disease	105 (31.5%)
- Oesophageal varices	18 (5.4%)
- Portal hypertension	30 (9%)
- Ascites	10 (3%)
- Steatosis	36 (10.8%)
- Peritonitis	1 (0.3%)
- Hepatic encephalopathy	4 (1.2%)
- Splenomegaly	41 (12.3%)
- Cholelithiasis	14 (4.2%)
- Cholangitis	1 (0.3%)
- Portal hypertensive gastropathy	6 (1.8%)
Extra-liver complications	16 (4.8%)
Viral load ($IU{\cdot}mL^{-1}$)	1,632,752 [571,586–3,613,188]
HCV genotype	
- 1	10 (3%)
- 1a	70 (21%)
- 1b	118 (35.4%)
- 2	3 (0.9%)
- 3	67 (20.1%)
- 4	32 (9.6%)
- Co-infected	33 (9.9%)
Naïve	247 (74.2%)

[a]N represents the number of patients treated, considering that if any of the patients included in the study did not reach the therapeutic objective and was treated with a different regimen that incorporated DAAs, the new scenario was studied as if it were a new patient.

BMI: Body Mass Index; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus.

Table 2. Prescribed pharmacotherapeutic regimens.

Pharmacotherapeutic regimen (N = 333)[a]	8 weeks	12 weeks	16 weeks	24 weeks
SOF/RBV, n(%)	-	6 (1.8%)	1 (0.3%)	2 (0.6%)
SOF/LDV, n(%)	31 (9.3%)	84 (25.2%)	-	18 (5.4%)
SOF/LDV/RBV, n(%)	1 (0.3%)	47 (14.1%)	-	7 (2.1%)
SOF/SMV, n(%)	-	17 (5.1%)	-	1 (0.3%)
SOF/SMV/RBV, n(%)	-	5 (1.5%)	-	
SOF/DCV, n(%)	-	35 (10.5%)	1 (0.3%)	5 (1.5%)
SOF/DCV/RBV, n(%)	-	3 (0.9%)	-	4 (1.2%)
OMV/PTV/Rtv/DSV, n(%)	-	32 (9.6%)	-	-
OMV/PTV/Rtv/DSV/RBV, n(%)	-	18 (5.4%)	-	7 (2.1%)
OMV/PTV/Rtv/RBV, n(%)	-	3 (0.9%)	-	4 (1.2%)
OMV/PTV/Rtv/SOF/RBV, n(%)	-	-	-	1 (0.3%)

[a]N represents the number of pharmacotherapeutic regimens prescribed.
SOF: sofosbuvir; RBV: ribavirin; LDV: ledipasvir; SMV: simeprevir; DCV: daclatasvir; OMV: ombitasvir; PTV: paritaprevir; Rtv: ritonavir; DSV: dasabuvir;

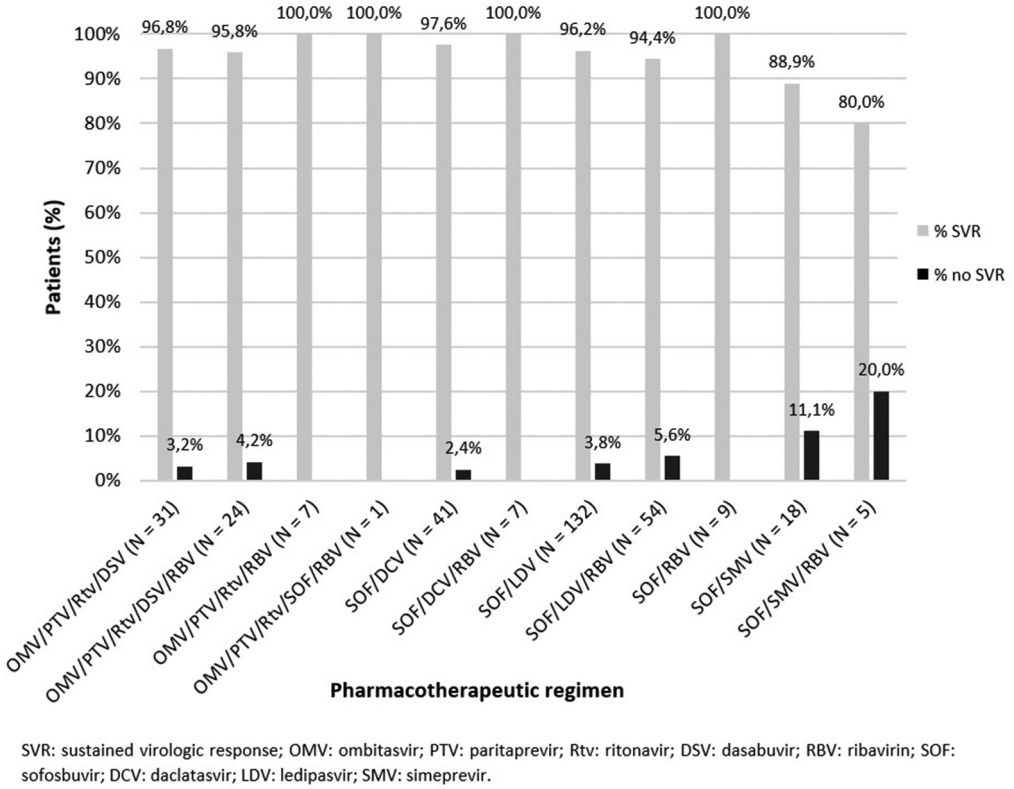

Figure 1. SVR rate obtained according to the pharmacotherapeutic regimen used. Pharmacotherapeutic regimens are represented in the abscissa axis. The ordinate axis represents the SVR rate achieved (grey) or not (black) for each therapeutic regimen.

90.6% (29/32) co-infection. Likewise, the percentage of SVR achieved was also higher than 90% with the different stages of fibrosis: 100% (56/56) F0-F1, 93.8% (61/65) F2, 98.6% (68/69) F3, 93.5% (130/139) F4.

During the DAAs therapy, 67.9% (226/333) of the patients experienced ADRs. Six hundred and nineteen ADRs, 109 different ones, were reported during the treatment. The most frequent ones were increase in total cholesterol (>200 $mg{\cdot}dL^{-1}$) (11.6%), fatigue (11.3%), headache (10.3%), grade 1 anemia (6.3%) and nausea (5.1%). The frequency of the rest of the ADRs was less than 5%. The majority of the ADRs reported were mild (92.2% grade 1, 6.3% grade 2). However, severe ADRs have been reported in a very low percentage of patients: 1% grade 3 (anemia, hyperbilirubinemia, kidney failure) and 0.5% grade 4 (pancytopenia, drug rash, staphylococcal impetigo). The appearance of ADRs was the reason for discontinuation of antiviral treatment with DAAs in 0.9% of patients.

The univariate analysis of the sociodemographic, epidemiological, histological, and hepatopathy related variants (Table 3), as well as that of laboratory features and virological and pharmacotherapeutic variables (Table 4) carried out, identified a higher baseline of platelets, albumin and total cholesterol as predictive factors of SVR ($p < 0.05$). The presence of diabetes and complications related to liver disease (specifically splenomegaly, portal hypertension, and portal hypertensive gastropathy), BMI ≥30 $kg{\cdot}m^{-2}$,

Table 3. Univariate analysis of sociodemographic, epidemiological, histological and related to liver disease variables.

Variable	SVR (N = 315)[a] Mean ± standard deviation or n(%)	No SVR (N = 14)[a] Mean ± standard deviation or n(%)	p value	Odds Ratio (95%CI)
Male	201 (67%)	12 (85.7%)	0.432	NA
Age (years)	53.7 ± 11.1	54.4 ± 8.4	0.329	NA
BMI ≥ 30 kg·m$^{-[2]}$	29 (9.2%)	6 (42.9%)	0.003	8.483 (2.31–31.06) (Φ = 0.219)
HIV co-infection	94 (29.8%)	4 (28.6%)	1	NA
HBV co-infection	4 (1.3%)	0	1	NA
Diabetes mellitus	39 (12.4%)	5 (35.7%)	0.027	3.932 (1.25–12.33) (Φ = 0.137)
Other comorbidities	215 (68.3%)	13 (92.8%)	0.072	NA
FibroScan® (kPa)	14.4 ± 11.5	23.5 ± 13.6	0.001	1.040 (1.008–1.074)
Cirrhosis	129 (41.9%)	11 (78.6%)	0.085	NA
Complications related to liver disease	91 (28.9%)	11 (78.6%)	0.002	6.514 (1.882–20.124) (Φ = 0.183)
Oesophageal varices	17 (5.4%)	1 (7.1%)	0.553	NA
Portal hypertension	26 (8.2%)	4 (28.6%)	0.030	4.45 (1.303–15.166) (Φ = 0.119)
Ascites	7 (2.2%)	1 (7.1%)	0.297	NA
Steatosis	32 (10.2%)	2 (14.3%)	0.645	NA
Peritonitis	1 (0.3%)	0	1	NA
Hepatic encephalopathy	3 (0.9%)	1 (7.1%)	0.160	NA
Splenomegaly	36 (11.4%)	5 (35.7%)	0.020	4.306 (1.367–13.557) (Φ = 0.147)
Cholelithiasis	36 (11.4%)	3 (21.4%)	1	NA
Cholangitis	1 (0.3%)	0	1	NA
Portal hypertensive gastropathy	4 (1.2%)	2 (14.3%)	0.023	12.958 (2.158–77.819) (Φ = 0.172)
Extra-liver complications	14 (4.4%)	0	1	NA

[a]N represents the number of subjects with response data to antiviral treatment.
SVR: sustained virologic response; BMI: Body mass index; HIV: human immunodeficiency virus; HBV: hepatitis B virus; NA: Not Applicable.

Table 4. Univariate analysis: laboratory parameters and virological and pharmacotherapeutic variables.

Variable	SVR (N = 315) [a] Mean ± standard deviation or n(%)	No SVR (N = 14) [a] Mean ± standard deviation or n(%)	p value	Odds Ratio (95%CI)
Leucocytes cells·mL$^{-[1]}$	6,858 ± 2,693	6,182 ± 2,693	0.125	NA
Haemoglobin g·dL$^{-[1]}$	15 ± 1.8	14.8 ± 1.9	0.807	NA
Platelets cells·mL$^{-[1]}$	184,519 ± 71,723	128,929 ± 71,751	0.003	1.004 (1.001–1.006)
Glucose mg·dL$^{-[1]}$	100 ± 27	125 ± 68	0.005	1.013 (1.003–1.024)
Creatinine mg·dL$^{-[1]}$	0.85 ± 0.29	1.04 ± 0.52	0.184	NA
Total cholesterol mg·dL$^{-[1]}$	165 ± 34	145 ± 23	0.024	0.979 (0.961–0.999)
Albumin g·dL$^{-[1]}$	4.4 ± 0.5	4.1 ± 0.6	0.010	0.322 (0.132–0.786)
AST IU·L$^{-[1]}$	61 ± 42	87 ± 44	0.007	1.010 (1.001–1.019)
ALT IU·L$^{-[1]}$	74 ± 57	86 ± 36	0.047	1.003 (1.001–1.005)
GGT IU·L$^{-[1]}$	107 ± 60	171 ± 113	0.066	NA
ALP IU·L$^{-[1]}$	81 ± 34	115 ± 60	0.034	1.015 (1.006–1.025)
Bilirubin mg·dL$^{-[1]}$	0.78 ± 0.62	0.81 ± 0.55	0.395	NA
Viral load IU·ml$^{-[1]}$	2,938,756 ± 2,135,867	4,856,817 ± 3,514,727	0.051	NA
Non-1 genotype	127 (40.3%)	6 (42.9%)	0.989	NA
RBV	102 (32.4%)	5 (35.7%)	0.777	NA
SMV	20 (6.3%)	3 (21.4%)	0.042	3.856 (2.956–16.887) (Φ = 0.143)
SOF	255 (80.9%)	12 (85.7%)	1	NA
DCV	47 (14.9%)	1 (7.1%)	0.702	NA
DSV	53 (16.8%)	2 (14.3%)	1	NA
LDV	178 (56.5%)	8 (57.1%)	0.963	NA
OMV/PTV/Rtv	61 (19.4%)	2 (14.3%)	1	NA

[a]N represents the number of subjects with response data to antiviral treatment.
SVR: sustained virologic response; NA: Not Applicable; AST: aspartate-aminotransferase; ALT: alanine-aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; DCV: daclatasvir; DSV: dasabuvir; LDV: ledipasvir; OMV: ombitasvir; PTV: paritaprevir; Rtv: ritonavir.

greater liver fibrosis (FibroScan® value), receiving simeprevir, higher baseline levels of glucose, AST, ALT and ALP, have been identified as predictive factors of non-response ($p < 0.05$).

Subsequently, with these values that reach statistical significance, a multivariate analysis, which required two steps to reach the model, was carried out. The following emerged as significant predictors

Table 5. Independent variables included in the final logistic regression model.

	β	SE	Wald	Df	p value	Exp(B)	95CI% for EXP(B)	
							Inferior	Superior
BMI	1.706	0.772	4.886	1	0.027	5.505	1.213	24.979
Complications related to liver disease	2.452	1.102	4.954		0.026	11.310	1.340	100.574
Constant	-5.416	1.021	28.147					

BMI: Body Mass Index; β: β coefficient of Wald test; SE: standard error; Wald: Wald test; Df: degrees of freedom; Exp(B): Odds Ratio;

(Table 5): BMI ≥30 and presence of complications related to liver disease:

- there are 5.505 (95%CI: 1.213–24.979) times more chances of finding BMI ≥30 kg·m^{-2} in the patients that did not reach SVR than those who did.
- there are 11.610 (95%CI %: 1.340–100.574) times more chances of finding complications related to liver disease in the patients who did not achieve SVR than those who did.

The set of variables that remained in the analysis allows us to explain the 24.6% of the variation in the response to the antiviral treatment (Nagelkerke- R2 of 0.246). This model of logistical regression has a high level of specificity (100%). However, the model has not sensibility. This means that the model correctly classifies 100% of the patients who achieved SVR, but cannot classify those who did not. The said model correctly classifies 97% of the patients in this study.

4. Discussion

This study was carried out with a heterogeneous cohort of patients with cHCV, ideal for analyzing, in real life, the effectiveness of the regimens with DAAs, as well as the predictive factors of response to the treatment.

The intention-to-treat SVR rate was 94.6%, similar to that described in clinical trials, whose percentage ranges between 80%-100%, and in real-life studies, where it ranges around 95% [8–11]. This confirms the high power of these drugs when they are used in routine clinical practice. Likewise, it demonstrates the favorable safety profile and the high tolerability of DAAs: 67.9% of the patients have reported some sort of ADRs, which is consistent with data of other studies, reporting that ADRs with DAAs occur in a percentage of patients ranging between 66% and 90%, the majority of grade 1 (92,2%), followed by those of grade 2 (6.3%) [8,11–19]. The low percentage of grade 3 and 4 ADRs detected (1.5%) correlates to the low rate of premature treatment discontinuation for ADRs, already known for the DAAs [8,11–19].

Despite the high SVR rate achieved in the study, treatment failures did occur. The involvement of the different factors that can influence in the achievement of SVR is not well established for the DAAs as certain variables that can condition the antiviral treatment response have been detected in this study. A BMI ≥30 kg·m^{-2} affected negatively the response to antiviral treatment. This fact could be due to a lower bioavailability of RBV because there is more fatty tissue, as well as the chronic inflammatory state that the patients present associated with the release of cytokines and the development of more advanced steatosis and fibrosis. However, it is important to mention that the implication of this parameter in the achievement of SVR is controversial: in regimens based on PEG and RBV, a BMI ≥30 kg·m^{-2} is associated with worse SVR rates [20,21]; however, in DAA-based treatments it seems that it is not a factor that influences the outcome of the therapy [22,23]. Diabetes mellitus has been another predictive factor of non-response found in our work. Before DAAs arrival, both diabetes and high blood glucose levels were positioned as predictive factors of non-response [24,25]. This may be related to the presence of factors that inhibit the antiviral activity of interferon observed in this pathology. However, after the introduction of second-generation DAAs into therapeutics, this statement can be disputed: although, as seen in our study worse response rates continued to be observed in diabetic patients [26] as well as those with high blood glucose levels, recently it has been shown that its presence does not influence the outcome of antiviral treatments [25,27]. Therefore, its effect is not well established.

In our cohort, the SVR rate according to liver fibrosis degree follows the expected pattern, between 77%-100% [8,11–19]: patients with advanced fibrosis show a lower SVR percentage rate (93.5%) than F0–F1, F2 and F3 (97.3%). Liver cirrhosis has been established as a baseline predictive factor of non-response, not only with treatments based on dual therapy with PEG and RBV [28–30] but also with regimens with DAAs [22,27]. In our study, liver cirrhosis did not condition the response to antiviral therapy, most likely due to the maximum optimization of antiviral treatment at the time of initiating the antiviral therapy, which was adjusted to what is purposed in current clinical guidelines [6,11]. Nevertheless, it is important to mention that a greater FibroScan® value was observed in those patients who did not achieve SVR. Therefore, a higher degree of liver fibrosis negatively influences the response to antiviral treatment [10,22,25,26]. This

could be related to a worse perfusion of the drug associated with liver stiffness or with a lower probability of response to treatment in patients with more advanced liver disease [10,17,31–34]. Additionally, it is consistent that since patients with higher degrees of fibrosis present complications related to liver disease (such as splenomegaly, portal hypertensive gastropathy and portal hypertension), said complications are predictive factors of non-response. Furthermore, it is known that platelet count is a parameter inversely proportional with the fibrosis degree, this being a predictive factor of poor response [25,27]. Therefore, it is not surprising that, in our study, where a higher platelet count has acted as a predictive factor for SVR: patients who obtain SVR present a higher level of platelets than those who do not respond to the treatment.

Higher total serum cholesterol has been identified as a predictive factor of SVR in this study, as previously described in the literature [35–37]. This could be related to the fact that patients with higher VL present less total serum cholesterol, due to the hypolipidemia induced by HCV, as a consequence to the formation of a lipoviral complex that facilitates the union of HCV with low-density lipoprotein cholesterol receptors [35,36]. Albumin has also been established as a predictive factor of SVR [22,25,26], something that may be associated with the fact that patients who have a higher amount of this protein also have better liver function. On the other hand, it is known that the elevation of AST, ALT, GGT and of ALP, constitutes an indirect indicator of liver inflammation; thus, higher baseline levels of these proteins act as predictive factors of non-response to the antiviral treatment [22,25,26] as it has been reproduced in our study, except for GGT. Although no significant differences have been found, the baseline level of GGT has been higher in patients who did not reach SVR. In our study baseline bilirubin lacks value as a predictive factor of response. This discrepancy with the literature may be due to the fact that the analysis carried out included cirrhotic and non-cirrhotic patients; therefore, the possible effect that the baseline bilirubin could have as a predictive factor in some of the subgroups of patients was not noticed [22,25,26].

The experience with DAAs suggests that the viral genotype is not a predictive factor of response since SVR percentage rates range between 80%-100%, even though somewhat lower SVR rates have been seen in patients with genotypes 2 and 3 [5,10,12,19,22,25,33,34]. These results have been reproduced in our study: SVR rate is over 90% in all genotypes. Additionally, this was expected since the most effective pharmacotherapeutic regimens were chosen for the management of the disease, as recommended by the current clinical guidelines [6,11]. No statistically significant differences were found in the achievement of SVR in the patients with genotype 1 (1, 1a, 1b) nor other genotypes and co-infection. This finding is relevant since the presence of genotype 1 was considered a predictive factor of treatment failure to PEG-based antiviral therapies but not in the DAA-based treatments, which is also demonstrated in our study. Furthermore, it is important to mention that the VL is a relevant factor when selecting antiviral treatment as it allows selection of therapeutic regimens with a shorter duration, specifically SOF/LVD during 8 weeks if the VL if lower than 6,000,000. $IU{\cdot}ml^{-1}$. Most likely due to the fact that the most effective treatment option was selected for each patient, the VL was not a predictive factor of response to the antiviral therapy treatment in this study, which is consistent with that described in the routine clinical practice studies with regimens that incorporate DAAs[22].

The high SVR rate achieved with the different treatment regimens is consistent with that published in clinical trials, showing the excellent effectiveness of these drugs in real-life situations. It is relevant that in our work the SVR rate obtained is slightly lower with the regimen SOF/SMV±RBV, a result consistent with the positioning of the presence of SMV in the treatment regimen as a predictive factor of non-response. This could be primarily related to two reasons. One of them is that SOF and SMV were the first DAAs incorporated into routine clinical practice, and, at that moment, priority was given to the treatment of patients with advanced fibrosis, that presented SVR rates <90% with those regimens [12,38,39]. The other reason is that these pharmacotherapeutic regimens are the ones with the lowest effectiveness in the published literature [12,13,38,39].

The multivariate analysis to which we have submitted our results detected the following independent factors of non-response: BMI ≥30 $kg{\cdot}m^{-2}$ and presence of complications related to liver disease. On the one hand, this result can be explained because high BMI is associated with a chronic inflammatory state and, in consequence, with a higher liver inflammation and degrees of hepatic fibrosis [20,21]. On the other hand, complications related to liver disease are also associated to more advanced disease, and therefore, worse response to antiviral treatment [10,17,31]. Despite this model explains only the 24.6% of the variation in the response to the treatment, this percentage is slightly higher than those explained by other models in order to predict the response to DAA treatment, that explain the 11.4%[25].

The retrospective study design and the low number of patients included in some subgroups are two of the limitations found in the study. Furthermore, due to the revolution in the field of HCV treatment, our results cannot be fully comparable in the present moment since the recommendations of the latest published guidelines have not been included and currently less used regimens have been studied.

5. Conclusions

In conclusion, it is important to note that the high rate of effectiveness with the second-generation DAAs shown in clinical trials has been maintained in routine clinical practice, as well as their safety, establishing these antivirals as safe and well-tolerated drugs. Despite this fact as DAAs treatment failures continue to occur, further research on predictive factors of response is required in order to develop more reliable and reproducible predictive models.

Acknowledgements

Doctoral thesis "Antivirales de acción directa frente al virus de la hepatitis C: efectividad e impacto de las intervenciones farmacéuticas realizadas durante el seguimiento farmacoterapéutico" .

Disclosure statement

All authors certify that there is no actual or potential conflict of interest in relation to this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon request.

Authorship statement

All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

- María E. Cárdaba-García has contributed to: the study concept and design, data acquisition, analysis and interpretation, drafting of the manuscript, critical revision of the manuscript and statistical analysis.
- Encarnación Abad-Lecha has contributed to: critical revision of the manuscript and study supervision.
- Miguel A. Calleja-Hernández has contributed to: critical revision of the manuscript and study supervision.

Ethics approval statement

This study was approved by the Research Commission of the Clinical University Hospital of Valladolid.

ORCID

María E. Cárdaba-García http://orcid.org/0000-0001-7933-1766
Miguel Á. Calleja-Hernández http://orcid.org/0000-0001-8449-5490

References

[1] World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection; 2014 [cited 2021 Mar 15]. https://apps.who.int/iris/bitstream/handle/10665/111747/9789241548755_eng.pdf;jsessionid=89B0E2C75E55C49262893DB9E04E8D5B?sequence=1.
[2] World Health Organization. Hepatitis C. Key facts 2019 [cited 2021 Mar 15] https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.
[3] Shaheen MA, Idrees M. Evidence-based consensus on the diagnosis, prevention and management of hepatitis C virus disease. World J Hepatol. 2015;7(3):616–627.
[4] Kholi A, Shaffer A, Sherman A, et al. Treatment of hepatitis C. A systematic review. JAMA 2014;312(6):631–640.
[5] Doyle JS, Aspinall E, Liew D, et al. Current and emerging antiviral treatments for hepatitis C infection. Br J Clin Pharmacol. 2013;75(4):931–943.
[6] European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C. J Hepatol. 2015;63:199–236.
[7] Ley Orgánica 3. 2018. de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. BOE, 6 de diciembre de 2018. núm. 294.
[8] Chamorro De Vega E, Rodríguez González CG, Giménez Manzorro A, et al. Hepatitis C virus infection and the role of a pharmaceutical care program. Am J Health Syst Pharm. 2020;77(6):479–486.
[9] Yamamoto H, Ikesue H, Ikemura M, et al. Evaluation of pharmaceutical intervention in direct-acting antiviral agents for hepatitis C virus infected patients in an ambulatory setting: a retrospective analysis. J Pharm Health Care Sci. 2018;4:17.
[10] Daniel KE, Saeian K, Rizvi S. Real-world experiences with direct-acting antiviral agents for chronic hepatitis C treatment. J Viral Hepat. 2020 Feb;27(2):195–204.
[11] Asociación Española para el Estudio del Hígado. Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Guías AEEH/SEIMC para el manejo de la Hepatitis C 2016 [cited 2020 Mar 30]. https://seimc.org/contenidos/gruposdeestudio/gehep/dcientificos/documentos/gehep-dc-2016-Manejo_HepatitisC.pdf.
[12] Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2014;384:414–426.
[13] Foster GR, Pianko S, Brown A, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology. 2015;149(6):1462–1470.
[14] Jacobson IM, Gordon SC, Kowdley KV, et al. POSITRON Study; FUSION Study. Sofosbuvir for hepatitis

C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;368(20):1867–1877.
[15] Zeuzem S, Dusheiko GM, Salupere R, et al. VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993–2001.
[16] Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and Sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889–1898.
[17] Reddy KR, Bourlière M, Sulkowski M, et al. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: an integrated safety and efficacy analysis. Hepatology. 2015;62(1):79–86.
[18] Pol S, Bourliere M, Lucier S, et al. Safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients. J Hepatol. 2017;66(1):39–47.
[19] Calleja JL, Crespo J, Rincon D, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real-world cohort. J Hepatol. 2017;66(6):1138–1148.
[20] Meer EG, Lee YJ, Osinusi A, et al. Effect of sofosbuvir and ribavirin treatment on peripheral and hepatic lipid metabolism in chronic hepatitis C virus, genotype 1-infected patients. Hepatology. 2015;61(3):790–801.
[21] Jain A, Kalra BS, Srivastava S, et al. Effect of sofosbuvir and daclatasvir on lipid profile, glycemic control and quality of life index in chronic hepatitis C, genotype 3 patients. Indian J Gastroenterol. 2019;38(1):39–43.
[22] De Pace V, Morelli MC, Ravaioli M, et al. Efficacy, safety and predictors of direct-acting antivirals in hepatitis C virus patients with heterogeneous liver diseases. New Microbiol. 2019;42(4):189–196.
[23] Bressler BL, Guindi M, Tomlinson G, et al. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. Hepatology. 2003;38:639–644.
[24] Romero Gómez M, Fernández Rodríguez CM, Andrade RJ, et al. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. J Hepatol. 2008;48:721–727.
[25] Shousa HI, Saad Y, Doa´a AS, et al. Simple predictors of nonresponse to direct acting antivirals in chronic hepatitis C patients. Eur J Gastroenterol Hepatol. 2020;32(8):1017–1022.
[26] Aziz H, Aziz M, Lateef M. Analysis of host and viral-related factors associated to direct acting antiviral response in hepatitis C virus patients. Viral Inmunol. 2018;31(3):256–263.
[27] Colussi G, Donnini D, Brizzi RF, et al. Sustained virologic response to direct-acting antiviral agents predicts better outcomes in hepatitis C virus-infected patients: a retrospective study. World J Gastroenterol. 2019;25(40):6094–6106.
[28] Snoeck E, Wade JR, Duff F, et al. Predicting sustained virological response and anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD) plus ribavirin. Br J Clin Pharmacol. 2006;6:699–709.
[29] Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002;347:975–982.
[30] Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med. 2000;343:1666–1672.
[31] Dultz G, Müller T, Petersen J, et al. Effectiveness and safety of direct-acting antiviral combination therapies for treatment of hepatitis C virus in elderly patients: results from the German hepatitis C registry. Drugs Aging. 2018;35(9):843–857.
[32] Leroy V, Angus P, Bronowicki JP, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: a randomized phase III study (ALLY-3+). Hepatology. 2016;63(5):1430–1441.
[33] Perelló C, Carrión JA, Ruiz Antoran B, et al. Effectiveness and safety of ombitasvir, paritaprevir, ritonavir ± dasabuvir ± ribavirin: an early access programme for Spanish patients with genotype 1/4 chronic hepatitis C virus infection. J Viral Hepat. 2017;24(3):226–237.
[34] Asselah T, Hézode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. Lancet Gastroenterol Hepatol. 2016;1(1):25–35.
[35] Akuta N, Suzuki F, Kawamura Y, et al. Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: amino acid substitutions in the core region and lowdensity lipoprotein cholesterol levels. J Hepatol. 2007;46:403–410.
[36] Del Valle J, Mira JA, De Los Santos I, et al. Baseline serum low-density lipoprotein cholesterol levels predict response to hepatitis C virus therapy in HIV/hepatitis C virus coinfected patients. AIDS. 2008;22:923–930.
[37] El Sagheera Gm Solimanb E, Ahmada A, Hamdyc L. Study of changes in lipid profile and insulin resistance in Egyptian patients with chronic hepatitis C genotype 4 in the era of DAAs. Libyan J Med. 2018;13(1):1435124.
[38] Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368:1878–1887.
[39] Alam I, Brown K, Donovan C, et al. Real-world effectiveness of simeprevir-containing regimens among patients with chronic hepatitis C virus: the SONET study. Open Forum Infect Dis. 2017;4(1):258.