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Influence of drug–drug interactions on effectiveness and safety of direct-acting antivirals against hepatitis C virus

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Abstract

Objectives. Direct-acting antivirals are the recommended treatment for hepatitis C-infected patients. Drug–drug interactions with concomitant treatments can cause lack of effectiveness and/or safety. The objective of this study is to characterise drug–drug interactions of direct-acting antivirals and to analyse their influence both on the effectiveness of antiviral treatment and on the overall safety of pharmacological treatment in hepatitis C-infected patients.

Methods. Observational and prospective cohort study for 3 years in the pharmaceutical care outpatient consultation of a general hospital, undertaking detection, evaluation and management of drug–drug interactions by clinical pharmacists and physicians. The main outcome measures were sustained virologic response at week 12 for effectiveness and serious drug-related adverse events for safety. Multivariate statistical analysis applied to: (a) patient basal characteristics related to presence of drug–drug interactions; (b) previous antiviral treatments, viral genotype, cirrhosis, decompensations and presence of drug–drug interactions related to the effectiveness of direct-acting antivirals.

Results. Of a total of 1092 patients, the majority of them were men, around 60 years old and HCV-genotype 1 mono-infected, with a high basal viral load, naive to antiviral treatment, treated with ledipasvir/sofosbuvir and without cirrhosis. 24.5% had drug–drug interactions. Proton pump inhibitors were the concomitant drugs that caused the most drug–drug interactions. Age ≥65 years and direct-acting antivirals based on protease inhibitors were independently related to the presence of drug-drug interactions ($p \leq 0.012$). All (100%) of the therapeutic recommendations based on detected drug–drug interactions were implemented; 97.7% of patients with interactions versus 99.0% without them reached sustained virologic failure ($p=0.109$). The serious adverse events rates were 1.5% and 1.3% in patients with and without drug-drug interactions, respectively ($p=0.841$).

Conclusions. Drug–drug interactions are frequent among hepatitis C-infected patients receiving treatment with direct-acting antivirals. However, the collaboration between physicians and clinical pharmacists makes it possible to detect, evaluate, avoid or clinically manage these drug–drug interactions, in order to maintain whole treatment therapeutic safety and the effectiveness of direct-acting antivirals.

INTRODUCTION

Chronic hepatitis C (CHC) is a liver disease caused by the hepatitis C virus (HCV). The WHO estimates that around 71 million people are chronically infected with HCV, which is estimated to be responsible for approximately 400 000 deaths per year worldwide.[1] Interferon (IFN) or pegylated interferon (Peg-IFN) alone, or in association with ribavirin (RBV), were initially used to treat hepatitis C. In 2011, two direct-acting antivirals (DAAs) were approved for HCV chronic infection in combination with Peg-IFN and RBV—telaprevir and boceprevir. Recently, second-generation

DAAs have been approved, and are currently the treatment of choice for CHC. DAAs act directly on HCV replication, interfering with structural or functional protein coding. Sofosbuvir (SOF) and dasabuvir (DBV) are inhibitors of RNA-dependent RNA polymerase (NS5B); ledipasvir (LDV), ombitasvir (OBV), daclatasvir (DCV), velpatasvir (VEL), elbasvir (ELB) and pibrentasvir (PIB) are NS5A protein inhibitors; simeprevir (SMV), paritaprevir (PTV), grazoprevir (GZV), glecaprevir (GRZ) and voxilaprevir (VOX) are NS3 or NS4A protein inhibitors.[2] The oral administration of two or three DAAs over 8–24 weeks, associated or not with RBV, achieves therapeutic efficacy rates of around 98% and has demonstrated a high level of clinical safety. For these reasons, DAAs are the gold standard of CHC treatment.[3]

The selection of DAAs against HCV requires an individualised approach based on virus-dependent factors (viral genotype, subtype), patient factors (presence of liver cirrhosis) or the previous use of antivirals.[4] It is also very important to incorporate other factors into this selection, dependent on the concomitant pharmacological treatment, such as drug–drug interactions (DDIs). This is due to the fact that DAAs share pharmacokinetic pathways, both at the level of transporters and the metabolisation/ elimination pathways (cytochrome P450 3A4, P-glycoprotein, breast cancer resistance protein or UDP-glucuronyltransferase), with drugs belonging to therapeutic groups widely used in patients chronically infected with HCV, such as antiretroviral drugs (ART) against the acquired HIV, illicit/ recreational drugs or drugs of abuse, lipid-lowering drugs, central nervous system drugs, cardiovascular agents, immunosuppressants, and anticoagulants/ antiplatelets or antacids.[5,6] Therefore, the potential pharmacokinetic interactions between these drugs and the DAAs could cause an increase (and, secondarily, a higher incidence of adverse events) or a decrease (with the consequent lack of effectiveness) in their plasma concentrations.[7–10]

In Spain, DAAs have been marketed as Hospital Use Drugs (H); they can be prescribed only by specialist hospital physicians (infectious disease specialists or hepatologists) and can be dispensed only by pharmacists in hospital pharmacy services. In addition, the prescription of DAAs requires compliance with the National Strategic Plan for the Approach of Hepatitis C in the National Health System Statements.[11] For this reason, clinical pharmacists specialising in clinical virology at our hospital have managed a large number of hepatitis C-infected patients in a monographic outpatient consultation,[12] carrying out, among other functions, the identification, evaluation and follow-up of DDIs[13 14] in collaboration with the medical team, as have been established in international recommendations.[15]

The aim of this study is to characterise the DDIs of the DAAs (identification, evaluation and clinical management) and analyse their influence, both in the effectiveness of antiviral treatment and in the overall safety of pharmacological treatment in hepatitis C-infected patients.

METHODS

Study design and patient selection

This is a unicentric, observational, prospective, cohort study of hepatitis C-infected patients who started DAA-based antiviral treatment and who had reached week 12 post-treatment. Antiviral treatment selection and prescription decisions corresponded to the hospital specialist doctors, under usual clinical practice conditions valid during the study period, in accordance with current international guidelines.[4,5] Adult patients, with CHC, treatment-naïve or treatment-experienced to peg-INF+ RBV or DAAs, in all fibrosis stages (F0-4), including patients with decompensated cirrhosis or portal hypertension, HIV co-infected patients or liver transplant patients, were included.

Drug–drug interaction variables

DDIs were identified by the clinical team (clinical pharmacists, hepatologists and infectious disease specialists) using the Hep Drug Interactions database of the University of Liverpool,[16] recommended as reference by the European Association for the Study of the Liver (EASL).[5] Where no information was available, Lexicom Drug Interactions,[17] IBM Micromedex,[18] analysis of pharmacokinetic parameters available in the technical data sheet, and consultation with the DAA manufacturing laboratory were employed. When a DDI was identified, the drugs and their therapeutic group, the enzymes and drug transporters involved, the pharmacokinetic effect (indeterminate, increase or decrease in plasma concentration) and interaction potency, that were stratified in three levels (high, that contraindicates the drug association, potential, or potential-weak) were registered; these variables (enzymes, drug transporters, mechanisms, potency, etc) were identified through the drug interaction databases previously mentioned.[16–18] Therapeutic recommendation for the concomitant drug secondary to DDIs was classified into: treatment continuation with effectiveness and/or safety monitoring, temporary suspension, administration time adjustment, dosage regimen adjustment or therapeutic substitution; both medical doctors and clinical pharmacists were responsible, although the latter implemented—without the intervention of the medical doctors—those recommendations related to effectiveness and/ or safety monitoring when no dose adjustment was required, temporary withdrawal of concomitant drug during antiviral treatment or adjustment of the administration schedule.

Effectiveness and safety variables

Pharmacological treatment effectiveness and safety follow-up were carried out through SiMON, an artificial intelligence monitoring system for CHC patients on treatment, that records effectiveness and safety events from clinical data.[19]

HCV viral load (defined as the RNA HCV in plasma) was determined using the real-time PCR technique with the Cobas AmpliPrep platform from Roche. The kit is the HCV Quantitative Test, version 2.0. The limits of detection and quantification in plasma (there is no significant difference in the serum) were 11 IU/mL (95% CI 10 to 13 IU/mL) for the lower limit of detection (LOD) with a 95% positive result rate and 15 UI/mL for LOD with positive results. Viral load determinations were made at the baseline, end-of-treatment and 12 weeks after the antiviral treatment was completed. Transient elastography was used for the staging of liver fibrosis (Fibroscan), stratifying patients according to stiffness results in fibrosis F0-1 (<7.6 kPa), F2 (7.6–9.5 kPa), F3 (9.6–14.4 kPa) or F4 (>14.4 kPa in HCV mono-infected patients and >14.0 kPa in HIV co-infected patients).

Adherence rates were made following continuous measurement of the medication acquisition (CMA) method,[20] during monthly visits to the Hospital Pharmacy Service where the study was conducted, from the beginning to the end of the treatment.

The primary effectiveness endpoint was the sustained virologic response 12 (SVR12), defined as RNA-HCV undetectable 12 weeks post-treatment. Secondary efficacy variables were null response (lack of RNA-HCV undetectability during DAA treatment) and recurrent (RNA-HCV detectable 12 weeks post-treatment in a patient with RNA-HCV undetectable at the end-of-treatment). The primary safety endpoint was the rate of serious drug-related AEs; secondary variables included drug-related AEs, DAA or concomitant treatment withdrawal due to drug-related AEs, emergency department or hospitalisation secondary to drug-related AEs and death secondary to drug-related AEs.

Statistical analysis

The intention-to-treat (ITT) evaluable population included all patients who took at least one dose of the prescribed treatment. Both baseline variables (demographics, clinical, histological and laboratory values and frequencies) and primary or secondary effectiveness and safety end-points were analysed by a modified ITT (mITT) analysis, including ITT evaluable population patients and excluding patients without quantification of RNA-HCV 12 weeks post-treatment for reasons other than treatment failure. Quantitative variables were expressed as mean±SD or as median and IQR if their distributions were normal or non-normal, respectively, and were analysed using the Student's t-test or the Mann-Whitney U-test, according to data distribution. Qualitative variables were expressed as count and percentage, with confidence intervals at 95% (95% CI), and were compared using a χ^2 test or Fisher's exact test. Primary end-points were expressed as a percentage and an exact 95% binomial CI. To determine any baseline factor influence on primary end-points, relative risk with a 95% CI (Katz) for cohort studies was calculated using the χ^2 association test without Yates correction, or Fisher's exact bilateral test according to the number of cases analysed. To detect differences between cohorts related to DDI presence based on demographic characteristics of the study population and the influence of DDI on virologic response, univariate and multivariate analyses were performed. Statistically significant results were considered at a value of $p<0.05$. Statistical analysis was carried out using the Epidat 4.2 programme.

Ethics approval

This study complies with the Declaration of Helsinki of Good Clinical Practice. It was classified in 2015 as 'Observational Post-Authorisation Study with Human Medicines' by the Spanish Agency of Medicines and Health Products, and it was authorised by the Clinical Research Ethics Committee (CREC) of the Regional Health Service (2015). Patients signed an informed consent approved by the CREC for their participation in the study and all their data were anonymised.

RESULTS

A total of 1092 patients who met the selection criteria were included in the study. The majority of patients were men, around 60 years old and HCV mono-infected, genotype 1, with a high basal viral load, naïve to antiviral treatment and without cirrhosis. A minority of patients had hepatocellular carcinoma or liver transplantation. The most frequent antiviral treatments were LDV/SOF±RBV and PTV/OBV/RTV+DBV± RBV for 12 weeks. table 1 summarises the main baseline characteristics of the study patients.

Table 1 Demographic and virological characteristics of the study Population

	Patients with DDI, % (n) 24.5% (267)	Patients without DDI, % (n) 75.6% (825)	P value
Gender			
Males	21.6% (147)	78.4% (534)	0.006
Females	29.2% (120)	70.8% (291)	
Age, mean±SD (years)	62.3±12.7	56.3±12.5	<0.001
Age ≥65 years	45.7% (122)	26.2% (226)	<0.001
HCV genotype			
1	83.9% (224)	65.6% (541)	<0.001
2	3.4% (9)	6.3% (52)	0.097
3	5.2% (14)	15.7% (130)	<0.001
4	7.5% (20)	12.4% (102)	0.037
Fibrosis stage			
F0-1	15.7% (42)	17.2% (142)	0.640
F2	29.6% (79)	32.5% (268)	0.419
F3	22.5% (60)	24.0% (198)	0.669
F4	32.2% (86)	26.3% (217)	0.073
HIV co-infection (excluding ART)	14.6% (39)	13.0% (107)	0.495
HIV co-infection (including ART)	39.3% (105)	5.0 (41)	<0.001
Hepatocellular carcinoma	5.2% (14)	2.9% (24)	0.106
Liver transplant recipient	5.2% (14)	3.5% (29)	0.207
HCV viral load, log UI/mL (median)	6.2 (3.7–8.3)	6.2 (2.0–8.9)	0.989
HCV viral load ≥ 61 UI/mL	59.9% (160)	59.9% (494)	
eGFR ≥60 mL/min	88.8% (237)	92.4% (762)	0.067
Previous antiviral treatment:			
Naive	75.7% (202)	71.6% (591)	0.201
Treatment-experienced	24.3% (65)	28.4% (234)	0.201
Response to previous antiviral treatment:			
Recurrent	52.3% (34)	54.3% (127)	0.779
Null responder	10.8% (7)	17.1% (40)	0.215
Regrowth	4.6% (3)	3.4% (8)	0.650
Partial responder	10.8% (7)	14.1% (33)	0.485
Unknown	21.5% (14)	11.1% (26)	0.029
DAAs:			
LDV/SOF±RBV	51.6% (138)	48.7% (402)	0.401
DCV/LDV±RBV	4.9% (13)	15.8% (130)	<0.001
VEL/SOF±RBV	1.9% (5)	3.2% (26)	0.274
PTV/OBV/RTV/DBV±RBV	33.7% (90)	17.8% (147)	<0.001
SMV/SOF±RBV	0.8% (2)	2.9% (24)	0.044
SOF+RBV	0.8% (2)	3.8% (31)	0.013
PTV/OBV/RTV+RBV	2.6% (7)	1.9% (16)	0.500
ELB/GRZ	3.7% (10)	5.9% (49)	0.168
DAAs adherence	99.6%	99.2%	0.707

ART, antiretroviral treatment; DAAs, direct-acting antivirals; DBV, dasabuvir; DCV, daclatasvir;DDI, drug–drug interactions; ELB, elbasvir; GRZ, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin;RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir; eGFR, estimated glomerular filtration rate.

It was found that 24.5% (95% CI 21.9% to 27.0%) of the patients had clinically significant DDIs between antiviral and concomitant treatments. A total of 427 DDIs in 267 patients were detected in the study population (1.60±0.95 DDIs per patient): 60.7% of patients had one DDI, 27.7% had two DDIs and the remainder (11.6%) had three or more DDIs. The mean age of women with DDIs was 66.7±11.6 years and of men was 58.4±12.3 years ($p<0.001$). Figure 1 shows the incidence of DDIs according to DAAs. The multivariate analysis revealed that only two variables were related to the DDIs' presence, namely having an age ≥65 years (OR 1.8, 95% CI 1.3 to 2.5; $p<0.001$) and antiviral treatment that includes protease inhibitors (OR 1.5, 95% CI 1.1 to 2.1; $p=0.012$). The main therapeutic group that generated clinically significant interactions was A02 (agents for the treatment of alterations caused by acids) with more than 25% of the cases, followed by N05 (psycholeptics) and C10 (lipid modifiers drugs) with percentages higher than 10%; 22.3% of the DDIs were generated by omeprazole, followed by amlodipine and atorvastatin, with percentages around 5–7%. Although the enzymes involved in the interactions are unknown in more than 25% of cases, those that are known include P-glycoprotein and CYP3A4, both with percentages around 20%. In relation to the potency of the interaction, 82.7% of the cases were of intermediate intensity (potential) and only 5.2% of cases contraindicate the concomitant use of the drug and antivirals. Two-thirds (67.2%) of the DDIs detected did not affect the DAAs. However, 66.3% of the DDIs detected affected the concomitant medication, increasing their pharmacokinetic exposure; as a consequence, 54.1% (95% CI 49.3% to 58.9%) of detected DDIs required any therapeutic recommendation on the concomitant treatment, mainly temporary withdrawal during antiviral treatment (47.3%), administration schedule adjustment (30.7%), dose adjustment (19.0%) or therapeutic alternative prescription (3.0%). The remaining detected DDIs (45.9%) were not avoided since they only required closer clinical patient monitoring (such as renal function control or blood pressure follow-up). The compliance rate for all types of therapeutic recommendations or clinical monitoring based on detected DDIs was 100%. The concomitant medication was interrupted during the antiviral treatment in 24.6% of cases with PTV/OBV/ RTV+DBV versus 24.5% with LDV/SOF ($p=0.919$). The most frequently discontinued drugs as a result of DDIs were atorvastatin (79.2%), simvastatin (72.7%) and pantoprazole (45.5%) ($p>0.109$). table 2 summarises the description of the DDIs in the studied population.

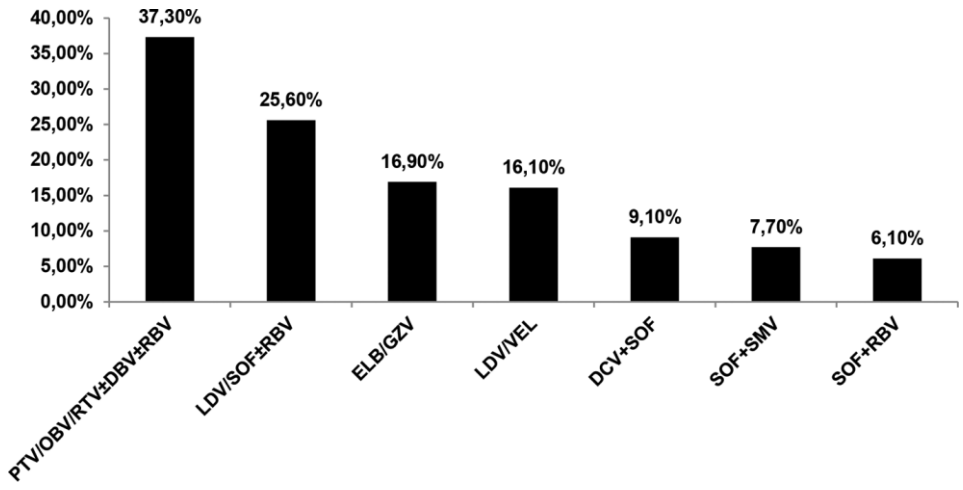

Figure 1 Incidence of drug–drug interactions according to direct-acting antiviral agent. DBV,dasabuvir; DCV, daclatasvir; ELB, elbasvir; GRZ, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir

Table 2 Descriptions of direct-acting antiviral drug-drug interactions in the study population

	% (n)
N° of DDIs	427
N° DDI/patient, median (range)	1 (1–6)
N° DDI/patient, mean±SD	1.6±1.0
Common DDIs by ATC:	
A02 (drugs for acid related disorders) 2	7.2% (116)
N05 (psycholeptics)	12.9% (55)
C10 (lipid modifying agents)	11.5% (49)
C09 (agents acting on the renin-angiotensin system)	9.8% (42)
C08 (calcium channel blockers)	7.7% (33)
DDI by concomitant drug (five most frequent)	
Omeprazole	22.3% (95)
Amlodipine	6.8% (29)
Atorvastatin	5.6% (24)
Lorazepam	3.3% (14)
Alprazolam	3.0% (13)
Main enzymes and drug transporters involved (five most frequent)	N=486
Indeterminate	25.9% (126)
P-gp	20.0% (97)
CYP3A4	19.8% (96)
OATP1B1	8.8% (43)
BCRP	8.2% (40)
Strength of DDI (%)	
Potential interaction	82.7% (353)
Potential weak interaction	12.2% (52)
Contraindicated	5.1% (22)
Concomitant drug pharmacokinetic effect on DAAs	
No effect	67.3% (287)
Decreased exposure	17.3% (74)
Indeterminate	8.4% (36)
Increased exposure	7.0% (30)
DAA pharmacokinetic effect on concomitant drug	
Increased exposure	66.3% (283)
No effect	24.1% (103)
Decreased exposure	7.0% (30)
Indeterminate	2.6% (11)
Therapeutic recommendation on concomitant drug	
No dose alteration is required	45.9% (196)
Temporary withdrawal during antiviral treatment	25.6% (109)
Administration schedule adjustment	16.6% (71)
Dose adjustment	10.3% (44)
Therapeutic alternative prescription	1.6% (7)

ATC, anatomical therapeutic classification; BCRP, breast cancer resistant protein; CYP3A4, cytochromo P450 3A4;DAA, direct-acting antiviral; DDI, drug–drug interactions; OATP1B1, organic-anion-transporting polypeptide 1B1; P-gp, P-glycoprotein.

Regarding the DDIs' impact on the effectiveness of antiviral treatment, 97.7% (95% CI 95.1% to 99.1%) of patients with clinically significant interactions, compared with 99.0% (95% 98.0% to 99.6%) of patients without them, reached SVR12 (p=0.109). The rates of virological non-response or relapse patients are clinically and statistically similar in both cohorts, between 1–2% (p≥0.258). The multivariate analysis did not detect that being naïve to treatment, viral genotype, liver cirrhosis, previous decompensations or presence of DDIs had an influence on the effectiveness of DAAs (p>0.25). The incidence of any adverse event degree in patients with versus without DDIs was clinically similar: 55.8% versus 48.0% (p=0.027). The rate of serious adverse events was 1.5% (95% CI 0.4% to 3.8%) and 1.3% (95% CI 0.7% to 2.4%) in patients with and without DDIs (p=0.841), respectively. After the initiation of antiviral treatment, the presence of any degree of adverse event had not led to antiviral or concomitant treatment withdrawal in either of the two cohorts. Likewise, no patient had attended the emergency department or had died as a result of the presence of DDIs. In the cohort of DDI patients, one with uncontrollable vomiting had to be hospitalised, although the patient already had this symptomatology before the start of antiviral treatment and was discharged a few days after being prescribed antiemetic treatment. The adverse events of greater incidence in both cohorts have been very similar, highlighting fatigue/asthenia and headache, which are the most frequent adverse events of DAAs treatment. The main data regarding the effectiveness and safety of patients with and without DDIs is shown in table 3.

Table 3 Effectiveness and safety of DAA treatment based on the presence of DDIs

	Patients with DDI N=267	Patients without DDI N=825	
	% (n)	% (n)	P value
Virologic response			
SVR12	97.7% (258)	99.0% (804)	0.109
Null responder	1.1% (3)	0.5 (4)	0.258
Recurrent	1.1% (3)	1.6% (13)	0.588
No data	1.1% (3)	1.6% (13)	0.593
Drug-related adverse events	55.8% (149)	48.0% (396)	0.027
Drug-related serious adverse events	1.5% (4)	1.3% (11)	0.841
DAA treatment withdrawal due to drugrelated AE	0.0% (0)	0.0% (0)	>0.999
Concomitant treatment withdrawal secondary to drug-related AE	0.0% (0)	0.0% (0)	>0.999
Emergency department admission secondary to drug-related AE	0.0% (0)	0.0% (0)	>0.999
On-treatment hospitalisation secondary to drug-related AE	0.38% (1)	0.0% (0)	0.552
Death secondary to drug-related AE	0% (0)	0% (0)	>0.999
Any grade AE with global incidence >2.0%:			
Fatigue/asthenia	32.2% (86)	35.4% (292)	0.342
Headache	15.0% (40)	20.6% (170)	0.043
Pruritus	6.4% (17)	6.4% (53)	0.974
Insomnia	5.6% (15)	5.4% (45)	0.919
Dry skin and mucous membranes	4.5% (12)	3.6% (30)	0.526
Nausea	4.1% (11)	3.4% (28)	0.579
Gastrointestinal upset	3.0% (8)	3.0% (25)	0.977
Dizziness	3.0% (8)	3.5% (29)	0.684
Diarrhoea	2.6% (7)	1.0% (8)	0.044
Myalgia	2.2% (6)	1.7% (14)	0.560

AE, adverse events; DAA, direct-acting antiviral; DDIs, drug–drug interactions; SVR12, sustained virologic response week 12.

DISCUSSION

DDIs are a critical factor in the effectiveness and safety of pharmacological treatments. Given the pharmacokinetic characteristics of the new DAAs against HCV, the clinical pharmacist must be able to detect, evaluate, and adequately and proactively manage DDIs in the pharmaceutical care outpatient consultation, and the DDIs must be evaluated in clinical practice in order to know their real impact on the effectiveness and safety of antiviral treatment and the concomitant treatments.

Data from this study reveal that almost a quarter of hepatitis C-infected patients present DDIs, a lower percentage than observed in previous studies in cohorts of patients with a similar average age, HCV viral genotype, degree of fibrosis and selected DAAs.[21 22] The vast majority of the DDIs detected had a 'potential' effect on the plasma concentrations of the drugs (according to the scale used), due mainly to an increase in the exposure of the concomitant medication and, as a consequence, temporary suspension, dose adjustment, administration scheme adjustment or the use of a therapeutic alternative were required. However, in most cases, DAAs did not modify their plasma concentrations and, therefore, modification of the dosage regimen was not required. In a very small percentage of cases, the presence of DDIs carried the concomitant medication withdrawal. Although univariate analysis revealed that the age and gender of the patient, HCV

genotype, antiretroviral treatment in HIV co-infected patients and DAAs used could determine the presence of DDIs, only age ≥65 years and treatment with protease inhibitors were associated with the presence of DDIs, as revealed by previous studies.[23–26] Other baseline factors, such as degree of liver fibrosis, advanced fibrosis or presence of cirrhosis, hepatocarcinoma, liver transplantation or impaired renal function, did not affect the incidence of DDIs in our study. It is important to highlight the repercussion that ART has on the presence of DDIs in our study; in this sense, the current recommendations on the treatment of HCV[4 5] emphasise that an ART assessment of the co-infected HIV–HCV patient should be performed due to the interactions derived from the inhibition or induction of CYP450, involved in the pharmacokinetics of ART and DAAs. This is especially significant when HIV treatment includes protease inhibitors or ART enhancers.[27–30] However, the recent changes in relation to recommended drugs for the treatment of HIV,[31 32] that positioned HIV integrase inhibitors as preferred, potentially reduce the incidence of DDIs with DAAs, as the results of this study show. Another subgroup of hepatitis C-infected patients with special attention in relation to DDIs are patients with chronic kidney disease and renal or hepatic transplant patients.[33–35] This is due to the elimination routes of immunosuppressants used to avoid organ rejection; however, our study did not detect a higher prevalence of DDIs in patients with impaired renal function, or liver transplant patients.

Proton pump inhibitors are the therapeutic group which causes most DDIs, specifically omeprazole. Previous studies of this specific interaction reveal that an adequate identification and follow-up of the recommendations in relation to their temporary suspension, substitution or administration schedule adjustment will not affect the effectiveness of the antiviral treatment.[36 37] Other medications related to the detection of DDIs in this study are those related to the cardiovascular system and the psycholeptics; an adequate control of blood pressure by dose adjustment of antihypertensive agents and the temporary suspension of lipid-lowering agents has allowed the control of the pathology of these patients.

According to our study's data, an adequate DDI identification, evaluation and implementation of the recommendations indicated for each DDI detected in all patients did not affect the antiviral effectiveness or therapeutic safety of hepatitis C-infected patients on DAA treatment. SVR12 rates in this study were very high and very similar in patients with or without DDIs; the same occurs with secondary efficacy variables, such as non-response or virological recurrence. In this sense, although several studies have evaluated the presence of DDIs in real clinical practice,[22 38–40] very few have analysed the impact on the general safety of the treatment or the antiviral effectiveness; the results of the study by Ottman *et al*[22] show no differences in SVR12 between patients who have at least one DDI versus those who do not have interactions. In relation to therapeutic safety, we can affirm that there is no clinically significant difference in the treatment safety between patients with and without DDIs. We have observed that although DDIs statistically increase the rate of patients with adverse events, these are of a mild nature and do not cause the DAA or concomitant treatment withdrawal, or admission to the emergency room or hospitalisation of the patient, or his/her death. Also, the type and frequency of the most characteristic adverse effects are similar in the two cohorts.

This is the first study to analyse the influence of detection, evaluation and management of DDIs on DAA and concomitant treatment, not only in terms of the antiviral effectiveness but also of therapeutic safety in hepatitis C-infected patients. It has the strengths of being a prospective, comparative study with more than 1000 patients analysed. Among the limitations is that it is a unicentric study, so the demographic characteristics and localhealthcare practice could have had an influence on the observedresults.

In conclusion, a significant percentage of hepatitis C-infected patients receiving DAA treatment presented clinically significant DDIs with their concomitant treatment. Being over 64 years of age and starting antiviral treatment based on protease inhibitors led to a higher incidence of DDIs. No clinical differences were observed between antiviral effectiveness and therapeutic safety among patients with or without clinically significant DDIs. Pharmaceutical care from clinical pharmacists

specialising in clinical virology in a multidisciplinary team allows not only the detection or evaluation of detected DDIs, but also the implementation of all the therapeutic recommendations in the hepatitis C-infected patient, helping to preserve the high levels of effectiveness and safety of these treatments.

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