Original

RESP

Impact of potential multiple drug-drug interactions on the adverse event profile of patients with hepatitis C treated with pangenotypic direct-acting antivirals in Spain

Juan Turnes[1], Antonio García-Herola[2], Ramón Morillo-Verdugo[3], Marinela Méndez[4], Cándido Hernández[5], Antoni Sicras-Mainar[6]

[1]Gastroenterology and Hepatology Department. CHU. Pontevedra. Spain.
[2]Digestive Medicine Department. Hospital Marina Baixa de Villajoyosa (Alicante). Spain.
[3]Hospital Pharmacy. Hospital de Valme. AGS Sur de Sevilla. Spain.
[4]Medical Affairs. Gilead Sciences S.L. Madrid. Spain.
[5]Global Medical Affairs. Gilead Sciences Europe Ltd. U.K.
[6]Health Economics and Outcomes Research. Atrys Health. Barcelona. Spain.

ABSTRACT

Objectives: Direct-acting antivirals (DAAs) share pharmacokinetic pathways with many comedications commonly administered to patients living with chronic hepatitis C virus (HCV) infection (PLWHCV). International guidelines recommend a thorough drug-drug interaction (DDI) risk assessment prior to starting DAA therapy and before starting comedications. This study aims to evaluate the impact of potential multiple DDIs in the real-life adverse event (AE) profile of PLWHCV treated with DAAs.

Material and method: This is a retrospective, observational study using electronic medical records. Patients included were PLWHCV and were treated with either the protease inhibitor (PI) free DAA sofosbuvir/velpatasvir (SOF/VEL) or glecaprevir/pibrentasvir (GLE/PIB) between 2017 and 2020. Potential (single and multiple) DDIs were identified using the Liverpool HEP Interaction Checker. AEs potentially associated to DDIs were identified during DAA treatment period.

Results: 1620 patients with DAA prescriptions (SOF/VEL or GLE/PIB) were included. Of these, 123 were predicted to have multiple DDIs (multi-DDI). About 10% (123/1256) of the patients receiving ≥2 comedications were at risk of multi-DDI with DAA. Most comedication-associated AEs were recorded in this multi-DDI population (88.9%, 16/18), meaning that 13% (16/123) of the multi-DDI population suffered AEs. According to DAA regimen, more comedication-associated AEs were reported in GLE/PIB-treated as compared with SOF/VEL-treated patients (18.3% [13/71] vs 5.8% [3/52] $p<0.05$). These AEs were mainly reported by primary care physicians (62.5%).

Discussion: PLWHCV predicted to have multiple DDIs are at high risk of AEs. Moreover, fewer comedication-associated AEs were identified with the PI-free DAA SOF/VEL as compared with GLE/PIB.

Key words: adverse events; clinical pharmacology; drug combinations; hepatology; polypharmacy; virology.

Text received: 11/07/2024 Text accepted: 16/10/2024

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major public health issue which affects an estimated 58 million people globally[1]. The development of pangenotypic direct-acting antiviral agents (DAAs) has brought about a major advance in HCV treatment, with sustained virological response rates ≥ 95%[2]. As well as being highly effective, these agents are well tolerated, with few restrictions on their use. This favourable efficacy and safety profile is reflected in simplified treatment regimens recommended by the European Association for the Study of the Liver (EASL) to facilitate rapid treatment algorithms. However, the number of patients with comorbidities and associated polypharmacy has increased[3,4]. In patients with polypharmacy there is an increased risk of potential drug-drug interactions (DDIs), and an association between adverse drug reactions, which represent a public health issue, and DDIs have been recently reported[5]. Therefore, it is essential to consider patient comorbidities, comedication and polypharmacy of PLWHCV for potential DDIs when choosing a DAA[6].

Antiviral treatments for HCV comprise three families of DAAs, each acting in different phases of the HCV life cycle[7]. DAAs can act as substrate, inhibitor and/or inducer of drug transporters and metabolising CYP enzymes, meaning that they can lead to DDIs with the concomitant medications administered to the patient[7-9]. DAAs share pharmacokinetic pathways with comedications commonly administered to PLWHCV[8–10], such as cardiovascular drugs, particularly statins and anti-hypertensives, neuropsychiatric drugs and proton pump inhibitors (PPIs). These drugs have a high potential for DDIs that either result in an increased exposure of the patient to comedication or DAA, with potential consequent drug toxicity, or a decrease in concentration of either DAA or comedication, and therefore reduced efficacy[8,9]. Moreover, polymedication increases the chance of multiple DDIs[11].

DDIs can be avoided by careful patient management. Awareness of DDIs can help avert potential drug toxicities and is essential to ensure optimal treatment outcomes[10]. Thanks to progress in HCV antiviral therapy, modern DAAs carry a significantly lower risk of DDIs than first-generation DAAs such as boceprevir and telaprevir[12]. Despite this, the prevalence of DDIs remains stable, affecting around 40% of PLWHCV, and attributable to polypharmacy (likely in an aging HCV patient population), or multiple comorbidities associated with HCV infection[12,13].

Current DDI evaluation with the Hep Interaction Checker developed by the University of Liverpool[14] is based on a theoretical analysis of pharmacokinetic pathways shared by DAAs and comedications. However, there is a lack of clinical practice data on the impact of multiple DDIs in hepatitis treatment, including effectiveness and reported adverse events (AEs). Several previous studies have evaluated DDIs by studying pairwise interactions in HCV patients receiving DAAs and another medication[3,15–20]. However, this does not reflect the polypharmaceutical reality of many PLWHCV.

Although a recent Italian study has characterized the polymedication regimens in PLWHCV treated with DAAs[11], the association between comedication-associated AEs and the multi-DDI profile of PLWHCV remains unknown. The aim of the present study was to evaluate for the first time the impact of potential multiple DDIs in the real-life adverse event profile of PLWHCV treated with the two currently widely used antiviral regimens in clinical practice in Spain: sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (GLE/PIB). Demographic characteristics, comorbidities, and the real-life safety profile of patients with potential multi-DDIs treated with SOF/VEL or GLE/PIB were analysed.

MATERIALS AND METHODS

This observational, retrospective study was carried out on a total of 1.81 million patients, and was conducted using electronic medical records (EMR) data from primary care and hospitals in Spain integrated in the BIG-PAC® database[18] and supplementary databases of public health services from seven autonomous communities in Spain.

Briefly, the BIG-PAC® database contains demographic and clinical data, including comorbidities/comedication, and healthcare resources and costs from EMR of patients. Records are anonymised prior to their inclusion in the database. Patient's data were analysed one month before treatment initiation, during DAA treatment (8 or 12 weeks) and in the 6-month post-treatment follow-up period. Patient demographics, comorbidities/comedications were identified at the index date (Figure 1) using the BIG-PAC® database. Patient comorbidities were recorded according to the International Classification of Diseases (9th edition) Clinical Modification (ICD-09-CM) and were characterised based on the Charlson

Rev Esp Sanid Penit. 2024;26(3):98-112
10.18176/resp.00095

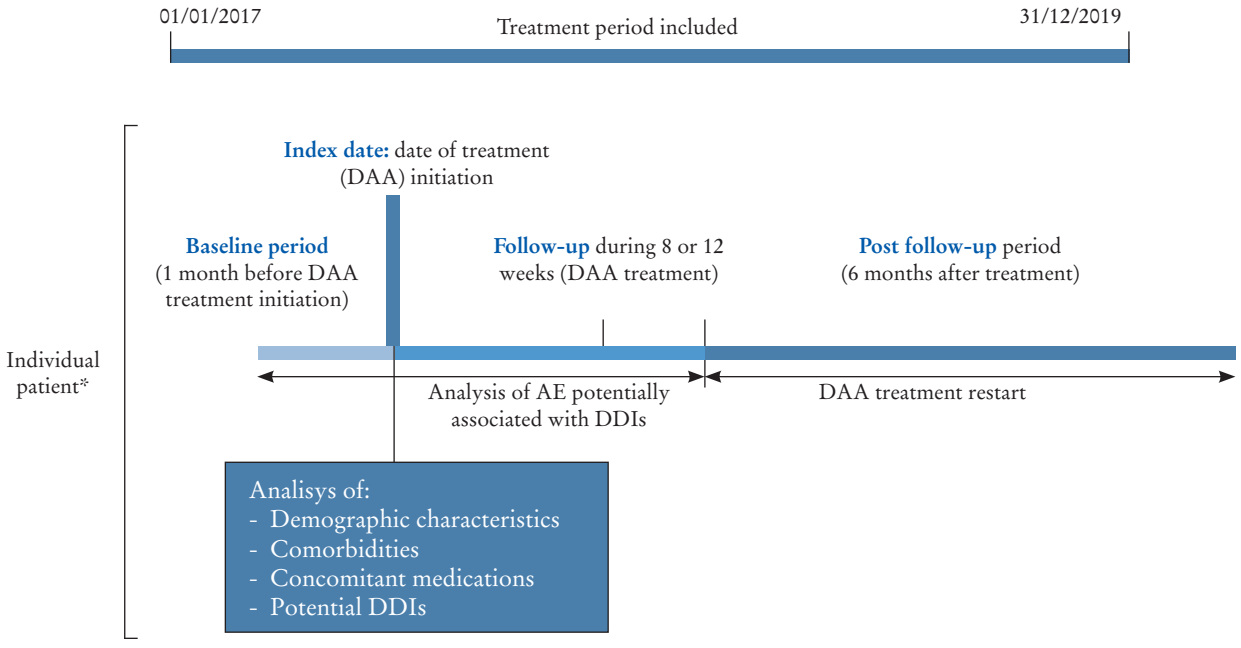
comorbidity index[21]. Patient comedication data were retrieved from prescription records (according to medical practice) and categorised under the Anatomical Classification (ATC) System[22].

Confidentiality of the EMR (anonymous and dissociated) was respected in accordance with the European General Data Protection Regulation (2016/679) and Organic Law (3/2018) on Data Protection and Guarantee of Digital Rights. This study was approved by the Clinical Research Ethics Committee of the Unió Catalana Balears de Hospitals de Barcelona, Spain (reference:15/49) and was carried out in compliance with the Helsinki Declaration of 1964, and its amendments. Patient consent was not obtained, as Spanish legislation excludes existing data aggregated for analysis.

Patients included in the study were ≥18 years old and initiated DAA treatment with SOF/VEL or GLE/PIB (index date was the date of initiation) between 2017-2020. Patients were required to meet the following criteria: (i) active patients defined as ≥2 EMR in the database at least 12 months before the index date, (ii) patients with regular monitoring (≥1 EMR during the DAA treatment period), and (iii) patients in the prescription programme (≥1 prescription during the 6-month post-treatment follow-up period). Patients who transferred to other centres, were displaced, out of the area or permanently institutionalised were excluded. There were no missing values in any patients; absence of treatment/studied characteristic was assumed as the patient not having that treatment/characteristic.

DDI analysis

Potential DDIs between comedication taken by patients and either SOF/VEL or GLE/PIB treatment were identified at the index date using the University of Liverpool's HEP Drug Interaction Checker (accessed November 2020)[14]. The University of Liverpool's HEP Drug Interaction Checker is a free resource from the University of Liverpool used to check drug-drug interactions; its use to assess DDI interactions prior to starting new DAA therapy is recommended by the European Association for the Study of the Liver (EASL)[6], the American Association



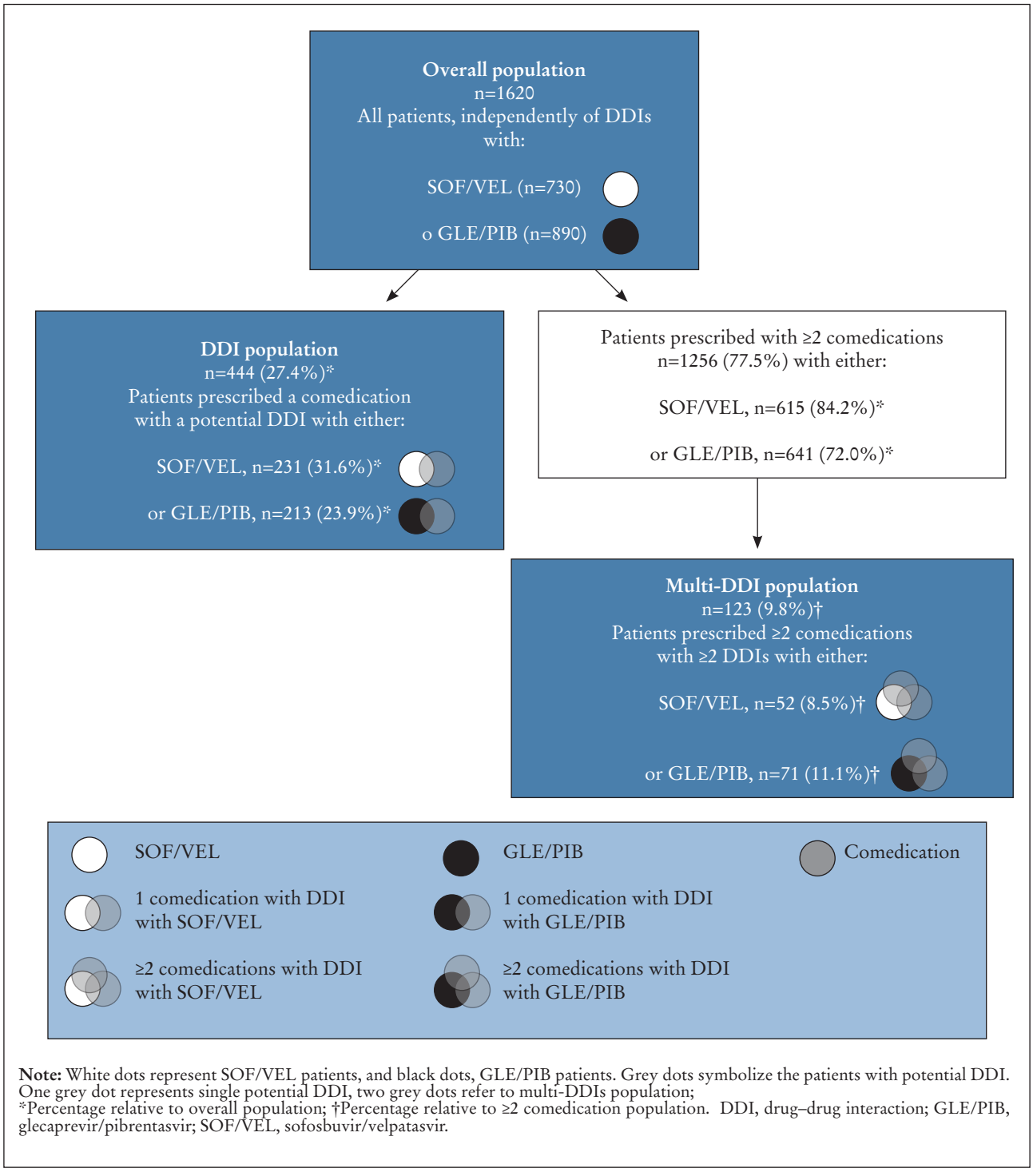
Note: * Inclusion criteria: (i) active patients defined as ≥2 Electronic Medical Records (EMR) in the database at least 12 months before the index date, (ii) patients with regular monitoring (≥1 EMR during the DAA treatment period), and (iii) patients in the prescription program (≥1 prescription during the 6-month post-treatment follow-up period). Patients who transferred to other centres, were displaced, were out of the area or permanently institutionalized were excluded. DAA refer to SOF/VEL and GLE/PIB. AE, adverse events; DAA, direct-acting antivirals; DDI, drug-drug interactions; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir.

Figure 1. Study summaries. Study diagram. Observational retrospective study.

for the Study of Liver Diseases and the Infectious Disease Society of America (AASLD-IDSA)[23,24] and the National Prisons Hepatitis Network (NPHN)[25].

Identified DDIs were recorded with the drug therapeutic group, the pharmacokinetic effect and the strength of the interaction as assigned in the Hep Drug Interaction Checker. Interactions were categorised as:

- contraindications (drugs that should not be coadministered).



Note: White dots represent SOF/VEL patients, and black dots, GLE/PIB patients. Grey dots symbolize the patients with potential DDI. One grey dot represents single potential DDI, two grey dots refer to multi-DDIs population;
*Percentage relative to overall population; †Percentage relative to ≥2 comedication population. DDI, drug–drug interaction; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir.

Figure 2. Study summaries. Study diagram and patient populations stratified by comedication use and risk of DDIs.

Rev Esp Sanid Penit. 2024;26(3):98-112
10.18176/resp.00095

- potential or clinically significant interaction (requires additional monitoring, alteration of drug dosage or timing of administration).
- weak interaction (additional action is unlikely).
- no interaction expected.

The effects of the DDI were categorised as:

- an increase in plasma concentration of comedication.
- an increase in plasma concentration of DAAs.
- a decrease in plasma concentration of DAAs.

Multiple DDI patients were those receiving ≥2 comedications with potential DDIs with the DAA.

AEs potentially connected to DDIs identified by the ICD-9-CM codes E930–E949 (identifies drugs, medicinal and biological substances causing adverse effects in therapeutic use) and 990-995 (identifies other unspecified effects of external causes) during the DAA treatment period were recorded together with the drug classification associated with these AEs. We also analysed the actions taken by physicians during the DAA treatment regarding comedication with potential multi-DDIs associated with AEs, the reporting medical specialty. Any modifications to treatment regimens, including discontinuation, dose decrease or change of comedications during DAA treatment, were recorded. Any requirement for a new DAA treatment within 6 months of the end of SOF/VEL or GLE/PIB treatment was considered as an indirect indicator of lack of effectiveness of the DAA regimen.

Statistical analysis

Data collected from the BIG-PAC® database were validated by Structured Query Language (SQL) commands and reviewed using an exploratory analysis to ensure quality and consistency[18]. A descriptive univariate statistical analysis was performed, and absolute and relative frequencies were calculated for qualitative data. Quantitative data were expressed using means, standard deviations (SD), medians and interquartile ranges (IQR). Bi-variant statistical analyses were carried out using the analysis of variance (ANOVA) and Chi-squared tests for independent groups. The duration of the DAA treatment was estimated in SOF/VEL and GLE/PIB treated patients. The statistical software IBM/SPSS was used for analyses. Values of $p<0.05$ were considered statistically significant.

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Identification of the overall population and comedications prescribed

A total of 1620 patients who met the selection criteria were included in the study (overall population), 730 patients were treated with SOF/VEL and 890 patients with GLE/PIB (Figure 2). The demographic characteristics of the overall population are summarized in Table 1.

Each of the 1620 patients were prescribed ≥1 comedication(s). In fact, 77.5% (1256/1620) were prescribed ≥2 comedications, 84.2% (615/730) with SOF/VEL treatment and 72.0% (641/890) with GLE/PIB treatment (Figure 2). A higher mean number of comedications/ patient were prescribed in the SOF/VEL treatment group compared with the GLE/PIB treatment group (3.8 vs 2.3, $p<0.001$) (Table 1).

The most frequent comedication classes were related to the central nervous system (CNS, 35.8%), the alimentary tract and metabolism (24.1%), and the cardiovascular system (14.2%) (Table 1).

Identification of patients with potential DDIs and multi-DDIs

The Hep Drug Interaction Checker identified the comedications with potential DDIs with DAA regimens[14]. A total of 444 out of the 1620 patients (27.4%) were prescribed ≥1 comedication with a potential DDI with their DAA treatment, 231 in the group of patients treated with SOF/VEL and 213 in the GLE/PIB treatment group. These patients comprised the DDI population (Figure 2).

Of the 1256 overall population patients prescribed ≥2 comedications, 123 patients were predicted to have multiple DDIs, defining the multi-DDI population (patients with ≥2 comedications with ≥2 DDIs with DAAs). Therefore, about 10% (123/1256) of the overall population prescribed ≥2 comedications with ≥2 DDIs are at risk of multi-DDI. The percentage of patients at risk of multi-DDI referring to the overall population was 7.6% (123/1620). Of 123 patients with multi-DDIs, 52 were in the SOF/VEL-treatment group and 71 in the GLE/PIB-treatment one (Figure 2).

Adverse events in the overall population

In the overall population, 18 AEs associated with comedications were identified, each in a different patient, (14 vs 4 [$p<0.05$]) with GLE/PIB and SOF/VEL, respectively) (Table 1; Figure 3A). All AEs reported were associated with the most prescribed

Table 1. Demographic and clinical characteristics, comedication and DDI profile, most common comedications, AEs by DAA, and actions taken during DAA treatment in the overall population.

Overall population				
	SOF/VEL (n = 730; 45.1%)	GLE/PIB (n = 890; 54.9%)	Total (N = 1,620; 100%)	*P* value
Demographic characteristics				
Median age, years (IQR)	55 (49-61)	53 (46-59)	54 (48-60)	
Male, n (%)	451 (61.8)	532 (59.8)	983 (60.7)	0.411
Clinical characteristics				
Comorbidities associated with CHC				
Arterial hypertension, n (%)	168 (23.0)	181 (20.3)	349 (21.5)	0.192
Diabetes, n (%)	102 (14.0)	100 (11.2)	202 (12.5)	0.097
Heart failure, n (%)	23 (3.2)	19 (2.1)	42 (2.6)	0.089
Renal insufficiency, n (%)	31 (4.2)	28 (3.1)	59 (3.6)	0.239
HIV, n (%)	33 (4.5)	28 (3.1)	61 (3.8)	0.148
General comorbidity				
Charlson index, mean (SD)	1.1 (1.7)	0.7 (1.3)	0.9 (1.5)	<0.001
0, n (%)	347 (47.5)	528 (59.3)	875 (54.0)	
1, n (%)	214 (29.3)	227 (25.5)	441 (27.2)	
2, n (%)	75 (10.3)	62 (7.0)	441 (8.5)	
≥3, n (%)	94 (12.9)	73 (8.2)	167 (10.3)	<0.001
Disease severity				
Hepatic cirrhosis, n (%)	57 (7.8)	41 (4.6)	98 (6.0)	0.007
FIB-4 score, n (%)				
F0–F1, <1.45 points	299 (41.0)	425 (47.8)	724 (44.7)	
F2, 1.45–3.25 points	155 (21.2)	216 (24.3)	371 (22.9)	
F3–F4, >3.25 points	276 (37.8)	249 (28.0)	525 (32.4)	<0.001
Other features				
Mean time since diagnosis, years (SD)	3.8 (4.1)	3.7 (3.9)	3.7 (4)	0.474
Mean BMI, kg/m^2 (SD)	28.3 (4.1)	28 (3.8)	28.1 (4)	0.105
Comedication and DDI profile				
Total prescribed comedications, n	2,790	2,031	4,821	
Prescribed comedications per patient (mean, SD)	3.8 (1.1)	2.3 (1.0)	3.0 (1.1)	<0.001
Medicines administered with potential DDI, n (%)*	293 (10.5)	326 (16.1)	619 (12.8)	
Concomitant medications				
Number of active ingredients prescribed (n, %)	2,790 (57.9)	2,031(42.1)	4,821 (100)	
Active ingredients prescribed / patient (mean, SD)	3.8 (1.1)	2.3 (1.0)	3.0 (1.1)	<0.001
ATC Therapeutic group (n, %) †				
A Digestive system and metabolism‡	680 (24.4)	480 (23.6)	1.160 (24.1)	
B Blood and hematopoietic organs	110 (3.9)	72 (3.5)	181 (3.8)	
C Cardiovascular system‡	408 (14.6)	277 (13.6)	685 (14.2)	
D Dermatological drugs	78 (2.8)	59 (2.9)	136 (2.8)	
G Genitourinary system	42 (1.5)	40 (2.0)	82 (1.7)	
H Systemic hormonal preparations	34 (1.2)	40 (2.0)	74 (1.5)	
J Anti-infectives for systemic use	48 (1.7)	23 (1.1)	71 (1.5)	
L Antineoplastics and immunomodulators	13 (0.5)	14 (0.7)	27 (0.6)	
M Musculoskeletal system	136 (4.9)	149 (7.4)	285 (5.9)	
N Nervous system‡	1,032 (37.0)	692 (34.1)	1,724 (35.8)	
P Antiparasitic products	4 (0.1)	10 (0.5)	14 (0.3)	
R Respiratory system	163 (5.8)	132 (6.5)	295 (6.1)	
S Sense organs	44 (1.6)	37 (1.8)	81 (1.7)	
V Various	1 (0.0)	7 (0.3)	8 (0.2)	<0.001

(continued)

Rev Esp Sanid Penit. 2024;26(3):98-112
10.18176/resp.00095

Table 1. Demographic and clinical characteristics, comedication and DDI profile, most common comedications, AEs by DAA, and actions taken during DAA treatment in the overall population (*continuation*).

Overall population				
	SOF/VEL (n = 730; 45.1%)	GLE/PIB (n = 890; 54.9%)	Total (N = 1,620; 100%)	*P* value
AEs by DAA treatment group and most common comedication				
Comedication group with AE				
Nervous system, n	0	4		
Antipsychotics, n (%; n/N)§	0 (0; 0/90)	2 (12.5; 2/16) (extrapyramidal, sedation)		
Fentanyl, n (%; n/N)§	0 (0; 0/9)	1 (33.3; 1/3) (digestive)		
Oxcarbazepine, n (%; n/N)§	0 (0; 0/4)	1 (33.3; 1/3) (digestive)		
Cardiovascular, n	4	9		
Lipid-lowering drugs, n (%; n/N)§	2 (5.0; 2/40) (myalgia/myopathy)	6 (17.1; 6/35) [myalgia/myopathy]		<0.001
Enalapril, n (%; n/N)§	1 (1.9; 1/52) (respiratory)	2 (6.1; 2/33) (respiratory)		<0.05
Carvedilol, n (%; n/N)§	1 (16.6; 1/6) (bradycardia)	1 (12.5; 1/8) (bradycardia)		
Alimentary, n	0	1		
Omeprazole, n (%; n/N)§	0 (0; 0/119)	1 (1.1; 1/95) (digestive)		
Total, n (%; n/total)‖	4 (0.5; 4/730)	14 (1.6; 14/890)		
Actions taken during DAA treatment for comedications with AE-associated comedications with potential DDIs				
AE	4	14		
Clinical actions to manage DDI (number of patients, AE-associated comedication)				
Clinical monitoring	1, Simvastatin¶	1, atorvastatin¶		
Monitoring ECG (Electrocardiogram)	0	1, carvedilol¶		
Discontinuation (DAA)	1, Carvedilol¶**	3, quetiapine**, atorvastatin (2)**		
Discontinuation (co-medication)	1, Atorvastatin¶	2, oxcarbazepine¶, simvastatin**		
Dose Reduction	1, Enalapril¶	5, pravastatin¶, paliperidone**, enalapril (2)¶, simvastatin¶		
Switch	0	2, fentanyl**, omeprazole¶		
Total	4	14		

Note. *Percentage relative to total prescribed comedications; †percentage relative to the total of active ingredients prescribed; ‡these therapeutic groups were the most prescribed; §n indicates the number of patients with AEs, N, the number of patients receiving the specific comedication (with DDI with any of the DAA regimens) /comedication class linked to AEs, the percentage is relative to patients treated with the comedication/comedication class with AEs; ||Percentage relative to the overall population; ¶AEs associated with comedications were reported by primary care physicians (61.1% [10/18]); **AEs associated with these comedications were reported by gastroenterologists (38.9% [7/18]).

AE, adverse event; BMI, body mass index; CHC, chronic hepatitis C; DAA, direct-acting antiviral; DDI, drug–drug interaction; FIB-4, Fibrosis-4 Index for liver fibrosis; GLE/PIB, glecaprevir/pibrentasvir; HIV, human immunodeficiency virus; IQR, interquartile range; multi-DDI, multi drug-drug interaction; SD, standard deviation; SOF/VEL, sofosbuvir/velpatasvir.

comedication therapeutic groups, cardiovascular, CNS and alimentary comedications.

For cardiovascular system comedications, most AE were associated with lipid-lowering drugs, with a greater number associated with atorvastatin or simvastatin (contraindicated for GLE/PIB) in the GLE/PIB group as compared to SOF/VEL treated patients (17.1% [6/35] vs 5% [2/40], respectively, p<0.001) (Table 1). No AEs were reported for CNS comedications in SOF/VEL-treated patients and no action from the physician was required. However, AEs were reported within the GLE/PIB-treated group involving antipsychotics, fentanyl, and oxcarbazepine (Table 1). Out of the two reported AEs associated with antipsychotics: one was related to paliperidone (sedation), requiring a dose reduction of the comedication and another with quetiapine (extrapyramidal syndrome), resulting in DAA discontinuation (Table 1).

Adverse events associated with multiple potential DDIs

Analysis of patients with recorded AEs showed that 88.9% (16/18) had a multi-DDI profile, therefore, 13.0% of the patients in the multi-DDI population (16/123) had AEs. Around three times more AEs were reported in GLE/PIB-treated patients as compared to SOF/VEL-treated patients (18.3% [13/71]) vs 5.8% [3/52] p<0.05) (Table 2; Figure 3B). Most multi-DDI patients with reported AEs (94% [15/16]) were prescribed ≥1 comedication with a potential DDI predicted to increase comedication exposure. Moreover, two thirds of the multi-DDI patients who reported AEs (62.5% [10/16]) were prescribed ≥2 comedications, all with a potential DDI predicted to increase comedication (Table 2). These AEs were mainly reported by primary care physicians (62.5%) and to a lesser extent by specialists that prescribed the DAA (37.5%) (Table 3).

Resource utilization and medical actions taken for AE management in the multi-DDI population

All AE required medical actions or resource utilizations. The most frequent actions were discontinuation (of comedication or DAA) and dose reduction of comedication, and these were more frequent in the GLE/PIB-treated group, as this group presented almost three times more AE than the SOF/VEL-treated group. Three DAA discontinuations were reported in GLE/PIB-treated patients, two associated with atorvastatin, and one with quetiapine; one was reported in the SOF/VEL treated group associated with carvedilol. Regarding dose reductions, all were reported in the GLE/PIB-treated group associated with paliperidone, enalapril and simvastatin (Table 3).

Demographic characteristics and comorbidities in the multi-DDI population

DDA treatment groups (SOF/VEL vs GLE/PIB) in the multi-DDI population were compared by analysing the following: demographic variables, general comorbidity (estimated by the Charlson index), and hepatic fibrosis prediction according to the FIB-4 (Fibrosis-4 Index for liver fibrosis) score. In the multi-DDI population, 52 patients (median age, 59 years; 57.7% male) were treated with SOF/VEL, and 71 patients (median age, 61 years; 53.5% male) were treated with GLE/PIB. Comorbidities were balanced between both treatment groups (Table 3).

DAA effectiveness and DDIs in the overall population and multi-DDI population

DAA treatment effectiveness was assessed indirectly by recording new DAA regimens started within the 6 months following the end of the SOF/VEL or GLE/PIB treatment (these was designated as a treatment restart). In total, 17 DAA restarts were recorded in 1% (17/1620) of the overall population; 1% (7/730) of the SOF/VEL-treated patients and 1% (10/890) of the GLE/PIB-treated patients (Table 4).

Of the SOF/VEL-treated patients with DAA restarts, 5/7 patients had a risk of ≥1 DDI linked to decreased exposure to DAA. 10/10 of the GLE/PIB-treated patients with recorded DAA restarts had at least one potential DDI linked to decreased plasma concentration to DAA (Table 4).

Regarding multi-DDI population, 9.8% (12/123) did not achieve effectiveness and had to restart with a new DAA within 6 months after completing DAA treatment: 9.9% (7/71) for GLE/PIB-treated and 9.6% (5/52) of SOF/VEL-treated patients. Of these, 91.7% (11/12) were multi-DDI patients with at least one predicted DDI decreasing DAA concentration (Table 4).

DISCUSSION

The development of effective, well-tolerated pangenotypic DAAs has allowed a wide population of PLWHCV to be considered for treatment. As the population eligible for therapy broadens, there is an increasing need to understand the potential

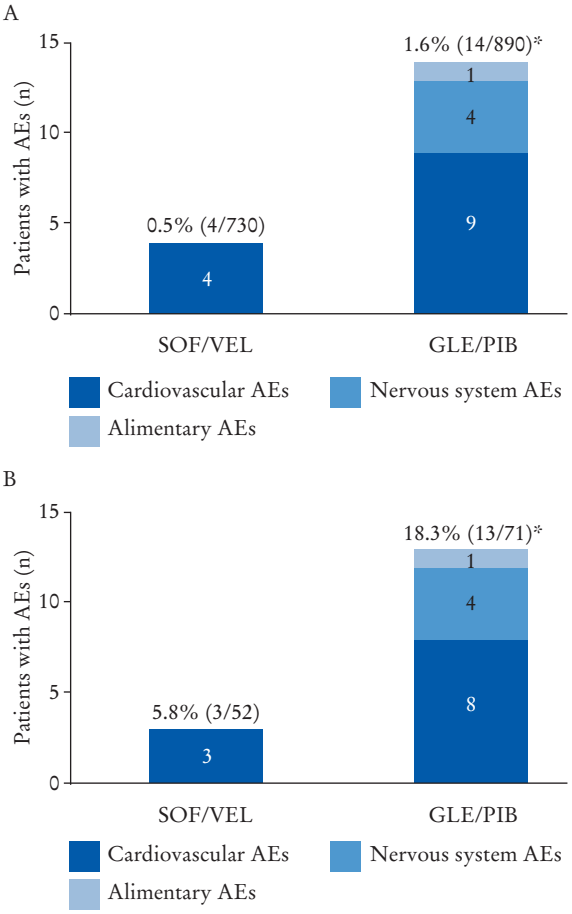
Rev Esp Sanid Penit. 2024;26(3):98-112
10.18176/resp.00095

Table 2. Reported AEs associated with comedications in SOV/VEL and GLE/PIB treated patients with a multi-DDI profile.

DAA*	Comedication group associated with AE†	AE and comedication associated‡	% AE by therapeutic group (n/N)§	Comedications by potential DDI outcome‖								Nº of patients with AEs¶
				↑ Comedication				↓ DAA		↑ DAA		
SOF/VEL (n = 52)	Cardiovascular (n = 24)	Myalgia/myopathy (atorvastatin)	12.5% (3/24)	Atorvastatin	Carvedilol**			Omeprazole				1
		Myalgia/myopathy (simvastatin)		Simvastatin	Silodosin			Omeprazole				1
		Bradycardia (carvedilol)		Carvedilol**				Metamizole	Omeprazole			1
GLE/PIB (n = 71)	Cardiovascular (n = 43)	Myalgia/myopathy (atorvastatin)	18.6% (8/43)	Atorvastatin	Quetiapine			Omeprazole				1
		Myalgia/myopathy (simvastatin)		Simvastatin				Rabeprazole		Candesartan		1
		Myalgia/myopathy (atorvastatin)		Atorvastatin	Enalapril			Dulaglutide	Omeprazole			1
		Myalgia/myopathy (atorvastatin)		Atorvastatin	Carvedilol**	Repaglinide	Tacrolimus	Ranitidine				1
		Myalgia/myopathy (simvastatin)		Simvastatin	Fentanyl	Quetiapine	Tacrolimus	Metamizole	Omeprazole			1
		Bradycardia (carvedilol)		Carvedilol**	Amiodarone			Liraglutide				1
		Respiratory (enalapril)		Atorvastatin	Enalapril			Metamizole	Omeprazole			1
		Respiratory (enalapril)		Enalapril				Metamizole				1
	Nervous system (n = 29)	Digestive (oxcarbazepine)	13.8% (4/29)					Oxcarbazepine	Omeprazole			1
		Extrapyramidal (quetiapine)		Carvedilol**	Quetiapine							1
		Sedation (paliperidone)		Paliperidone				Pantoprazole				1
		Digestive (fentanyl)		Fentanyl	Bilastine	Tacrolimus		Omeprazole	Sevelamer			1
	Alimentary (n = 58)	Digestive (omeprazole)	1.7% (1/58)	Olmesartan				Metamizole	Omeprazole			1
	Strength of interaction	Contraindicated	Significant	Weak							Total	16

Note. *Patients with multi-DDI profile treated with each DAA regimen (SOF/VEL or GLE/PIB). †Patients treated with comedications associated with an AE and stratified by comedication group (cardiovascular, nervous system or alimentary). The total number of patients within each therapeutic comedication group is higher than the total number of multi-DDI patients as patients are prescribed comedications from different therapeutic groups. ‡Comedication associated with an AE type; §Percentage of AEs by therapeutic group resulting from the ratio between n (the number of patients with AEs according to therapeutic classification), and N (the number of multi-DDI patients prescribed at least one comedication with a potential DDI with DAA and associated with AEs according to comedication therapeutic classification). ‖Comedications associated with an AE in patients at risk of multiple DDIs are coloured according to strength of DDI. The potential outcome is defined as an increase in comedication (↑ comedication, associated with a possible impact on safety), a decrease in DAA (↓ DAA, possible impact on efficacy), and/or increase in DAA (↑ DAA, associated with a possible impact on safety); ¶Number of multi-DDI patients with AEs associated with comedication according to comedication therapeutic classification (cardiovascular, nervous system or alimentary); **Carvedilol is also predicted to increase DAA exposure. No AEs were reported in SOF/VEL-treated patients with potential multiple DDIs within the nervous system (0/24) or alimentary tract and metabolism (0/49) therapeutic classifications.
AE, adverse event; DAA, direct-acting antiviral; DDI, drug–drug interaction; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir.

clinical impact of the interaction between DAAs and comedications used to manage basal comorbidities. International HCV management guidelines, including the EASL, recommend a thorough DDI risk assessment prior to starting DAA therapy and before starting comedications[6,26,27].



Note: 18 AEs were identified in total, each in a different patient.
A) Number of AEs associated with comedications in the SOF/VEL-treated and GLE/PIB treated patients overall. AEs are shown as composite (4 vs 14).
*p-value < 0.05, and stratified by comedication therapeutic categories;
B) Percentages indicate the ratio of AEs associated with comedications in the SOF/VEL-treated and GLE/PIB treated patients in the multi-DDI population, respectively.
**P*-value < 0.05
AE, adverse event; DAA, direct-acting antiviral; DDI, drug–drug interaction; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir.

Figure 3. Comedications-associated reported AEs according to DAA treatment A) AEs in the overall population; B) AEs associated with comedications in patients with a multi-DDI profile.

This observational retrospective study evaluates for the first time the impact of potential multi-DDIs in the real-life AE profile of PLWHCV treated with the two widely used DAA treatments in clinical practice in Spain.

Previous studies assessing the risk of DDI between comedications and DAA treatment regimens, have estimated that 12-60% of patients prescribed DAAs are at risk of a potential DDI[4,12,15].

In agreement, we observed that 27.4% of the patients in our setting were prescribed ≥1 comedications, each one with a potential DDI with their DAA treatment. However, most of the previous studies have evaluated DDIs by studying pairwise interactions in PLWHCV receiving DAAs and another medication[3,15–20], and do not therefore reflect the polypharmaceutical reality of many PLWHCV, who, according to our data, are prescribed a mean of three medications per patient.

This study went one step further and identified 1256 patients with ≥2 basal comedications plus DDA treatment. Of these, 123 patients were predicted to have multiple DDIs with either SOF/VEL or GLE/PIB, meaning that about 10% of the Spanish population treated with a DAA regimen with ≥2 comedications prescribed are at risk of multiple DDIs, which is a ratio similar to that observed by Margusino-Framiñán L, *et al.*[17].

A recent Italian study that analysed characteristics of PLWHCV treated with DAAs that have a multi-DDI profile reported that the rate of PLWHCV with ≥2 comedications at risk of multi-DDIs with DAAs was higher in GLE/PIB (19.6%) than in SOF/VEL treated patients (11.6%), but no data was shown on this study for AE in multi-DDIs[11].

Our results show that SOF/VEL and GLE/PIB treatment regimens achieved similar treatment effectiveness. However, effectiveness was lower in the multi-DDIs, with 9.8% of multi-DDI population restarting with new DAA 6 months after end of treatment vs 1% in the overall population. In view of these data, it would be interesting to conduct further analyses to elucidate if receiving ≥2 comedications that show a risk of decreasing the DAA exposure would lead to a significant change in the sustained virologic response (SVR).

The polypharmacy in PLWHCV treated with SOF/VEL or GLE/PIB was recently characterized[11]. However, to our knowldege, the association between comedication-associated AEs and the multi-DDI profile of the PLWHCV treated with DAA remains unexplored. Using real-life clinical practice data, we found that most comedication-associated AEs were

Rev Esp Sanid Penit. 2024;26(3):98-112
10.18176/resp.00095

Table 3. Multi-DDI population: demographic and clinical characteristics.

Multi-DDI population	SOF/VEL (n = 52)	GLE/PIB (n = 71)	Total (n = 123)	*P* value
Demographic characteristics				
Median age, years (IQR)	59 (54-73)	61 (52-72)	60 (53-73)	
Male, n (%)	30 (57.7)	38 (53.5)	68 (55.3)	0.411
Comorbidities associated with CHC				
Arterial hypertension, n (%)	24 (46.2)	42 (59.2)	71 (57.7)	0.153
Diabetes, n (%)	17 (32.7)	29 (40.8)	46 (37.4)	0.097
Heart failure, n (%)	5 (9.6)	7 (9.9)	12 (9.8)	0.964
Renal insufficiency, n (%)	3 (5.8)	4 (5.6)	7 (5.7)	0.753
General comorbidity				
Charlson index, mean (SD)	2.0 (2.1)	1.9 (1.8)	1.9 (1.9)	0.627
0, n (%)	12 (23.1)	19 (26.8)	31 (24.9)	
1, n (%)	13 (24.6)	19 (26.8)	32 (25.7)	
2, n (%)	10 (19.6)	13 (18.3)	23 (19.0)	
3+, n (%)	17 (32.7)	20 (28.2)	37 (30.1)	0.162
Specific comorbidities, n (%)				
Hepatic cirrhosis	4 (7.7)	4 (5.6)	8 (6.5)	0.647
HIV	3 (5.8)	3 (4.2)	6 (5.0)	
Fibrosis prediction FIB-4 score, n (%)				
Without fibrosis (F0–F1), <1.45 points	7 (13.5)	15 (21.1)	23 (17.9)	
Intermediate (F2), 1.45–3.25 points	14 (26.9)	20 (28.2)	34 (27.6)	
Fibrosis (F3–F4), >3.25 points	31 (59.6)	36 (50.7)	67 (54.5)	0.487
Other features				
Mean time since diagnosis, years (SD)	4.4 (4.3)	4.5 (4.4)	4.5 (4.3)	0.893
Mean BMI, kg/m^2 (SD)	29.4 (4.7)	29.8 (4.8)	29.7 (4.8)	0.636
Actions taken during DAA treatment for comedications with AE-associated comedications with potential DDIs				
Suspected AE	3	13		
Clinical actions to manage DDI (number of patients, AE-associated comedication)				
Clinical monitoring	1, simvastatin*	1, atorvastatin*		
Monitoring ECG (Electrocardiogram)	0	1, carvedilol*		
Discontinuation (DAA)	1, carvedilol†	3, quetiapine†, atorvastatin (2)†		
Discontinuation (co-medication)	1, atorvastatin*	2, oxcarbazepine*, simvastatin†		
Dose Reduction	0	4, paliperidone†, enalapril (2)*, simvastatin*		
Switch	0	2, fentanyl†, omeprazole*		
Total	3	13		

Note. *AEs associated with comedications without asterisk were reported by primary care physicians (62.5% [10/16]); †AEs associated with these comedications were reported by gastroenterologists (37.5% [6/16]).
AE, adverse event; BMI, body mass index; CHC, chronic hepatitis C; DAA, direct-acting antiviral; DDI, drug–drug interaction; SD, standard deviation; FIB-4, Fibrosis-4 Index for liver fibrosis; GLE/PIB, glecaprevir/pibrentasvir; HIV, human immunodeficiency virus; IQR, interquartile range; multi-DDI, multi drug-drug interaction; SOF/VEL, sofosbuvir/velpatasvir.

Table 4. Patients with DAA regimen restart and risk of DDI linked to patient decreased exposure to DAA.

	SOF/VEL	GLE/PIB	Total
Total number of patients	730	890	1,620
Patients with a DAA treatment restart	7 (0.96%)	10 (1.1%)	17 (1%)
Multi-DDI patients (with ≥2 comedication with potential DDIs)	5 (9.6%)	7 (9.9%)	12 (9.8%)
Patients without DDIs ↓ DAA	1	0	1
Patients with 1 comedication ↓ DAA	3	4	7
Patients with ≥2 comedications ↓ DAA	1	3	4
Single-DDI patients (with only 1 comedication with potential DDIs)	2	3	5
Patients without DDIs ↓ DAA	1	0	1
Patients with 1 comedication ↓ DAA	1	3	4
Patients without comedication or with comedications without DDIs	0	0	0

Note. No information about total number of comedication taken, fibrosis /cirrhosis status, adherence, persistence, or comorbidities were individually provided for these patients.
DAA, direct antiviral agent; DDI, drug–drug interaction; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir.
↓DAA: DDIs decreasing DAA plasma concentration.

reported in multi-DDI patients in Spain. Moreover, most patients reporting comedication-associated AEs were prescribed ≥2 comedications with a potential DDI predicted to increase comedication plasma levels, which might have an impact on safety. In fact, 62.5% of patients with AEs, were taking ≥2 comedications with DDIs all predicted to increase plasma concentration of comedication. Altogether, our data indicate that polypharmacy increases the risk of AEs in multi-DDIs and, in turn, multi-DDIs might affect the concurrence of certain AEs, which were detected more frequently in GLE/PIB-treated patients (although the percentage of patients taking ≥2 comedications and the mean number of comedications was higher in the SOF/VEL group). There were almost three times more comedication-associated AEs in GLE/PIB-treated patients in comparison with SOF/VEL-treated patients, and this was accompanied by more actions related to comedication associated AEs required by the physicians in the first group. Of note, three DAA discontinuations were detected in GLE/PIB-prescribed patients: two associated with atorvastatin, and one with quetiapine (dose <300mg/day) due to an extrapyramidal syndrome, whereas only one DAA discontinuation was observed in SOF/VEL treated patients, due to an AE associated with carvedilol[28].

Likewise, fewer actions and less resource utilization were needed to manage potential DDIs with SOF/VEL than with GLE/PIB when treating PLWHCV with cardiovascular and CNS comorbidities[29]. Importantly, more AEs were reported by primary care physicians than by Hepatitis C specialists, which invites to consider the need to consider a multidisciplinary approach to guarantee patient safety.

The comedication-associated AEs reported occurred with drugs in the cardiovascular, CNS, or alimentary therapeutic groups. In particular, GLE/PIB-treated patients were associated with all three groups, whereas in SOF/VEL-treated patients, AEs were only associated with cardiovascular comedications. Indeed, more cardiovascular AEs associated with cardiovascular comedications, particularly statins, were reported in GLE/PIB patients. Regarding this, it has been described that co-administration of GLE/PIB with atorvastatin, simvastatin or lovastatin results in a strongly increased area under the curve values for the statins and their metabolites; coadministration of atorvastatin, lovastatin, and simvastatin with GLE/PIB is in fact not recommended[14,30].

Moreover, there was a lower number of AEs associated with lipid-lowering drugs and no AEs with antipsychotics in the SOF/VEL-treatment group compared with GLE/PIB. Sofosbuvir combination DAA regimens are actually recommended for concomitant use with psychoactive medications in preference to protease inhibitor (PI)-based regimens like GLE/PIB, as PI-free regimens are predicted to have fewer DDIs[19,31]; this recommendation was validated by our analysis on comedication-associated AEs.

Pharmacists' evaluations of DDIs have proven to be effective for the prevention of AEs in patients treated with DAAs coupled with multiple comorbidities and polypharmacy[32]. Currently, there is a large amount of

Rev Esp Sanid Penit. 2024;26(3):98-112
10.18176/resp.00095

information on potential single DDIs in HCV, which should be used to guide clinical decisions and to select the most appropriate DAA, following international guidelines. This real-world data study highlights the relevance of a comprehensive evaluation of single and multi-DDIs before DAA treatment initiation to help mitigate DDI risk and associated AEs. DDI analysis for any additional prescriptions during the treatment should also be considered.

The limitations of this study are the ones inherent in retrospective and observational studies, such as underreporting of the disease and possible differences among health professionals and patients[33].

In this regard, the potential for inaccuracies in diagnostic coding and registration of deaths and other comorbidities, or the lack of any variables that could influence the results (i.e., socioeconomic level, occupational hazards, or smoking) may be considered as limitations.

Other limitations of the study include the lack of a severity classification for AEs due to the nature of reporting and the number of cases. There were 1620 HCV cases treated with DAAs in the database and, of these, only 123 had a multi-DDI profile. This prevented us from performing a propensity score matching adjustment between patients with multi-DDIs treated with SOF/VEL and GLE/PIB, since it would have left the study with no patients for the analysis. P-values indicating differences observed among the SOF/VEL and GLE/PIB treatment groups should be taken as descriptive. In addition, treatment restart with a new DAA in the 6 months after finalizing SOF/VEL or GLE/PIB treatment was used as a proxy for DAA effectiveness since the viral load registry value was not available in the database, and, although reinfection in the general population tends to be low, we should not reject the possibility that some patients whose treatment was classified as ineffective were in fact reinfected.

Finally, given the observational nature of the study, only associations and not causal relationships can be identified. It should also be noted that these results were based on the DDI guidelines of the University of Liverpool published in November 2020. Whilst the database is continually updated, there may have been amendments to the predicted DDIs since the initial analysis.

Conclusions

This real-world data shows for the first time that PLWHCV predicted to have multiple DDIs with comedications taken and DAA treatment, may be at high risk of AEs, which could require medical actions and resources utilization for their clinical management.

This situation is especially important in the context of HCV treatment simplification, where HCV specialists usually interact with patients just at the beginning of HCV treatment; therefore, the DAA regimen showing less potential DDIs with the comedication(s) taken by the patient should be the one selected.

In addition, special focus should be put on DDIs with cardiovascular and CNS comedication, as the majority of AEs were reported in these groups, particularly in the PI-based DAA GLE/PIB compared to the PI-free DAA SOF/VEL in the Spanish setting.

Future work is needed to confirm these results in other settings and cohorts.

ACKNOWLEDGMENTS

The authors would like to thank Gilead as funding body. The authors would like to thank Ignacio Hernández, Dr Jorge Morales, and Dr Elena Rebollo-Gómez (Atrys Health) for their data analysis and medical writing support.

ETHICAL CONSIDERATIONS

Patient consent was not necessary, according to the Article 5 of Royal Decree 957/2020, of 3 November, which regulates observational studies with medicines for human use. This study was approved by the Clinical Research Ethics Committee of the Uni o Catalana Balears de Hospitals de Barcelona, Spain (reference:15/49).

FUNDING

The authors declare that this study received funding from Gilead. The funder was involved in study design and preparation of the manuscript.

CONFLICT OF INTEREST

Authors have received funding not conditional on results for their participation as Speaker/consultant/research: JT (AbbVie, Gilead Sciences, MSD), AGH (AbbVie, Gilead Sciences), RMV (AbbVie, Gilead Sciences, Janssen, MSD, ViiV Healthcare), MM and CH are Gilead employees, and ASM, Atrys Health employee.

CORRESPONDENCE

Antoni Sicras-Mainar
Health Economics and Outcomes Research, Atrys Health, Barcelona, Spain
E-mail: ansicras@atryshealth.com

BIBLIOGRAPHY

1. World Health Organization. Hepatitis C. [Internet]. En: Who.int. WHO. 9 Abr 2024. Disponible en: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
2. Falade-Nwulia O, Suárez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection. Ann Intern Med. 2017;166(9):637-48.
3. Boff da Costa R, Boff Costa M, Longo L, Miotto DE, Hirata Dellavia G, *et al.* Direct antiviral agents for hepatitis C and drug interaction risk: A retrospective cohort study with real and simulated data on medication interaction, prevalence of comorbidities and comedications. PLoS One. 2021;16(2):e0245767.
4. Sicras Mainar A, Navarro Artieda R, Hernández I, Morillo R. Prevalence of the potential drug-drug interactions between pangenotypic direct-acting antivirals and the concomitant medications associated with patients with chronic hepatitis C virus infection in Spain. Gastroenterol Hepatol. 2019;42(8):465-75.
5. Jiang H, Lin Y, Ren W, Fang Z, Liu Y, Tan X, *et al.* Adverse drug reactions and correlations with drug–drug interactions: A retrospective study of reports from 2011 to 2020. Front Pharmacol. 2022;13:923939.
6. European Association for the Study of the Liver; Clinical Practice Guidelines Panel: Chair; EASL Governing Board representative; Panel members. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol. 2020;73(5):1170-218.
7. Néant N, Solas C. Drug-Drug Interactions Potential of Direct-Acting Antivirals for the treatment of Chronic Hepatitis C Virus infection. Int J Antimicrob Agents. 2020;56(1):105571.
8. Gao LH, Nie QH, Zhao XT. Drug-Drug Interactions of Newly Approved Direct-Acting Antiviral Agents in Patients with Hepatitis C. Int J Gen Med. 2021;14:289-301.
9. Talavera Pons S, Boyer A, Lamblin G, Chennell P, Châtenet FT, Nicolas C, *et al.* Managing drug-drug interactions with new direct-acting antiviral agents in chronic hepatitis C. Br J Clin Pharmacol. 2017;83(2):269-93.
10. Dick TB, Lindberg LS, Ramírez DD, Charlton MR. A clinician's guide to drug-drug interactions with direct-acting antiviral agents for the treatment of hepatitis C viral infection. Hepatology. 2016;63(2):634-43.
11. Fagiuoli S, Toniutto P, Coppola N, Ancona DD, Andretta M, Bartolini F, *et al.* Italian Real-World Analysis of the Impact of Polypharmacy and Aging on the Risk of Multiple Drug-Drug Interactions (DDIs) in HCV Patients Treated with Pangenotypic Direct-Acting Antivirals (pDAA). Ther Clin Risk Manag. 2023;19:57-65.
12. Schulte B, Wübbolding M, Marra F, Port K, Manns MP, Back D, *et al.* Frequency of Potential Drug–Drug Interactions in the Changing Field of HCV Therapy. Open Forum Infect Dis. 2020;7(2):ofaa040.
13. Moore KJ, Gauri A, Koru-Sengul T. Prevalence and sociodemographic disparities of Hepatitis C in Baby Boomers and the US adult population. J Infect Public Health. 2019;12(1):32-6.
14. University of Liverpool. Interaction Checker. En: HEP Drug Interactions. [Internet]. University of Liverpool. Disponible en: https://www.hep-druginteractions.org/
15. Curry MP, Flamm SL, Milligan S, Tsai N, Wick N, Younossi Z, *et al.* Prevalence of drug-drug interactions with pangenotypic direct-acting antivirals for hepatitis C and real-world care management in the United States: a retrospective observational study. J Manag Care Spec Pharm. 2021;27(9):1239-48
16. Mangia A, Scaglione F, Toniutto P, Pirisi M, Coppola N, Di Perri G, *et al.* Drug-Drug Interactions in Italian Patients with Chronic Hepatitis C Treated with Pangenotypic Direct Acting Agents: Insights from a Real-World Study. Int J Environ Res Public Health. 2021;18(13):7144.
17. Margusino-Framiñán L, Cid-Silva P, Giménez-Arufe V, Mondelo-García C, Fernández-Oliveira C, Mena-de-Cea Á, *et al.* Influence of drug-drug interactions on effectiveness and safety of direct-acting antivirals against hepatitis C virus. Eur J Hosp Pharm. 2021;28(1):16-21.
18. Sicras-Mainar A, Enriquez JL, Hernández I, Sicras-Navarro A, Aymerich T, Leon M. PMU146 Validation and representativeness of the Spanish BIG-PAC database: integrated computerized medical records for research into epidemiology, medicines and health resource use (real world evidence). Value Health. 2019;22:S734.

19. Sicras-Mainar A, Morillo-Verdugo R. Uso concomitante de antivirales de acción directa (AAD) y fármacos con acción sobre el sistema nervioso central: Consideraciones en el perfil actual del paciente con hepatitis C. Adicciones. 2022;34(4):279-84.
20. Sicras-Mainar A, Morillo-Verdugo R. Potential interactions between pangenotypic direct-acting antivirals and concomitant cardiovascular therapies in patients with chronic hepatitis C virus infection. J Int Med Res. 2020;48(10):300060520964659.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
22. World Health Organization. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). [Internet]. En: Who.int. WHO. [Actualización 2023]. Disponible en: https://www.who.int/standards/classifications/other-classifications/the-anatomical-therapeutic-chemical-classification-system-with-defined-daily-doses
23. Bhattacharya D, Aronsohn A, Price J, Lo Re V, AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2023:ciad319.
24. American Association for the Study of Liver Diseases, Infectious Disease Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. [Internet]. [Actualización 24 Oct 2022]. Disponible en: https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_October_24_2022.pdf
25. Winter RJ, Sheehan Y, Papaluca T, Macdonald GA, Rowland J, Colman A, *et al.* Consensus recommendations on the management of hepatitis C in Australia's prisons. Med J Aust. 2023;218(5):231-7.
26. Ghany MG, Morgan TR, AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology. 2020;71(2):686-721.
27. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, *et al.* Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1-98.
28. Turnes J, García-Herola A, Verdugo RM, Méndez M, De Álvaro C, Hernández C, *et al.* Use of psychiatric medication and drug interactions in patients with hcv infection treated with pangenotypic direct-acting antivirals. Dig Liver Dis. 2023;55(1):S71.
29. Molina E, Torrens M, Ampuero J, Roncero C, Alameda M, Martín-Escudero V, *et al.* Resource utilization associated with the management of potential interactions between direct-acting antivirals for chronic hepatitis C treatment and cardiovascular and central nervous system drugs. Rev Esp Econ Salud. 2022;17(5):108-19.
30. Garrison KL, German P, Mogalian E, Mathias A. The Drug-Drug Interaction Potential of Antiviral Agents for the Treatment of Chronic Hepatitis C Infection. Drug Metab Dispos. 2018;46(8):1212-25.
31. Smolders EJ, De Kanter CTMM, De Knegt RJ, Van der Valk M, Drenth JPH, Burger DM. Drug–Drug Interactions Between Direct-Acting Antivirals and Psychoactive Medications. Clin Pharmacokinet. 2016;55(12):1471-94.
32. Chamorro-de-Vega E, Rodríguez-González CG, Giménez-Manzorro Á, Herranz A, Sanjurjo M, on behalf of the GRUviC Study Group. Hepatitis C virus infection and the role of a pharmaceutical care program. Am J Health Syst Pharm. 2020;77(6):479-86.
33. González-Colominas E, López-Mula C, Martínez-Casanova J, Luque S, Conde-Estévez D, Monge-Escartín I, *et al.* Primary care electronic medication record discrepancies in patients starting treatment at a hospital-based ambulatory care pharmacy and impact on prevalence of potential drug-drug interactions. Eur J Hosp Pharm. 2023;30(6):333-9.