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

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Abstract

Objective: Patients with chronic Hepatitis C Virus Infection (HCV) present high rates of comorbidity and polypharmacy. We aimed to assess the additional actions and resource utilization required for the management of potential drug-drug interactions (pDDIs) in HCV patients showing cardiovascular (CVS) and central nervous system (CNS) comorbidities, treated with sofosbuvir/velpatasvir (SOF/VEL) compared to glecaprevir/pibrentasvir (GLE/PIB) in routine clinical practice in Spain.

Methods: The most prevalent CVS and CNS drugs in HCV patients were identified from real-world published data. The pDDIs between SOF/VEL, GLE/PIB and comedications, and their management recommendations were identified on the University of Liverpool Hepatitis Drug Interaction Group website. An expert panel defined real-world management of pDDIs, and a consensus was reached on actions required on the concomitant drug and resource utilization.

Results: Additional actions are required in 89% of the CVS drugs when co-administered with GLE/PIB, while 39% were required with SOF/VEL (dose adjustment: 39% vs 17%; drug suspension: 28% vs 11%; drug substitution: 22% vs 11%; drug restart after DAA treatment: 33% vs 22%); additional visits and/or tests are needed in 50% and 22%, respectively. Regarding CNS drugs, 71% required additional actions when co-administered with GLE/PIB, while 14% require them with SOF/VEL (dose adjustment: 57% vs 0%; drug substitution: 14% vs 14%); additional visits and/or tests are needed in 71% and 14%, respectively.

Conclusion: In routine clinical practice, fewer actions and less resource utilization are needed to manage pDDIs with SOF/VEL than with GLE/PIB, when treating HCV patients with CVS and CNS comorbidities.

Keywords: chronic hepatitis C; drug-drug interactions; pangenotypic direct acting antivirals; resource utilization; comorbidity.

Resumen

Objetivo: Evaluar las acciones y el uso adicional de recursos sanitarios para el manejo de las potenciales interacciones farmacológicas (pIF) en pacientes con virus de la hepatitis C (VHC), que presentan comorbilidades cardiovasculares (SCV) y del sistema nervioso central (SNC), tratados con sofosbuvir/velpatasvir (SOF/VEL) en comparación con glecaprevir/pibrentasvir (GLE/PIB) en la práctica clínica habitual en España.

Métodos: A partir de datos publicados de vida real, se identificaron los fármacos para el SCV y SNC más utilizados en pacientes con VHC. Las pIF y las recomendaciones sobre su manejo, fueron identificadas utilizando la base de datos de interacciones para las hepatitis virales de la Universidad de Liverpool. Mediante un panel de expertos se definió el manejo de las pIF en práctica clínica habitual, y se consensuaron las acciones necesarias así como la utilización de recursos asociada al uso de estos fármacos concomitantes.

Resultados: El 89% de los fármacos del SCV coadministrados con GLE/PIB requiere acciones adicionales; un 39% las requiere con SOF/VEL (ajuste dosis: 39% vs 17%; suspensión fármaco: 28% vs 11%; sustitución fármaco: 22% vs 11%; reinicio fármaco tras tratamiento antiviral: 33% vs 22%). El 50% y 22% requieren visitas y/o pruebas adicionales, respectivamente. El 71% de los fármacos del SNC coadministrados con GLE/PIB requiere acciones adicionales; un 14% las requiere con SOF/VEL (ajuste dosis: 57% vs 0%; sustitución fármaco: 14% vs 14%). El 71% y 14% requieren visitas y/o pruebas adicionales, respectivamente.

Conclusión: En la práctica clínica, es necesario un menor porcentaje de acciones y uso de recursos para manejar las pIF con SOF/VEL que con GLE/PIB, en pacientes con VHC y comorbilidades del SCV y del SNC.

Palabras clave: Hepatitis C crónica; interacciones farmacológicas; antivirales pangenotípicos de acción directa; uso de recursos; comorbilidad.

INTRODUCTION

Chronic infection with the hepatitis C virus (HCV) is a global healthcare problem[1]. An estimated 58 million people have chronic hepatitis C virus infection worldwide, with about 1.5 million new infections occurring per year[2]. In the European Union, an estimated 3.2 million people were living with chronic HCV, corresponding to 0.64% of the population[3]. In Spain, the weighted prevalence of antibodies against HCV in the population aged 20-80 years is estimated in 0.85% (IC95% 0.64%-1.08%), and the weighted prevalence of active infection in 0.22% (IC95% 0.12%-0.32%)[4].

The introduction of direct-acting antivirals (DAAs) has meant a qualitative improvement in the management of HCV patients, reaching cure rates (sustained viral response) unimaginable until a few years ago. Furthermore, the introduction of pangenotypic DAAs, effective against all viral genotypes and well tolerated, has meant a significant advance in the treatment of HCV[1].

However, DAAs have been associated with potential drug-drug interactions (DDIs) in patients treated with concomitant medication[5] and may have consequences on patients' health if they are not detected and/or managed on time. There are three different classes of DAAs, which affect three different phases of the HCV replication process: NS3/4A protease inhibitors (ending in "-previr"), NS5A replication complex inhibitors (ending in "-asvir") and NS5B polymerase inhibitors (ending in "-buvir", their metabolism does not generally depend on cytochrome P450)[1]. DAAs could be both substrates and inhibitors/inducers of drug-metabolizing enzymes and drug transporters, making them victims (when their plasma concentration is affected by another drug) and perpetrators (when they have the ability to influence plasma concentrations of drugs)

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of DDIs[6]. Generally speaking, and accordingly to Liverpool Interaction checker, the main clinical outcomes of DDIs could be summarized in three: an increase in the concomitant blood levels, a decrease in the DAA blood levels, and an increase in DAA levels. The first and third outcomes would imply a safety/tolerability risk, and the second one a risk of lacking efficacy[7,8].

In Spain, a recent observational study carried out in patients with HCV has determined the comorbidity and the prevalence of the potential DDIs between pangenotypic DAAs and concomitant medication in routine clinical practice[1]. Fifty per cent of the patients included in the study received at least three medications simultaneously. Weak potential DDIs were present in 8.6% of the cases, clinically significant DDIs in 40.5%, and contraindication of the medication was present in 10% of the cases[1], which highlights the importance of taking into account the patient's concomitant medication when a new DAA is prescribed, following the main recommendations[5]. The study concluded that the combination of sofosbuvir/velpatasvir (SOF/VEL) presented a lower percentage of potential DDIs compared to glecaprevir/ pibrentasvir (GLE/PIB) and sofosbuvir/ velpatasvir/ voxilaprevir. Additionally, based on their results, it is known that the most commonly prescribed therapies with potential DDIs were those related to the cardiovascular (CVS) system and the central nervous system (CNS)[1]. Moreover, a study to describe the proportion of HCV patients with multiple DDIs and their impact on the safety and effectiveness of patients treated with SOF/VEL or GLE/PIB, observed that 10% of HCV patients taking two or more comedications are at risk of multi-DDIs (≥2 comedications, each with a DDI with their DAA treatment) in Spain[8]. In line with previous results, a higher risk of increased comedication concentration and adverse events exists in GLE/ PIB-treated patients compared to SOF/VEL-treated patients[8].

Current clinical practice guidelines recommend taking a full and detailed drug history (including all prescribed medications, over-the-counter drugs, herbal and vitamin preparations, and any illicit drug) prior to starting treatment with a DAA and assessing each patient's risk profile to simplify the future treatment[5]. Additionally, the actions to avoid the risk of incurring DDIs (changes in administration patterns and doses, intensification of monitoring of these patients, contraindication of concomitant medications associated with potential clinically relevant DDIs with serious effects) are indicated[5]. This fact underlines the importance of evaluating the management of these patients when starting treatment with a DAA.

SOF/VEL and GLE/PIB, two of the most prescribed DAAs for HCV treatment[9], are associated with different profiles of potential DDIs. To evaluate the complexity of patient management with each of these treatments, considered relevant for decision-making, we assessed and compared the additional actions and resource utilization required for the management of potential DDIs in HCV patients showing CVS and CNS comorbidities (two of the most prevalent comorbidities in these patients) treated with SOF/VEL and GLE/PIB in routine clinical practice in Spain.

METHODS

We performed a use of resources analysis, assessing the additional actions and the associated resource utilization in real-world practice for managing potential DDI in HCV patients showing CVS and CNS comorbidities, according to an expert panel's opinion.

To identify the most used CVS and CNS drugs in HCV patients, data provided by the Spanish real-world cohort previously used by Sicras et al. in their study of the prevalence of the potential DDI between pangenotypic DAAs and the concomitant medications in HCV patients in Spain was used[1,10,11]. A review of the literature was also performed to search for additional real-world data in our country, not obtaining more recent results.

The population of Sicras et al. cohort was obtained from anonymized medical records of healthcare providers at various hospitals in 7 Spanish autonomous communities and included adult patients (≥ 18 years) with a

diagnosis of HCV (at least 12 months), visited and treated with any combination of pangenotypic DAAs (n= 3430). CVS and CNS drugs used by more than ten patients in the cohort were established as the most prevalent. Additionally, the selected drugs had to present some degree of interaction or contraindication with the DAAs studied[1,10,11]. Therefore, 18 CVS and 7 CNS drugs were included in our study (Table 1, Table 2, Supplementary Table S 1, Table S 2).

TABLE 1

CVS DRUGS INCLUDED IN THE STUDY. POTENTIAL DDIS DEGREE AND EXPECTED CLINICAL OUTCOME WITH GLE/PIB AND SOF/VEL ACCORDING TO LIVERPOOL HEPATITIS DRUG INTERACTION GROUP

Concomitant drugs		Potential DDIs with GLE/PIB	Potential DDIs with SOF/VEL
Antiarrhythmics	Amiodarone	↑concomitant drug blood levels	Unknown
	Digoxin	↑concomitant drug blood levels	↑concomitant drug blood levels
Anticoagulants	Acenocumarol	↑concomitant drug blood levels	
Lipid-lowering drugs	Atorvastatin	↑concomitant drug blood levels	↑concomitant drug blood levels*
	Simvastatin	↑concomitant drug blood levels	↑concomitant drug blood levels
	Pravastatin	↑concomitant drug blood levels	
	Rosuvastatin	↑concomitant drug blood levels	↑concomitant drug blood levels
	Pitavastatin	↑concomitant drug blood levels	↑concomitant drug blood levels
	Gemfibrozil	↑concomitant drug blood levels; ↑DAA blood levels	
	Ezetimibe	↑concomitant drug blood levels	
	Colestyramine	↓DAA blood levels	↓DAA blood levels
Antihypertensives	Enalapril	↑concomitant drug blood levels	
	Candesartan	↑DAA blood levels	
	Olmesartan	↑concomitant drug blood levels	
	Irbesartan	↑concomitant drug blood levels	
	Telmisartan	↑concomitant drug blood levels	
Cardiac Insufficiency	Carvedilol	↑concomitant drug blood levels; ↑DAA blood levels	↑concomitant drug blood levels
	Diltiazem	↑concomitant drug blood levels	↑concomitant drug blood levels

No interaction expected | Potential weak interaction | Potential interaction | Co-administration contraindicated

CVS: cardiovascular; DAA: Direct-acting antiviral.
* The European SmPC advises that no adjustment of sofosbuvir/velpatasvir or atorvastatin is required.

Source: own resource.

TABLE 2

CNS DRUGS INCLUDED IN THE STUDY. POTENTIAL DDIS DEGREE AND EXPECTED CLINICAL OUTCOME WITH GLE/PIB AND SOF/VEL ACCORDING TO LIVERPOOL HEPATITIS DRUG INTERACTION GROUP

Concomitant drugs		Potential DDIs with GLE/PIB	Potential DDIs with SOF/VEL
Analgesics	Fentanyl	↑concomitant drug blood levels	
	Oxycodone	↑concomitant drug blood levels	
Antipsychotic	Quetiapine	↑concomitant drug blood levels	
	Paliperidone	↑concomitant drug blood levels	
	Aripiprazole	↑concomitant drug blood levels	
	Clotiapine	↑concomitant drug blood levels	
Anticonvulsants	Oxcarbazepine	↓DAA blood levels	↓DAA blood levels

No interaction expected | Potential weak interaction | Potential interaction | Co-administration contraindicated

CNS: Central Nervous system; **DAA**: Direct-acting antiviral.
***** The European SmPC advises that no adjustment of sofosbuvir/velpatasvir or atorvastatin is required.

Source: own resource.

University of Liverpool Hepatitis Drug Interaction Group website[7] was consulted on September 2021 to update the potential DDIs between the identified drugs with SOF/VEL or GLE/PIB, previously shown by Sicras et al[1]. The actions recommended when these drugs are co-administered with SOF/VEL and GLE/PIB were identified from the website by two different investigators. Liverpool classifies potential DDIs according to their degree of interaction in a) green: no interaction expected; b) yellow: potential weak interaction which does not require dose adjustments and/or additional monitoring; c) orange: potential interaction that may require dose adjustments, alterations in the administration pattern and/or additional monitoring; d) red: co-administration contraindicated. Additionally, the expected clinical outcome with GLE/PIB and SOF/VEL, according to Liverpool Hepatitis Drug Interaction Group was consulted[7] (Table 1, Table 2).

Management in the real-world clinical practice of potential DDIs was obtained through a multidisciplinary expert panel (two hepatologists, two psychiatrists, one cardiologist, and one hospital pharmacist). The expert panel was composed of professionals from different parts of Spain, which allowed reflecting differences in disease management throughout the Spanish territory. An Excel questionnaire was used, which included the selected CVS and CNS drugs and the actions recommended by the University of Liverpool Hepatitis Drug Interaction Group when these drugs are co-administered with SOF/VEL and GLE/PIB. The experts had to indicate the actions that would be taken in clinical practice to manage the potential DDIs between DAAs and the patient's medication. These actions were classified as a) concomitant drug dose adjustment: an adjustment of the patient's medication dose may be necessary when starting DAA treatment. Similarly, when this treatment is completed, the dose of the concomitant drug may need to be re-adjusted; b) concomitant drug suspension and concomitant drug substitution: suspension or substitution of the patient's usual medication may be necessary during DAA treatment; and c) concomitant drug restart after DAA treatment: when the concomitant drug is suspended,

it will need to be restarted when the DAA treatment finishes; when the concomitant drug is substituted, the patient may either return to the original drug or keep the substitute to avoid a further change in medication (to note that b and c are not mutually exclusive). Additionally, they were asked about the resource utilization, in terms of additional visits and additional clinical tests, that would be consumed because of these actions and/or the potential DDI. A subsequent meeting (teleconference) addressed discrepancies in their responses, and a consensus was reached.

Finally, the additional actions and resource utilization involved in the concomitant treatment of the most prevalent drugs for CVS and CNS with GLE/PIB and SOF/VEL in HCV patients were compared.

RESULTS

Eighteen CVS drugs and 7 CNS drugs were considered in the study. The drugs requiring actions and additional resource utilization are shown in Table 3 and Table 4.

Actions to manage DDIs with Cardiovascular System comedications

Eighty-nine per cent of the CVS drugs (n=16) required additional actions when co-administered with GLE/PIB, while 39% (n=7) required them with SOF/VEL. Regarding resource utilization, 50% (n=9) of the CVS drugs needed additional resource utilization when co-administered with GLE/PIB, compared to 22% (n=4) when co-administered with SOF/VEL.

TABLE 3

CVS DRUGS: ACTIONS AND RESOURCE UTILIZATION DURING AND AFTER DAA TREATMENT

Actions during DAA treatment	**GLE/PIB**	Dose adjustment	Amiodarone, acenocumarol, pravastatin, rosuvastatin, pitavastatin, enalapril, diltiazem
		Drug suspension	Digoxin, atorvastatin, simvastatin, gemfibrozil, ezetimibe
		Drug substitution	Olmesartan, irbesartan, telmisartan, carvedilol
	SOF/VEL	Dose adjustment	Rosuvastatin, pitavastatin, diltiazem
		Drug suspension	Digoxin, simvastatin
		Drug substitution	Amiodarone, carvedilol
Resource utilization during DAA treatment	**GLE/PIB**	Additional visits	Amiodarone (2 additional visits), digoxin (1 additional visit), acenocumarol (4 additional visits), enalapril (1 additional visit), olmesartan (1 additional visit), irbesartan (1 additional visit), telmisartan (1 additional visit), carvedilol (1 additional visit), diltiazem (1 additional visit)
		Additional tests	Amiodarone (2 ECG), acenocumarol (4 INR), enalapril (blood pressure monitoring), diltiazem (1ECG)
	SOF/VEL	Additional visits	Amiodarone (2 additional visits), digoxin (1 additional visit), carvedilol (1 additional visit), diltiazem (1 additional visit)
		Additional tests	Diltiazem (1 ECG)
Actions after DAA treatment	**GLE/PIB**	Dose adjustment	Amiodarone, acenocumarol, pravastatin, rosuvastatin, pitavastatin, enalapril, diltiazem
		Drug restart	Digoxin, atorvastatin, simvastatin, gemfibrozil, ezetimibe, carvedilol
	SOF/VEL	Dose adjustment	Rosuvastatin, pitavastatin, diltiazem
		Drug restart	Amiodarone, digoxin, simvastatin, carvedilol
Resource utilization after DAA treatment	**GLE/PIB**	Additional visits	Digoxin (1 additional visit), acenocumarol (1 additional visit), enalapril (1 additional visit), carvedilol (1 additional visit), diltiazem (1 additional visit)
		Additional tests	Acenocumarol (1 IRN)
	SOF/VEL	Additional visits	Amiodarone (1 additional visit), digoxin (1 additional visit), carvedilol (1 additional visit), diltiazem (1 additional visit)
		Additional tests	-

DAA: direct-acting antivirals; **SOF/VEL**: sofosbuvir/velpatasvir; **GLE/PIB**: glecaprevir/pibrentasvir; **ECG**: electrocardiogram.

Source: own resource.

TABLE 4

CNS DRUGS: ACTIONS AND RESOURCE UTILIZATION DURING AND AFTER DAA TREATMENT

Actions during DAA treatment	**GLE/PIB**	Dose adjustment	Fentanyl, oxycodone, clotiapine, quetiapine
		Drug suspension	-
		Drug substitution	Oxcarbazepine
	SOF/VEL	Dose adjustment	-
		Drug suspension	-
		Drug substitution	Oxcarbazepine
Resource utilization during DAA treatment	**GLE/PIB**	Additional visits	Fentanyl (2-8 additional visits), oxycodone (2 additional visits), clotiapine (2 additional visits), oxcarbazepine (1 additional visit), quetiapine (2 additional visits)
		Additional tests	Quetiapine (1 ECG)
	SOF/VEL	Additional visits	Oxcarbazepine (1 additional visit)
		Additional tests	-
Actions after DAA treatment	**GLE/PIB**	Dose adjustment	Fentanyl, oxycodone, clotiapine, quetiapine
		Drug restart	-
	SOF/VEL	Dose adjustment	-
		Drug restart	-
Resource utilization after DAA treatment	**GLE/PIB**	Additional visits	Fentanyl (1 additional visit), oxycodone (1 additional visit), clotiapine (1 additional visit), oxcarbazepine (1 additional visit), quetiapine (1 additional visit)
		Additional tests	-
	SOF/VEL	Additional visits	Oxcarbazepine (1 additional visit)
		Additional tests	-

DAA: direct-acting antivirals; **SOF/VEL**: sofosbuvir/velpatasvir; **GLE/PIB**: glecaprevir/pibrentasvir; **ECG**: electrocardiogram.

Source: own resource.

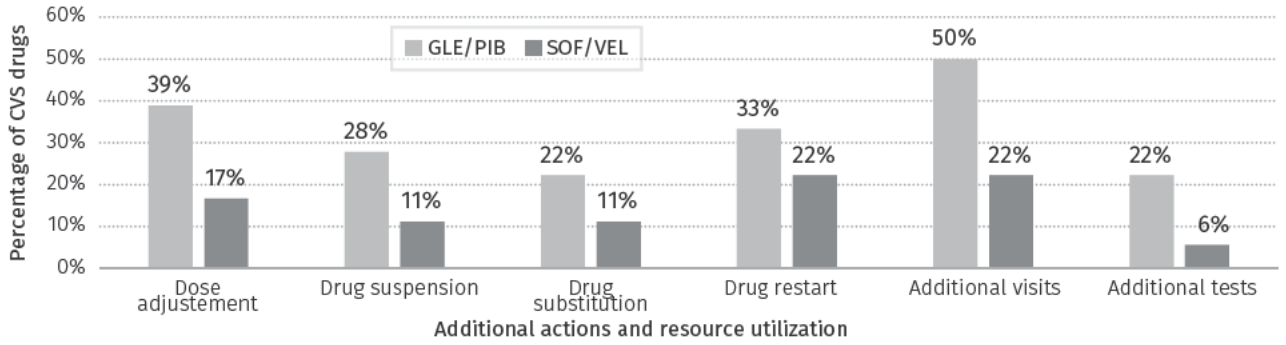
Concerning concomitant drug dose adjustment, 39% (n=7) of the CVS drugs considered would need dose adjustment when co-administered with GLE/PIB, and 17% (n=3) would need it when co-administered with SOF/VEL, both during and after DAA treatment; regarding concomitant drug suspension and drug substitution, 28% (n=5) of the most prevalent CVS drugs would need to be suspended and 22% (n=4) substituted when co-administered with GLE/PIB. In contrast, 11% (n=2) would need to be suspended, and 11% (n=2) substituted when co-administered with SOF/VEL; about concomitant drug restart after DAA treatment, 33% (n=6) of the studied CVS drugs would need to be restarted after GLE/PIB treatment, while 22% (n=4) would need it after SOF/VEL treatment; lastly, concerning the resource utilization (additional visits and clinical tests), during DAA treatment, 50% (n=9) of the CVS drugs included will require additional visits, and 22% (n=4) of them additional clinical tests, when co-administered with GLE/PIB, whereas 22% (n=4) and 6% (n=1) will need them, respectively, when co-administered with SOF/VEL. When DAA treatment finishes, 28% (n=5) of the CVS drugs will require additional visits, and 6% (n=1) additional clinical tests when co-administered with GLE/PIB, whereas 22% (n=4) and none will need them, respectively, when co-administered with SOF/VEL (Figure 1). The detail of the number of additional visits and additional clinical tests required is shown in Table 3.

Actions to manage DDIs with Central Nervous System comedications

Seventy-one per cent of the CNS drugs (n=5) required additional actions and additional resource utilization when co-administered with GLE/PIB, while 14% (n=1) required them with SOF/VEL.

FIGURE 1

PERCENTAGE OF CVS DRUGS THAT REQUIRE ADDITIONAL ACTIONS AND RESOURCE UTILIZATION DURING AND/OR AFTER DAA TREATMENT

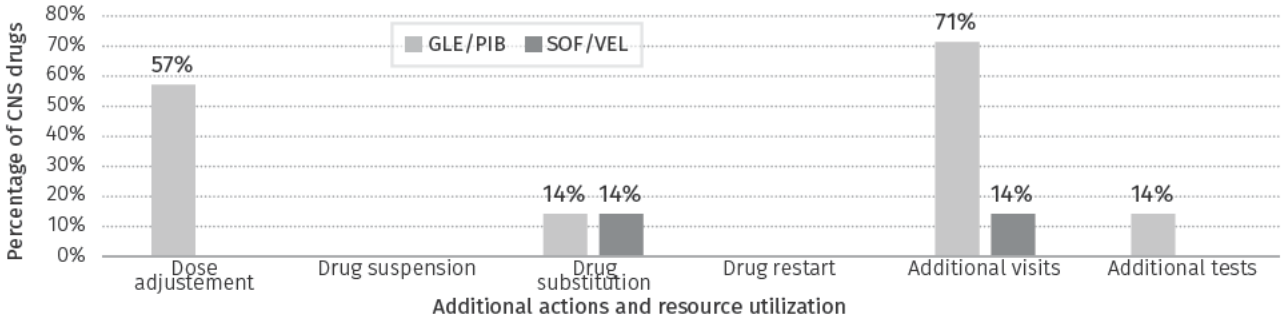


Source: own resource.

Concerning concomitant drug dose adjustment, 57% (n=4) of the CNS drugs considered would require a dose adjustment when co-administered with GLE/PIB, both during and after DAA treatment, while none would need it when co-administered with SOF/VEL; regarding concomitant drug suspension and drug substitution, 14% (n=1) of the most prevalent CNS drugs would need to be substituted when co-administered with both GLE/PIB and SOF/VEL, and none would require to be suspended; about concomitant drug restart after DAA treatment, none of the CNS drugs considered would need to be restarted after DAA treatment when co-administered with GLE/PIB or SOF/VEL; lastly, concerning the resource utilization (additional visits and clinical tests), during DAA treatment, 71% (n=5) and 14% (n=1) of the CNS drugs included will require additional visits and additional clinical tests, respectively, when co-administered with GLE/PIB. In contrast, 14% (n=1) will need additional visits, and none will need additional clinical tests when co-administered with SOF/VEL. After DAA treatment, 71% (n=5) will require additional visits and none additional clinical tests when co-administered with GLE/PIB, whereas 14% (n=1) will need additional visits and none additional clinical tests when co-administered with SOF/VEL (Figure 2). The detail of the number of additional visits and additional clinical tests required is shown in Table 4.

FIGURE 2

PERCENTAGE OF CNS DRUGS THAT REQUIRE ADDITIONAL ACTIONS AND RESOURCE UTILIZATION DURING AND/OR AFTER DAA TREATMENT



Source: own resource.

DISCUSSION

SOF/VEL and GLE/PIB combinations are DAA drugs frequently used for treating HCV patients, associated with different profiles of potential DDIs.

Based on a previous observational study, we know that CVS and CNS comorbidities are two of the most prevalent in HCV patients in Spain and that there is concomitant use of associated drugs in one out of three HCV patients[1,10,11]. Therefore, the degree of interaction between the most frequent CVS and CNS comedications administered to these patients and SOF/VEL and GLE/PIB has been checked, and the complexity of patient management, following the recommendations, to handle the potential DDI has been assessed through a broad expert panel.

Our results show that a higher amount of CVS and CNS drugs are susceptible to potential DDI when co-administered with GLE/PIB (CVS: n=18; CNS:n=7) compared to SOF/VEL (a protease inhibitors (PI) free regimen) (CVS: n=9; CNS: n=2), in line with previous studies, where is reported that NS3/4A PI are more likely to be involved in DDIs[12,13].

These DDIs may have consequences on patients' health if not identified, and the necessary actions are not initiated, as the efficacy and safety of the drugs may be adversely affected when a DDI occurs[8]. Moreover, the possible consequences of these interactions could have not only clinical consequences but also economic implications that will affect both the patient and the national healthcare system.

Our study identified that a greater percentage of CVS and CNS drugs require actions and greater resource utilization to deal with their DDI when co-administered with GLE/PIB compared to SOF/VEL, both during and after co-administration. Among the CVS drugs, the action most frequently required was dose adjustment of the concomitant drug, followed by drug suspension and drug substitution. In most cases, the initial drug needed to be restarted after finishing DAA treatment. Within the CNS drugs, the action most frequently required was dose adjustment of the concomitant drug, followed by drug substitution. In most cases, these actions led to major resource utilization in terms of additional visits and tests.

These results are aligned with previous studies carried out in other settings. Smolders et al[6] published a review to describe DDIs between CVS drugs and DAAs, finding that HCV patients with CVS comorbidities are affected mainly by DDIs with DAAs. Most of these DDI can be managed by closely monitoring drug efficacy and toxicity, discontinuing the drug when possible, or switching the CVS drug or the DAA. Davidson et al.[14] studied the management of three of the CNS drugs included in our study (aripiprazole, paliperidone and quetiapine) based on data from a real-world cohort. It concluded that clinical monitoring was the most common strategy followed for these patients. From their results, we can observe that patients treated with GLE/PIB required a higher number of actions compared to SOF/VEL, being the most common the clinical monitoring, followed by substitution of the concomitant drug.

To the best of our knowledge, this is the first study in our setting that evaluates the complexity of managing DDI in clinical practice for two of the DAA frequently used to treat HCV patients, assessing the additional actions and resource utilization required. Our results could help in decision-making when a new HCV treatment must be initiated to simplify patient management. As mentioned above, being aware of the potential DDI and managing them appropriately will lead not only to better clinical outcomes but also to better economic outcomes.

Our study is not exempt from limitations. Firstly, its results are based on the opinion of an expert panel. However, expert panel consensus is a well-accepted methodology in healthcare research and is widely used when treatment decisions and resource utilization in the actual clinical practice need to be identified. In this respect, it allows the inclusion of the perspectives of a heterogeneous expert panel, and allows these experts to participate with complete anonymity, preventing domination by any individual who might otherwise be overly influential. In our study, the expert

panel included professionals of four different specialities who were practising in different areas of Spain, which guaranteed the quality of the responses as participants based their answers on their own experience and enabled us to obtain a consensus from different points of view. Secondly, the study has focused only on CVS and CNS comedications. However, the rationale is that CVS and CNS comorbidities are two of the most prevalent in HCV patients. One out of three HCV patients uses CVS or CNS drugs concomitantly with their DAA medication in Spain[1,10,11]. Thirdly, our results do not directly quantify the cost of each of the necessary actions; however, the percentage of actions to be taken indicates the complexity of treating these patients when they are exposed to potential interactions between concomitant drugs and the antiviral. In terms of resource use, these actions translate into a higher number of visits and/or tests, where we could see the impact in terms of resource use.

In conclusion, selecting a DAA with no interactions or lesser interactions with the patient's concomitant medication is essential to simplify HCV treatment. In this regard, fewer actions and less resource utilization are needed in routine clinical practice to manage potential DDIs with SOF/VEL than with GLE/PIB, when treating HCV patients with CVS and CNS comorbidities. Future real-life studies that collect and compare the resource use of patients with CVS and CNS comorbidities treated with GLE/PIB and SOF/VEL could also support our conclusions and help decision-making. ■

Conflict of interest

Esther Molina: none

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S 1

PREVALENCE OF USE OF THE SELECTED CVS DRUGS IN SICRAS ET AL. COHORT (N=3430) AND POTENTIAL DDIS DEGREE WITH GLE/PIB AND SOF/VEL ACCORDING TO LIVERPOOL HEPATITIS DRUG INTERACTION GROUP

Concomitant drugs		n	Prevalence of use	Potential DDIs with GLE/PIB	Potential DDIs with SOF/VEL
Antiarrhythmics	Amiodarone	18	0.52%		
	Digoxin	13	0.38%		
Anticoagulants	Acenocumarol	77	2.24%		
Lipid-lowering drugs	Atorvastatin	170	4.96%		
	Simvastatin	154	4.49%		
	Pravastatin	31	0.90%		
	Rosuvastatin	37	1.08%		
	Pitavastatin	22	0.64%		
	Gemfibrozil	29	0.85%		
	Ezetimibe	22	0.64%		
	Colestyramine	12	0.35%		
Antihypertensives	Enalapril	357	10.41%		
	Candesartan	37	1.08%		
	Olmesartan	109	3.18%		
	Irbesartan	35	1.02%		
	Telmisartan	12	0.35%		
Cardiac Insufficiency	Carvedilol	38	1.11%		
	Diltiazem	25	0.73%		

CVS: cardiovascular; DDIs: drug-drug interactions. No interaction expected | Potential weak interaction | Potential interaction | Co-administration contraindicated

Source: own resource.

SUPPLEMENTARY TABLE S 2

PREVALENCE OF USE OF THE SELECTED CNS DRUGS IN SICRAS ET AL. COHORT (N=3430) AND POTENTIAL DDIS DEGREE WITH GLE/PIB AND SOF/VEL ACCORDING TO LIVERPOOL HEPATITIS DRUG INTERACTION GROUP

Concomitant drugs		n	Prevalence of use	Potential DDIs with GLE/PIB	Potential DDIs with SOF/VEL
Analgesics	Fentanyl	79	2.30%		
	Oxycodone	26	0.76%		
Antipsychotic	Quetiapine	117	3.41%		
	Paliperidone	79	2.30%		
	Aripiprazole	33	0.96%		
	Clotiapine	19	0.55%		
Anticonvulsants	Oxcarbazepine	32	0.93%		

CNS: Central Nervous System; DDIs: drug-drug interactions. No interaction expected | Potential weak interaction | Potential interaction | Co-administration contraindicated

Source: own resource.