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Structured review of establishing and evaluating clinical relevance of drug interactions in hepatitis C virus treatment (Update 2015 - 2017)

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Abstract

Objective: This study-s objective is to establish and evaluate the clinical relevance of drug interactions during treatment of patients with hepatitis C. **Method:** A PubMed/MedLine search was conducted for articles published in English and Spanish from January 1, 2015 to March 30, 2017 using the terms Mesh: Hepatitis C AND drug interactions OR herb-drug interactions OR food-drug interactions, from studies conducted in humans. The clinical relevance of drug interactions was established and evaluated based on probability of occurrence and severity of interactions. **Results:** Of the 184 four articles identified, 92 were selected by title and abstract for full review. The full texts of two articles could not be accessed. Of the remaining articles, 57 describ ed relevant interactions. Of the 155 pairs of drugs that interact that were identified, 154 (99.4%) were pharmacokinetic, and one (0.6%) was pharmacodynamic. Thirty-four of the 155 pairs (21.9%) were assessed at level 1; 73 (47.1%) were assessed at level 2; 48 (31.0%) were assessed at level 3, none were assessed at level 4. In addition, 29 pairs of interacting drugs had no evidence of clinical relevance. **Conclusions:** More than 99% of clinically relevant drug interactions are pharmacokinetics and are associated with changes in metabolism and transport of drugs. Simeprevir and 3D (Paritaprevir/Ritonavir+ Ombitasvir+Dasabuvir) therapy had the greatest number of interactions.

Keywords

Drug interactions, hepatitis c, antivirals.

INTRODUCTION

Viral hepatitis is considered to be a public health problem worldwide. It has high morbidity and mortality rates, multiple virus serotypes, various transmission routes, and coinfections with human immunodeficiency virus (HIV). In addition, various drugs are used to treat complications and comorbidities, and access to diagnostic methods and effective and safe treatments is limited. (1-3) According to the World Health Organization (WHO), it is estimated that prevalence of hepatitis C virus (HCV) infections in the United States is 1.0%, or 7,000,000. Some authors have estimated that, globally, there are approximately 185 million people who have HCV. (4, 5)

HCV is characterized by two phases of infection. In the first asymptomatic acute phase, 15% to 45% of patients eliminate the virus spontaneously within 6 months and do not progress to the next phase. The other 55% to 85% of patients enter the chronic infection phase which involves the onset of complications such as liver fibrosis, cirrhosis and hepatocellular carcinoma. (3, 4)

In recent years, treatment for HCV has undergone considerable changes. In 2011, the first direct-acting antivirals (DAA) boceprevir and telaprevir (NS3/4A protease inhi-

bitors) appeared. (4) They have increased sustained viral responses (SVR) from 60% to 75% in patients without prior treatment. (6) Since then, new DAAs such as nonstructural protein 5A (NS5A) inhibitors, NS5B nucleoside analogue inhibitors, polymerase inhibitors, and non-nucleoside NS5B polymerase inhibitors have been developed. They attack virus replication by inhibiting different proteins to achieve better SVR rates (> 90% to 95%), increased tolerability of treatment, less associated adverse events and less drug interactions. (3)

Some of the new DAAs as well as other drugs that are widely used in clinical practice converge on metabolism through cytochrome P450 (CYP) isoenzymes and transporters such as glycoprotein-p (Gp-p), organic anionic transporter polypeptides (OATP), and breast cancer resistant protein (BCRP). (7) This makes it necessary to update previously systematized information on severity and probability of occurrence of drug interactions in patients with HCV genotype 1. (8, 9)

METHOD

We searched PubMed/MedLine for articles published in Spanish or English from January 1, 2015 to March 30, 2017 using the following Mesh terms: Hepatitis C AND drug interactions OR herb-drug interactions OR food-drug interactions.

Inclusion Criteria

We considered systematic reviews, metaanalyses, multicenter studies, randomized controlled clinical trials, quasi-experimental studies (non-randomized), observational studies, guidelines, letters and case reports as long as they were human studies in Spanish or English and there was access to the full text. Articles about drug interactions between drugs used to treat HCV and other drugs were considered and, in some cases, references used in those articles were added to increase context and document results.

Exclusion Criteria

We excluded articles about in-vitro and/or animal studies, articles about experimental drugs, and those that did not address drug interactions related to treatment of HCV.

Review Methods

The articles included were independently selected by three researchers. Titles and abstracts of all the articles identified were reviewed to decide upon eligibility. The three authors together analyzed articles selected and decided about inclusion or exclusion of each article by consensus.

Outcome Measures and Assessment of Clinical Relevance of Interactions

Clinical relevance of drug interactions was defined using the severity and probability of occurrence of the interaction. (9) Three categories of severity were considered:

- *Severe:* The interaction may harm or injure the patient. The consequence of a negative clinical outcome of pharmacotherapy might cause patient death, risk to life, hospitalization, permanent or significant disability, congenital anomalies, or malformations at birth. In addition, there may be other effects that, in medical judgment, could compromise the integrity of a patient and require surgical intervention to avoid death, hospitalization or congenital anomalies.
- *Moderate:* The interaction requires monitoring of the patient. The consequence of a negative clinical outcome of pharmacotherapy could modify, change or interruption pharmacotherapy or require the use of additional drugs to treat a problem related to drugs or to prolongation of hospitalization.
- *Mild:* The interaction does not harm the patient. The consequence of a negative result from the drug does not require modification, change or withdrawal of the pharmacotherapy and does not require the use of new drugs to treat a drug-related problem or prolongation of hospitalization.

Three categories of probability of interaction occurrence were established on the basis of the type of study documenting the interaction.

- Defined: interaction documented in metaanalyses, systemic reviews, randomized clinical trials or non-randomized clinical trials.
- Likely: interaction documented in analytical studies or by three or more clinical cases.
- Possible: interaction documented by less than three clinical cases.

From the possible combinations of severity and probability of occurrence, the interactions can be grouped into 4 categories.

- Level 1 (very high risk) results from a combination of serious and defined, or serious and probable. Simultaneous use of drugs is considered to be absolutely contraindicated.
- Level 2 (high risk) results from a combination of serious and possible, moderate and defined, or moderate and

probable. Concomitant use of drugs requires dose adjustment from the dosage schedule and assessment of signs and symptoms of effectiveness and safety of pharmacotherapy, ideally quantitatively.

- Level 3 (medium risk) results from a combination of moderate and possible, mild and defined, or mild and probable. Simultaneous use of drugs requires dosage adjustment or assessment of signs and symptoms of effectiveness and safety of treatment, ideally quantitatively.
- Level 4 (low risk) results from the combination of mild and possible. The interaction is of little clinical relevance.
- Evidence of absence of interaction results from safe combinations of drugs that do not change the magnitude and effect of the drugs involved.

Information Collection Form

A form for collection and tabulation of data about drug-drug interactions related to treatment of HCV was designed on Excel 2016 for Windows®. It had the following structure: pharmacological group of the concomitant drug; interaction class (drug-drug, phytotherapeutic drug, drug-food, drug-disease); pair of interacting drugs; level, severity and probability of occurrence of the interaction; bibliography; interaction mechanism (pharmacokinetics or pharmacodynamics); details of the mechanism of interaction; observations; and recommendations.

RESULTS

The search terms *Hepatitis C AND drug interactions OR herb-drug interactions OR food-drug interactions* identified 184 articles, of which 90 met the inclusion criteria. Of these, 57 reported new HCV treatment drug interactions and met the inclusion criteria (Figure 1). One hundred eighty-four pairs of interacting drugs were identified, of which 155 contributed new interactions or updates to the previous review (Table 1): 34 (21.9%) were level 1, 73 (47.1%) were level 2, and 48 (31.0%) were level 3. Of the new interactions,

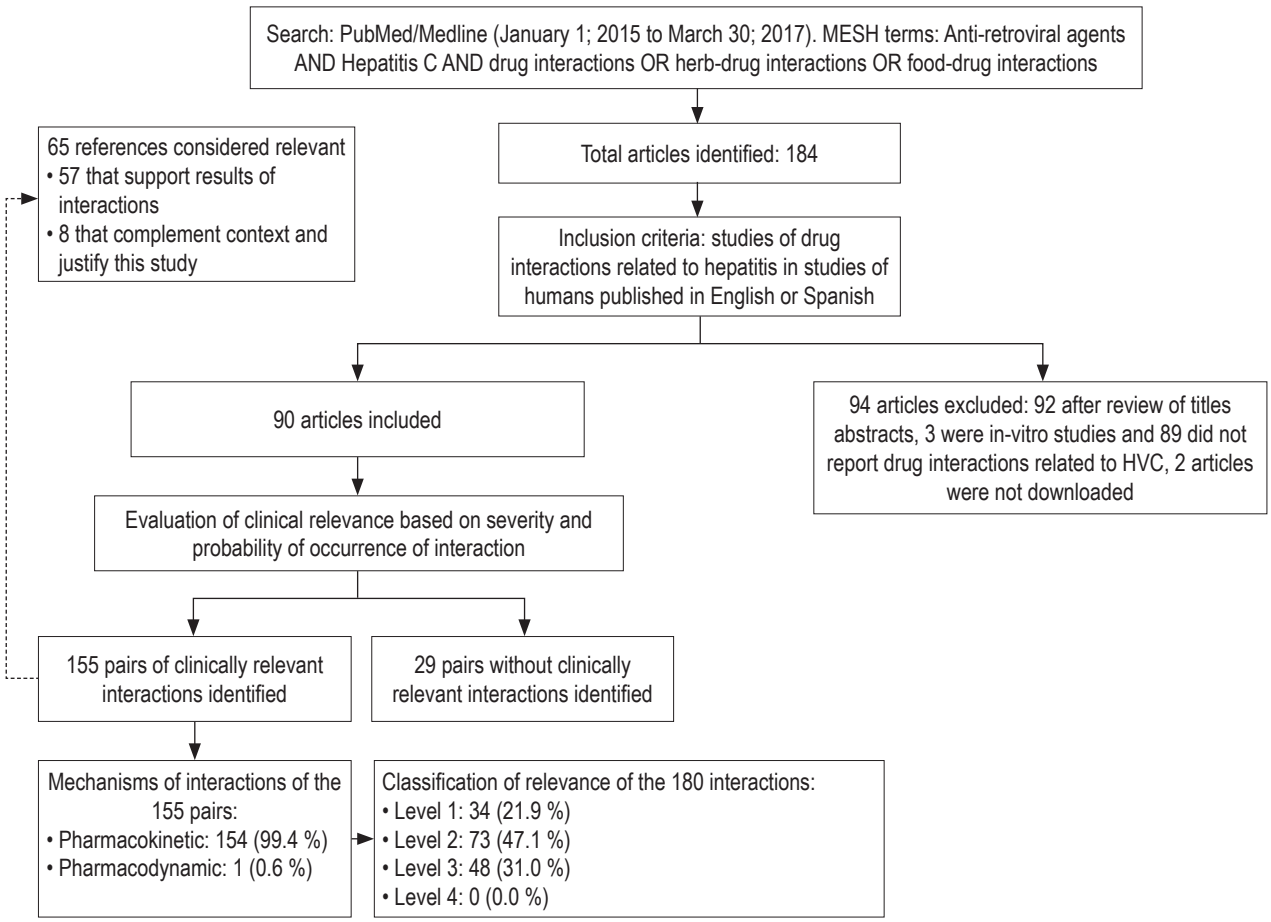

Figure 1. General scheme of structured review of clinical relevance of drug interactions in the treatment of patients infected with HCV.

Table 1. Overall results from 155 pairs of clinically relevant drug interactions

Mechanisms of the 155 pairs of interactions
Pharmacodynamics: 1 (0.6%)
Pharmacokinetics: 154 (99.4%)
Synergism: 1 (0.6%)
Enzymatic inhibition: 70 (45.2%)
Enzymatic induction: 25 (16.1%)
Change in bioavailability: 56 (36.2%)
Excretion inhibition: 3 (1.9%)

Drug	Detail of pharmacokinetic mechanism				Clinical relevance of drug interaction				
	Enzymatic inhibition	Enzymatic induction	Changes in bioavailability	Excretion inhibition	Level 1 n (%)	Level 2 n (%)	Level 3 n (%)	Level 4 n (%)	Total n (%)
ASV	4	1	2	0	2 (1.3)	1 (0.6)	4 (2.6)	0 (0.0)	7 (4.5)
DCV	4	3	1	1	0 (0.0)	5 (3.3)	4 (2.6)	0 (0.0)	9 (5.9)
DNV	1	0	0	0	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
DNV/RTV	1	0	0	0	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
EBR	3	1	0	0	0 (0.0)	4 (2.6)	0 (0.0)	0 (0.0)	4 (2.6)
FDV	2	0	1	0	0 (0.0)	2 (1.3)	1 (0.6)	0 (0.0)	3 (1.9)
GZR	3	1	0	0	3 (1.9)	1 (0.6)	0 (0.0)	0 (0.0)	4 (2.6)
GZR/EBR	0	1	0	0	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
IFN	0	2	0	0	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.3)
LDV	1	1	4	0	0 (0.0)	4 (2.6)	2 (1.3)	0 (0.0)	6 (3.9)
OMB	0	1	0	0	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
PTV/RTV, OMB + DSB	24	6	4	0	10 (6.5)	16 (10.3)	8 (5.2)	0 (0.0)	34 (21.9)
PTV/RTV, OMB	2	1	6	0	1 (0.6)	5 (3.3)	3 (1.9)	0 (0.0)	9 (5.9)
SIM	22	5	4	1	13 (8.4)	10 (6.5)	9 (5.8)	0 (0.0)	32 (20.7)
SOF	1	0	15	1	4 (2.6)	3 (1.9)	10 (6.5)	0 (0.0)	17 (11.0)
SOF/LDV	0	1	12	0	0 (0.0)	8 (5.2)	5 (3.3)	0 (0.0)	13 (8.4)
SOF/RBV	0	0	2	0	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.3)
SOF/DCV/RBV	1	0	0	0	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
VEL	1	1	5	0	0 (0.0)	7 (4.5)	0 (0.0)	0 (0.0)	7 (4.5)
Total	70	25	56	3	33 (21.3)	73 (47.1)	48 (31.0)	0 (0.0)	154 (99.4)

ASV: asunaprevir; DNV: danoprevir; DSB: dasabuvir; EBR: elbasvir; FDV: faldaprevir; GZR: grazoprevir; IFN: interferon; LDV: ledipasvir; OMB: ombitasvir; PTV: paritaprevir; RTV: ritonavir; RBV: ribavirin; VEL: velpatasvir.

140 (90.3%) were pairs of drug-to-drug interactions, five (3.2%) were phytotherapeutic drugs, eight (5.2%) were medicines with special conditions, and two (1.3%) were medicines with food. Of the 155 pairs, 154 reported interactions of the pharmacokinetic mechanism, especially enzymatic inhibition (70; 45.2%), enzymatic induction (25; 16.1%), changes in bioavailability (56; 36.2%) and excretion inhibition (3; 1.9%).

In one of these three cases of excretion inhibition, it was shown that exposure to daclatasvir (DCV) increases up to two times in patients with severe renal impairment but remains within the range of therapeutic safety and does not require adjustments. (7, 10) Simeprevir (SIM) exposure increases 62% which requires monitoring and dose adjustment. (11-13) Sofosbuvir (SOF) is contraindicated in patients with creatinine clearance over 30 mL/min by increased plasma SOF levels and circulating inactive metabolite GS-331007. (4, 6, 7, 10, 11, 14-20)

Only one case (0.6%), that of DCV and the amiodarone antiarrhythmic, was an interaction using a pharmacodynamic mechanism. It resulted in asymptomatic severe bradycardia. (21)

Table 2 shows levels of clinical relevance. One hundred eight interactions (69.7%) were assessed with a higher

risk of generating problems of effectiveness and safety of DAA drugs. Of these, 53 (34.2%) were due to enzymatic inhibition, 17 (11.0%) were due to enzymatic induction (Table 3) and 34 (21.9%) were due to changes in bioavailability (Table 4). Twenty-nine pairs of drugs were identified with evidence of absence of clinically relevant interactions. Of these, eight were related to ASV, six to LDV, three to DCV, three to OMB, two to DSB, two to SIM, two to SOF, two to PTV/RTV, and one to SOF/LDV (Table 5).

Table 2. Enzyme inhibition drug interactions related to HCV drugs

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Anesthetic/benzodiazepine			
MDL (13)	SIM	2: high risk	MDL's AUC increased 1.45 times after concomitant use with SIM. Monitor parameters of effectiveness and safety of MDL due to its narrow therapeutic margin, dose adjustment may be necessary.
MDL (22)	FDV	2: high risk	240 mg of FDV 2 times/day increases systemic exposure (AUC and Cmax) to MDL (CYP3A substrate) 192% and 104% as a result of hepatic and intestinal CYP3A inhibition. Monitor and adjust the dose of MDL.
Antibiotic/Macrolide			
Erythromycin (13)	SIM	1: very high risk	AUC increased up to 7.47 times and AUC of the macrolide increased up to 1.90 times due to the inhibition of CYP3A4 and Gp-p. Concomitant use is not recommended, the combination is contraindicated.
Contraceptives			
Ethinyl estradiol and norgestimate /NOR (23-25)	PTV/RTV, OMB + DSB	1: very high risk	Joint administration generated changes in exposure to PTV. Its Cmax increased 24% and its AUC increased 23%. NGMN, a metabolite of norgestimate, increased the Cmax by 101% and the AUC by 160%. NG, another metabolite, increased Cmax by 126% and AUC by 154%. The AUC of EE also increased 22% while that of NOR increased 29%. ALT levels increased from 3 to 4 times. Co-administration is contraindicated due to the potential for increasing ALT levels.
Azole antifungals			
KCZ (7, 26)	ASV	2: high risk	KCZ is a potent inhibitor of Gp-p and CYP3A4, which increases the AUC of ASV (substrate of Gp-p and metabolized via CYP3A4) from 7 to 10 times. Monitor ASV safety parameters; a dose adjustment is recommended.
KCZ (27)	PTV/RTV, OMB	2: high risk	Increases AUC by 105%, increases Cmax of PTV exposure by 72% and AUC of PTV exposure by 116%. Limit the dose of KCZ to 200 mg/day.
KCZ (7, 24, 25, 28, 29)	PTV/RTV, OMB + DSB	2: high risk	There is an increase in exposure to KCZ: Cmax increases 37% and AUC increases 117%. T1/2 increases more than 4 times (up to 15.7 times) due to inhibition by CYP3A4. In addition, the AUC of PTV doubles, its Cmax increases 16% and its AUC increases 42%. The dose of KCZ should not exceed 200 mg/day for patients being treated for HCV. 3D treatment and azole antifungals should be used with caution.
KCZ (30)	VEL	2: high risk	KCZ is a potent inhibitor of CYP3A4 and Gp-p and slightly inhibits CYP2C8. VEL is a substrate of Gp-p and is affected by inhibitors of CYP3A4 and CYP2C8. Co-administration increased the AUC of VEL by 70% and its by 29%. T1/2 increased from 16.9 to 23.7 hours. Requires monitoring and dose adjustment.
Antihypertensive drugs/CCB			
Amlodipine (25, 28, 29)	PTV/RTV, OMB + DSB	2: high risk	The Cmax of amlodipine, a CYP3A4 substrate, increased 26% and its AUC increased 157% while the Cmax of PTV decreased by 23% and its AUC decreased 22%. It is recommended to reduce the dose of CCB by half (50%) with clinical monitoring.
ARV/CCR5 antagonist			
MVC (31)	PTV/RTV, OMB + DSB	2: high risk	Simultaneous administration could increase plasma levels of MVC, a CYP3A4 substrate. ARV may need dose adjustment after concomitant use, because RTV is a potent CYP3A4 inhibitor.

Table 2. Enzyme inhibition drug interactions related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
ARV/CCR5 antagonist			
Elvitegravir/c/emtricitabine/ TDF (31, 32)	PTV/RTV, OMB + DSB	1: very high risk	Plasma levels of the anti-HCV scheme are expected due to the inhibitory effect of c on CYP3A4. Concomitant use is not recommended, both regimens contain pharmacokinetic reinforcement; contraindicated.
Elvitegravir/c/emtricitabine/ TDF (31, 33, 34)	SIM	1: very high risk	C increases plasma levels of SIM by interaction via CYP3A4 which increases the possibility of supratherapeutic effects. Concomitant use is not recommended.
ARV/PI			
ATV/RTV (7, 10, 16, 32-38)	DCV	2: high risk	Exposure to DCV increased from 2.1 to 3 times (110%) due to CYP3A4 inhibition. Reduce the dose of DCV from 60 to 30 mg if the DAA is co-administered with potent CYP inhibitors.
DRV/RTV (33-37)	DCV	2: high risk	Exposure to DCV increased 1.4 times due to CYP3A inhibition by DRV/RTV. Reduce the dose of DCV from 60 to 30 mg if co-administered with potent CYP inhibitors.
RTV (39)	DNV	2: high risk	Cmax of DNV 2 increased 40% and its AUC increased 73%. Effect of RTV can involve not only the inhibition CYP450 but also the inhibition of transporters involved in gastrointestinal absorption (first-pass effect). Monitor DNV, a dose adjustment may be necessary.
ATV/RTV (36)	EBR	2: high risk	EBR's AUC increased by up to 376% after use with ATV boosted by RTV. DAA safety parameters must be monitored. A dose adjustment may be necessary.
DRV/RTV (36)	EBR	2: high risk	EBR's AUC increased by 66% after joint use with DRV enhanced with RTV. The DAA safety parameters must be monitored. A dose adjustment may be necessary.
LPV/RTV (36)	EBR	2: high risk	EBR's AUC increased 271% after concomitant administration with LPV enhanced with RTV. Joint use is not recommended. DAA safety parameters must be monitored. A dose adjustment may be necessary.
ATV/RTV (36)	GZR	1: very high risk	GZR's AUC increased by up to 958% after being administered with ATV boosted by RTV. Due to the significant increase in exposure to GZR, it is necessary to suspend concomitant use and avoid unwanted toxic effects.
DRV/RTV (36)	GZR	1: very high risk	GZR's AUC increased by 650% when it was administered with DRV/RTV. Due to the significant increase in exposure to GZR it is necessary to suspend concomitant use and avoid toxic effects.
LPV/RTV (36)	GZR	1: very high risk	GZR's AUC increased 1,186% when it was administered with LPV enhanced with RTV. Due to the significant increase in exposure, it is necessary to suspend use and avoid unwanted toxic effects.
Fosamprenavir/RTV (5, 31, 32)	PTV/RTV, OMB + DSB	2: high risk	Simultaneous administration could increase plasma levels of the anti-HCV scheme. Concomitant use is not recommended. PIs should not be reinforced with RTV in 3D treatment since it contains 100 mg of RTV.
ATV (10, 29, 35-37, 40)	PTV/RTV, OMB + DSB	2: high risk	PTV's AUC increased 94%, its Cmax increased 46%, and its Cmin increased 226%. Nighttime administration increased PTV exposure to 1,095%. ATV's Cmax and AUC increased by as much as 19%. When ATV is administered at night, it increases the Cmin 68%. There is a risk of hyperbilirubinemia. Use is not recommended, unless the PI is enhanced with RTV. Monitor safety parameters, adjust doses, and monitor administration conditions.
LPV/RTV (3, 5, 10, 14, 16, 29, 31, 32, 37, 40)	PTV/RTV, OMB + DSB	1: very high risk	PTV's AUC increased 119% and its Cmax increased 216 % due to CYP3A inhibition and cumulative dose of RTV (300 mg). When administered 1 time/day, the AUC of PTV increased 87% and its Cmin increased 723%. When administered twice a day the Cmax increased 104%, the AUC increased 117%, and the Cmin increased 136%. Concomitant use is contraindicated. Accumulation of doses of RTV with 3D is not recommended since it contains 100 mg of RTV.
Saquinavir/RTV (5, 31, 32)	PTV/RTV, OMB + DSB	2: high risk	Joint administration could increase PTV plasma levels so is not recommended. PIs should not be reinforced with RTV in 3D treatment since it contains 100 mg of RTV.

Table 2. Enzyme inhibition drug interactions related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
ARV/PI			
Tipranavir/RTV (5, 31, 32)	PTV/RTV, OMB + DSB	2: high risk	Simultaneous administration could increase plasma levels of the anti-HCV scheme so is not recommended. PIs should not be reinforced with RTV in 3D treatment since it contains 100 mg of RTV.
ATV/RTV (16, 24, 31, 34, 41, 42)	SIM	1: very high risk	Concomitant use of PI with SIM could significantly increase SIM PC due to inhibition of CYP3A4. SIM administration with any HIV PI, with or without RTV, is not recommended.
DRV/RTV (10, 13, 16, 24, 31, 34, 36, 37, 41, 42)	SIM	1: very high risk	DRV/RTV increases SIM's AUC by 159%, increases its by 180%, and increases its Cmin by 460% due to inhibition of CYP3A4. Concomitant use of PI, with or without RTV, is not recommended.
Fosamprenavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Concomitant use of PIs, whether or not they are boosted, and SIM could significantly increase SIM PC by inhibition of CYP3A4. Concomitant use is not recommended.
LPV/RTV (24, 31, 41, 42)	SIM	1: very high risk	Significant increase in SIM PC enables adverse effects to arise at lower doses than therapeutic doses. The concomitant use of these drugs is not recommended.
Nelfinavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Significant increase in SIM PC enables adverse effects to arise at lower doses than therapeutic doses. The concomitant use of these drugs is not recommended.
RTV (3, 13, 24, 31, 34, 41, 42)	SIM	1: very high risk	RTV increases the AUC of the SIM by 618%. RTV is a potent CYP3A enzyme inhibitor whereby SIM is metabolized. The SIM safety profile must be monitored, concomitant use is not recommended.
Saquinavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Administration of enhanced PI plus SIM could significantly increase SIM levels due to CYP3A4 inhibition. Do not administer SIM with any PI, with or without RTV.
Tipranavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Administration of PI enhanced with RTV plus SIM could significantly increase SIM PC. Concomitant use of SIM with PI, enhanced or not, is not recommended.
ARV/NNRTI			
Rilpivirine (10, 14, 16, 24, 29, 31, 32, 34, 36, 37)	PTV/RTV, OMB + DSB	1: very high risk	Rilpivirine levels increase 3.25 times with increased risk of elevating QT interval. AUC, Cmax and Cmin increase 225%, 155% and 262%, respectively. AUC and Cmax of PTV increase 23% and 30%, respectively. AUC and Cmax of OMB increase 9% and 11%, AUC and Cmax of DSB increase 17% and 18%. It is not recommended; contraindicated.
EFZ (14, 16, 24, 29, 32)	PTV/RTV, OMB + DSB	1: very high risk	Liver enzymes increase and neurological and gastrointestinal side effects of EFZ worsen. ARV exposure increases more than 200%. Concomitant use is not recommended; contraindicated.
Delavirdine (16, 24, 41)	SIM	1: very high risk	Plasma levels of SIM could increase due to CYP3A4 inhibition exposing the patient to possible adverse effects from doses higher than therapeutic ones. The concomitant use of these drugs is not recommended.
Tuberculosis Treatment			
RFP (26)	ASV	1: very high risk	RFP increases the AUC of ASV 14.8 times. Their joint use is not recommended due to toxicity and possible increase in ALT; contraindicated.
DAA/NS5A protein inhibitor			
DCV (13)	SIM	2: high risk	Plasma levels of both drugs increased, the Cmax of DCV increased 1.50 times and that of SIM increased 1.39 times. Monitor safety of drugs, dose adjustment may not be necessary.
Special Conditions			
Moderate/severe hepatic impairment (7, 17, 19, 26, 32)	ASV	1: very high risk	In Child-Pugh B and C liver failure, ASV increased its Cmax 5 to 10 times and its AUC 23 to 32 times. There is a risk of hepatotoxicity. Use is contraindicated; if used, requires monitoring of therapeutic safety.
Moderate hepatic impairment (6, 7, 10, 17, 28, 43)	PTV/RTV, OMB + DSB	2: high risk	Administration of 3D caused the AUC of PTV to increase 62%, while those of OMB, DSB and RTV decreased more than 30%. Use is not recommended, monitor safety parameters.

Table 2. Enzyme inhibition drug interactions related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Special Conditions			
Severe hepatic impairment (6, 7, 10, 17, 19, 28, 43)	PTV/RTV, OMB + DSB	1: very high risk	The AUC of DSB increases 325%, and the AUC of PTV increases 920% while the AUC of OMB decreases 55%. The use of 3D in severe hepatic impairment is contraindicated by significant increases and decreases in exposure to DAAs.
Moderate/severe hepatic impairment (4, 7, 10-13, 17, 19, 20, 32)	SIM	2: high risk	Since SIM is mainly metabolized in the liver, use in this condition can lead to drug accumulation. The AUC of SIM increases 2.4 to 5.2 times in in hepatic insufficiency classes B and C. Do not use due to the risk of hepatotoxicity, monitor safety parameters and adjust the dose. Patients with class C cirrhosis should be referred for transplantation. If transplantation is not an option, the recommended therapy is 48 weeks of SOF/RBV.
Hypolipidemic and Antilipidemic Drugs			
GFB (25, 28, 29)	PTV/RTV, OMB + DSB	1: very high risk	GFB with 3D inhibits CYP2C8. PTV's Cmax increases by 21%, and its AUC increases 38%. The Cmax of DSB increases 101% while its AUC increases 1,030%. T1/2 increased from 5 to 90 hours resulting in risk of prolongation of the QT interval. Concomitant use is contraindicated.
Immunosuppressants			
TAC (19, 44)	DCV	2: high risk	The concentration of TAC increased the first 2 weeks after starting DCV, but this ratio decreased from the third week. Therapy should be monitored and the dose adjusted according to the increase in exposure.
CsA (39)	DNV/RTV	2: high risk	CsA (39) DNV/RTV 2: high risk DNV's AUC increased 14 times and its Cmax increased 7 times after co-administration of the calcineurin inhibitor. The use of ADR enhanced with RTV plus CsA increases DNV exposure significantly. Monitoring and dose adjustment are required.
CsA (3, 7, 10, 15, 19, 24, 29, 31, 45-48)	PTV/RTV, OMB + DSB	2: high risk	The AUC of CsA increased 482%, and there was a 2-fold increase in the AUC of PTV. At the beginning of therapy, the dose of CsA should be reduced to 20% of the current dose, the PC should be measured to determine subsequent modifications. Once 3D therapy is complete, the dose of CsA should be guided by blood concentration assessment. Frequent evaluation of renal function and side effects is recommended.
Mycophenolate mofetil (31)	PTV/RTV, OMB + DSB	2: high risk	Joint administration increased mycophenolate levels. Monitor the safety parameters of mycophenolate mofetil. A dose adjustment may be necessary.
TAC (14, 15, 19, 31, 45, 46, 48)	PTV/RTV, OMB + DSB	1: very high risk	Joint administration of 3D and TAC increased the AUC of TAC 57.1 times due to CYP3A4 inhibition. Do not use together. If they are used together, monitor therapy and adjust the dose or time of administration. If RTV is used, use immunosuppressive therapy with CsA with TAC as the first choice.
SRL (31)	PTV/RTV, OMB + DSB	1: very high risk	Plasma levels of SRL increase: Cmax increases by 6.4 times, AUC by 38.0 times and Cmin by 19.6 times due to CYP3A4 inhibition. Co-administration is contraindicated unless the benefits outweigh the risks in which case the dose should be adjusted.
TAC (24, 47)	PTV/RTV, OMB	1: very high risk	Enzymatic inhibition of TAC via CYP3A4 evidenced by increase of AUC by 5613%. The simultaneous use of these drugs is contraindicated.
CsA (3, 7, 10, 11, 13, 14, 19, 24, 31, 42, 45, 47-50)	SIM	1: very high risk	SIM PC can increase up to 6 times when administered with CsA. There is a 4.74 fold increase in AUC due to the inhibition of CYP3A, Gp-p and OATP 1B1. Joint use is contraindicated.
TAC (7, 10, 13, 24, 31, 45, 48, 49, 51)	SIM	2: high risk	SIM exposure was not significantly altered, Cmax and AUC increased by 1.8 and 1.9 times, respectively. AUC and Cmax of TAC decreased by 17% and 24%, respectively. Therapeutic effectiveness and safety should be monitored. A dose adjustment may be necessary.

AUC: area under the curve; ALT: alanine transaminase; ARV: antiretroviral; ATV: atazanavir; CCB: calcium channel blocker; c: cobicistat; CCR5: type 5 receptor chemokine; Cmax: maximum concentration; Cmin: minimum concentration; PC: plasma concentration; CsA: cyclosporine; CYP: cytochrome P450; CYP2C8: cytochrome P450 2C8; CYP3a4: cytochrome P450 3A4; DRV: darunavir; EE: ethinylestradiol; GFB: gemfibrozil; Gp-p: glycoprotein p; IP: protease inhibitor; NNRTI: Non-nucleoside reverse-transcriptase inhibitors; KCZ: ketoconazole; LPV: lopinavir; MDL: midazolam; MVC: maraviroc; NG: norgestrel; NGMN: norelgestromin; NOR: norethindrone; RFP: rifampicin; SRL: sirolimus; TAC: tacrolimus; t1/2: average life time; TDF: tenofovir disoproxil fumarate; 3D: PTV/RTV/OMB + DSB.

Table 3. Drug interactions induced by enzymes related to HCV drugs

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Anticonvulsants			
CBZ (carbamazepine) (23-25, 28, 29)	PTV/RTV, OMB + DSB	1: very high risk	Induction of CYP3A by CBZ affects 3D by decreasing exposure of DAA: the Cmax of PTV decreases by 66%, and its AUC decreases by 70% (decrease in exposure up to 87%); the Cmax of DSB decreases by 55% and its AUC by 70% (decrease in exposure up to 87%); and the Cmax of OMB decreases by 31% while is AUC decreases by 30%. The results are losses of antiviral activity and therapeutic effectiveness. Concomitant use of these drugs is contraindicated.
ARV/IP			
DRV (16, 24, 29, 31, 34-36, 40)	PTV/RTV, OMB + DSB	2: high risk	3D therapy can reduce plasma DRV levels and cause therapeutic ineffectiveness. The AUC of DRV decreased by 24% and its Cmax decreased by 48%. In addition, DAAs decreased. The AUC of PTV decreased 41%, its Cmax decreased 30% (decrease up to 59%); the AUC of DSB decreased between 27% and 53%; and the AUC of OMB decreased 27%. The effectiveness parameters of the therapies should be monitored. A dose adjustment may be necessary.
ARV/NNRTI			
EFZ (6, 7, 10, 16, 33, 34, 36-38)	DCV	2: high risk	EFZ decreases the AUC of DCV from 32% to 50% by induction of CYP3A4, but the interaction's significance is unknown. The parameters of therapeutic effectiveness should be monitored, and the dose of DCV should be increased to 90 mg/day.
Nevirapine (10, 16)	DCV	2: high risk	Nevirapine lowers plasma levels of DCV possibly via CYP3A4. Increasing the dose of DCV is required. There are no recommendations to avoid concomitant use.
Etravirine (31)	PTV/RTV, OMB + DSB	2: high risk	Co-administration of these drugs leads to decreased plasma levels in the 3D scheme. Concomitant use of these drugs is not recommended.
EFZ (36)	EBR	2: high risk	EBR's AUC decreases 54% when administered with EFZ, a known enzyme inducer. Effectiveness parameters should be monitored. A dose adjustment may be necessary.
EFZ (35, 36)	GZR	2: high risk	GZR's AUC decreased 84% when administered with EFZ. The parameters of therapeutic effectiveness should be monitored and the dose of GZR adjusted if necessary.
Nevirapine (31)	PTV/RTV, OMB + DSB	2: high risk	Joint administration decreases the plasma levels of the anti-HCV scheme and could increase the plasma levels of nevirapine. Joint administration is not recommended.
EFZ (10, 13, 16, 24, 31, 33-37, 42)	SIM	1: very high risk	This NNRTI lowers plasma SIM levels. AUC, Cmax and Cmin decreased 71%, 51% and 91%, respectively, due to CYP3A induction. Concomitant use is contraindicated and not recommended.
Etravirine (16, 24, 31, 33, 42)	SIM	2: high risk	This NNRTI can decrease SIM PC by induction of CYP3A which leads to therapeutic failure. Monitor effectiveness parameters. They should not be administered together.
Nevirapine (16, 24, 31, 42)	SIM	2: high risk	This NNRTI can lower plasma SIM levels and lead to therapeutic failure. Monitor effectiveness parameters. Joint administration is not recommended.
Tuberculosis Treatments			
RFP (13, 42)	SIM	2: high risk	SIM's AUC is decreased by 48% due to induction of CYP3A4 and inhibition of OATP 1B by RFP. Monitor therapeutic effectiveness and adjust the dose of SIM. Concomitant use is not recommended.
RFP (30)	VEL	2: high risk	RFP induces CYP3A4 and is a potent OATP inhibitor. VEL is a OATP substrate and inhibitor as well as a CYP3A4 substrate. Concomitant use of these drugs and multiple doses of RFP decrease VEL exposure. Its AUC decreased by 82%, and its Cmax decreased by 711%. In addition, T1/2 went from 18.0 to 11.7 hours. Monitor and adjust dose.
Special Conditions			
Severe hepatic impairment (17)	OMB	2: high risk	AUC of OMB decreases by as much as 54%. Use of OMB is not recommended. Monitor effectiveness of therapy and adjust dose.

Tabla 3. Interacciones medicamentosas por inducción enzimática relacionadas con medicamentos en el tratamiento del VHC (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Immunosuppressants			
CsA (19)	IFN	2: high risk	CsA's PC decreases due to increased calcineurin inhibitor metabolism. Monitor effectiveness of immunosuppressant. A dose adjustment may be necessary.
TAC (19)	IFN	2: high risk	TAC's PC decreases due to increased calcineurin inhibitor metabolism. Monitor effectiveness of immunosuppressant. A dose adjustment may be necessary.
Natural products			
St. John's Wort (28, 29)	PTV/RTV, OMB + DSB	2: high risk	Co-administration of 3D with natural products can decrease DAA exposure due to potent induction of CYP3A4. Co-administration is not recommended, and use is not indicated. If used, therapeutic monitoring and dose adjustment are required.

CBZ: carbamazepine; EFZ: efavirenz.

Table 4. Drug interactions due to changes in bioavailability related to HCV drugs

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Hepatoprotective agent			
GCR (52)	PTV/RTV, OMB	2: high risk	2D exposure was not affected. GCR's AUC increased by 49%. No dose adjustment of GCR is required under feeding conditions. Monitor therapeutically.
Antacids			
Aluminum and magnesium hydroxide (53)	SOF/LDV	2: high risk	Acid reducing drugs increase gastric pH which causes decreased LDV absorption. Antacids should be administered 4 hours before or after administration of SOF/LDV.
DIG (7, 42)	LDV	2: high risk	The PC of DIG (Gp-p substrate) increases because LDV is a Gp-p substrate and inhibitor. Monitor plasma DIG levels and consider dose adjustment.
DIG (27)	PTV/RTV, OMB	2: high risk	DIG is a Gp-p substrate while PTV is a potent Gp-p inhibitor. The Cmax and AUC of DIG increase 58% and 36%, respectively. Routinely monitor and reduce the dose of DIG 30% to 50%.
DIG (30)	VEL	2: high risk	DIG is a Gp-p substrate and VEL slightly inhibits this transporter. DIG's AUC and Cmax increase 34% and 88%, respectively. Monitor therapy and reduce the dose of DIG 30% to 50%.
Anticonvulsants			
CBZ (11, 20, 42)	SOF	1: very high risk	CBZ is a potent Gp-p inducer which decreases SOF's PC and its metabolite GS-331007 significantly leading to therapeutic failure. Joint administration is contraindicated.
Antihistamines			
FMT (24, 33, 53)	LDV	2: high risk	Acid reducing drugs such as FMT increase gastric pH causing decreased LDV absorption. PC is reduced by 50%, and viral resistance is of concern. Do not exceed 40 mg of FMT 2 times/day. Antihistamines should be taken within 12 hours of DAAs.
ARV/IP			
DRV/RTV (18, 24, 37, 54)	SOF	2 high risk	DRV/RTV can increase the AUC of SOF to 34%, and its Cmax to 55%. The increase is not considered clinically relevant, but safety parameters of the SOF should be monitored.
ATV/RTV + emtricitabine/TDF (34, 36)	SOF/LDV	2: high risk	Minimum levels of TDF increase between 40% and 60%, and ATV's PC increases by 63%. TDF levels are already increased between 20% and 30% by co-administration with the IP enhanced with RTV regardless of the DAA. Joint use is not recommended and should be avoided due to nephrotoxicity.

Table 4. Drug interactions due to changes in bioavailability related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
ARV/IP			
DRV/RTV + emtricitabine/TDF (34, 36)	SOF/LDV	2: high risk	Plasma TDF levels increase 40% to 60%, and LDV's AUC and Cmax increase 90% and 134%, respectively. TDF levels are already increased between 20% and 30% by co-administration with the DRV/RTV regardless of the DAA. Avoid use due to renal toxicity and indirect hyperbilirubinemia.
PPIs			
OMZ (24, 33, 53)	LDV	2: high risk	OMZ increases gastric pH and decreases LDV absorption. PC is reduced by approximately 50% and viral resistance can be worrisome. LDV's effectiveness should be monitored. OMZ should be used at doses <20 mg/day, 2 hours before or after administering the DAA.
ARV/Integrase inhibitor			
RAL (55)	FDV	2: high risk	FDV is a weak inhibitor of CYP3A4, Gp-p and UGT 1A1 which intervenes in the clearance of RAL, a substrate of Gp-p. Joint use increased the AUC and Cmax of RAL and its glucuronide metabolite 2.7 and 2.5 times, respectively. Monitor the safety profile of RAL, a dose adjustment may be necessary.
Tipranavir/RTV (3, 10, 16, 24, 31, 34, 42, 54, 56)	SOF/LDV	2: high risk	Tipranavir boosted with RTV can lower the PC of SOF and LDV (substrates of Gp-p) by induction of Gp-p. Joint administration should be avoided given the risk of viral susceptibility and development of resistance from sub-therapeutic levels of the drug. Monitor therapeutic effectiveness. A dose adjustment may be necessary.
ARV/NRTI			
Zidovudine/lamivudine/EFZ (41, 57)	SOF	2: high risk	SOF's Cmax decreases 49% due to induction of Gp-p and BCRP. Changes in exposure are modest but may require dose adjustment.
Emtricitabine/TDF/EFZ (14, 31, 34, 36, 37, 56)	SOF/LDV	2: high risk	TDF's AUC increases 98% and LDV's PC decreases 30%. Inhibition of the Gp-p and BCRP has been reported. Monitor renal function. Dose adjustment may be required.
Emtricitabine/TDF/rilpivirine (31, 34, 36, 37)	SOF/LDV	2: high risk	TDF's AUC increases 40% due to inhibition of Gp-p and BCRP. Monitor renal function if DAA therapy with TDF is administered. Dose adjustment may be needed.
TDF/GFR <60 mL/min (16)	SOF/LDV	2: high risk	LDV increases TDF's PC and, depending on decrease in the value of the GFR, may increase the risk of nephrotoxicity. Use is not recommended. Any use requires clinical monitoring and dose adjustment.
Tuberculosis Treatment			
RFB (11, 42)	SOF	2: medium risk	RFB induces Gp-p and can significantly decrease SOF's PC and lead to therapeutic failure. Administration is not recommended due to expected therapeutic ineffectiveness.
RFP (18, 20, 33, 42, 57)	SOF	1: very high risk	RFP is a potent Gp-p inducer. When combined with SOF, RFP's AUC decreases 72% and its Cmax decreases 77%. The use of RFP with powerful Gp-p inductors is contraindicated.
RFP (30)	VEL	2: high risk	RFP is a potent OATP inhibitor, VEL is a substrate and inhibitor of the same transporter. Joint administration increases exposure to VEL: AUC increases 47%, Cmax increases 28%. The safety of the VEL should be monitored and the dose adjusted.
Hypolipidemic drugs (Statins)			
RVS (7, 42, 54)	LDV	2: high risk	Plasma levels of RVS increase. LDV is a substrate and weak inhibitor of Gp-p and BCRP while RVS is a substrate of BCRP. Monitor the safety profile of the RVS, a dose adjustment may be necessary.
PRA (7, 23, 25, 28)	PTV/RTV, OMB + DSB	2: high risk	There is a 2-fold increase in exposure to PRA (OATP substrate 1B1/B3), Cmax and AUC increased 37% and 82% due to inhibition of OATP 1B1/B3 by PTV. Reduce the PRA dose by half when administered together with 3D therapy. Do not exceed 40 mg/day of PRA.

Table 4. Drug interactions due to changes in bioavailability related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Hypolipidemic drugs (Statins)			
RVS (3, 7, 23, 25, 28)	PTV/RTV, OMB + DSB	2: high risk	Exposure to RVS, a substrate of OATP and BCRP, increases: AUC increased 159% and Cmax increased 613%. The AUC and Cmax of PTV increased 52% and 59%, respectively. The dose of RVS should be adjusted. A dose of 10 mg/day is suggested.
PRA (27)	PTV/RTV, OMB	2: high risk	PRA is a substrate of OATP 1B1/B3 while PTV is an inhibitor of the same transporter. Joint use increased the Cmax of PRA 43%, and its AUC 76%. Those of PTV increased by 44% and 33%, respectively. The dose of PRA should be halved and the safety profile monitored.
RVS (27)	PTV/RTV, OMB	2: high risk	RVS is a substrate of OATP 1B1/B3 and BCRP while PTV is an inhibitor of these transporters. Joint use increases exposure to RVS: Cmax increases 161%, and AUC increases 33%. The Cmax and AUC of PTV increased by 40% and 22%, respectively. The dose of RVS should be halved and should not exceed 20 mg/day.
RVS (3, 7)	SIM	2: high risk	Joint use increases exposure to RVS: Cmax and AUC increased 3.17 and 2.81 times, respectively, due to inhibition of OATP 1B1. Restrict the dose of RVS to 10 mg/day when combined with SIM.
AVA (3, 7)	SIM	2: high risk	Exposure to VPA increases: AUC increased 2.2 and Cmax increased 1.7 times due to inhibition of OATP 1B1. Restrict the maximum dose to 40 mg/day when combined with SIM. Use the minimum dose necessary when the safety profile is affected.
PRA (30)	VEL	2: high risk	PRA is a substrate of OATP 1B1 while VEL is a substrate and inhibitor of this transporter. Co-administration increased PRA's AUC by 35% and its Cmax by 28%. It is necessary to monitor the safety profile of the lipid lowering agent and adjust the dose if necessary.
RVS (30)	VEL	2: high risk	RVS is a substrate of BCRP while VEL is a moderate inhibitor of this transporter in the intestines. Co-administration increased RVS's AUC by 170% and its Cmax by 160%. The safety of the RVS should be monitored and the dose adjusted if necessary.
Immunosuppressants			
SRL (31)	SOF/LDV	2: high risk	Concomitant use can significantly increase the PC of SRL. The safety profile of SRL must be monitored, and dose adjustment may be necessary.
CsA (19, 58)	SOF/RBV	2: high risk	CsA's PC decreases due to an increase in metabolism. Drugs administered concomitantly should be monitored, and a dose adjustment may be necessary.
TAC (19, 58)	SOF/RBV	2: high risk	CT's PC decreases due to the increase in metabolism. Drugs administered concomitantly should be monitored, and a dose adjustment may be necessary.
CsA (30)	VEL	2: high risk	CsA is a potent inhibitor of Gp-p while VEL is a substrate and a mild inhibitor of this transporter. Co-administration increased the AUC of VEL by 103% and its Cmax by 56%. The safety of VEL must be monitored, and a dose adjustment may be necessary.
Natural products			
St. John's Wort (18, 20, 33, 42, 57)	SOF	1: very high risk	SOF's PC decreases after concomitant use of this natural product, the mechanism of interaction is thought to be induction of Gp -p. They should not be used together due to possible therapeutic ineffectiveness.

AVA: atorvastatin; DIG: digoxin; FMT: famotidine; GCR: glycyrrhizin; PPI: proton pump inhibitor; NRTI: nucleoside analogue reverse transcriptase inhibitor. OMZ: omeprazole; PRA: pravastatin; RAL: raltegravir; RFB: rifabutin; RVS: rosuvastatin; GFR: glomerular filtration rate; UGT: Glucuronosyltransferase; 2D: PTV/RTV.

Table 5. Drugs with evidence of absence of clinically relevant interactions

Pharmacological group or drugs related to interaction	HCV Drug	Pharmacological group or drugs related to interaction	HCV Drug
Analgesic Opioid		**ARV /Integrase Inhibitor**	
Methadone (26) Buprenorphine (26)	ASV	RAL (13, 24)	SIM
		ARV/NNRTI	
Methadone (59) Buprenorphine (12, 59)	DCV	Rilpivirine (24)	SOF
		Rilpivirine (24)	LDV
Methadone (59) Buprenorphine (59)	DSB	**ARV/NRTI**	
		TDF (24)	DCV
Methadone (54, 59) Buprenorphine (54, 59)	LDV	TDF (24, 54)	LDV
		Emtricitabine/TDF (24)	OMB
Methadone (59) Buprenorphine (59)	OMB	**PPI**	
		OMZ (31)	ASV
Methadone (59) Buprenorphine (59)	PTV/RTV	**AAD**	
		DCV (26)	ASV
Methadone (54, 59) Buprenorphine (54, 59)	SOF	**Special Condition**	
		Decompensated Cirrhosis (31)	SOF/LDV
Buprenorphine (59)	SIM		
Antidepressant/SSRI		**CNS stimulant**	
Escitalopram (26)	ASV	Caffeine (26)	ASV
Sertraline (26)	ASV	**Immunosuppressants**	
Antihypertensive/ARA II		CsA (24, 42, 47, 54, 60)	LDV
Losartan (26)	ASV		

ARA II: angiotensin II receptor antagonist; SSRI: selective serotonin reuptake inhibitor; CNS: central nervous system.

DISCUSSION

Some HCV patients may have comorbidities that compromise their health status, among them HIV and hepatitis B virus (HBV) stand out for the similarity of their routes of infection. Other common comorbidities include dyslipidemia, arterial hypertension, diabetes, and arthritis typical of the passage of age. (28, 61) The emergence of new DAAs means that health professionals should be attentive to possible drug interactions, since DAAs' pharmacokinetic profiles involve isoenzymes, transporters and mechanisms that are shared with other medicines. This can contribute to development of drug-related problems thereby increasing the risk of adverse events. Consequently, continuous review of clinically relevant interactions with DAA related to HCV treatment is important for avoiding risks that alter the safety and effectiveness of treatment. (62)

This review identified 155 pairs of interactions: thirty-four (21.9%) were level 1, seventy-three (47.1%) were level 2, and forty-eight (31.0%) were level 3. One hundred fifty-four (99.4%) of these were pharmacokinetic, a finding similar to those of other reviews which have found that more than 90.0% of reported drug interactions were pharmacokinetic. Similarly, the most common mechanisms were enzyme inhibition and enzyme induction. This is a strong indication that clinicians should evaluate concomitant pharmacotherapy in cases where drugs used can affect enzymatic activity of the CYP450 complex. (37) Assessment of clinical relevance is based on severity and probability of an interaction occurring. (9) This method is one of the strengths of this review with respect to similar reviews since it allows identification of levels of drug interaction severity which can be used to discriminate among pharmacological choices. (10, 59, 63) In addition, 29 pairs of drugs with evidence of absence of clinically relevant interaction were identified.

Compared to our previous review of drug interactions in HCV patients,(8) there are 27 additional pairs of drug interactions that are the result of the development and marketing of new DAAs. IN that earlier review, pharmacokinetic drug interactions accounted for 93.7% of these pairs. Enzyme inhibition accounted for 64.0%, enzyme induction

accounted for 27.3%, changes in bioavailability accounted for 2.4%, pharmacodynamic interactions accounted for 6.3%. Drug interactions identified by the enzyme inhibition mechanism decreased by 12 in this new review while drug interactions identified by the enzyme induction mechanism decreased by 10. These were attributed to different DAAs since boceprevir and telaprevir have fallen out of use. On the other hand, drug interactions identified by changes in bioavailability increased 33.8% because the pharmacokinetic profiles of the new DAAs include carriers such as OATP, Gp-p and BCRP. (7, 29, 36, 50, 53 , 64) Pharmacodynamic interactions decreased 5.7% because of the greater number of interactions with RBV associated with mitochondrial toxicity, lactic acidosis and hematological toxicity identified during concomitant use with NRTI, telaprevir, boceprevir and IFN in the previous review. (8)

The 3D therapy composed of PTV/RTV, OMB + DSB presented 34 drug interactions. Of these, 24 (70.6%) were due to enzymatic inhibition, six (17.6%) were due to induction, and four (11.8%) were due to changes in bioavailability. These interactions were mainly due to the drugs' pharmacokinetic profiles since the drugs that make up 3D therapy are substrates and inhibitors of Gp-p and BCRP. In addition, PTV is an OATP substrate. PTV is a substrate of CYP3A4 while OMB is metabolized by hydrolysis, DSB is metabolized by CYP2C8 and, to a lesser extent, by CYP3A4. For its part, RTV is used as a pharmacokinetic enhancer of PTV. (29, 36)

Although SOF is a prodrug that does not inhibit or induce the CYP450 complex or transporters, it is also a substrate of Gp-p and BCRP. This is metabolized in hepatocytes into a pharmacologically active nucleoside (GS-461203 triphosphate analog) and in greater proportion (> 78%) to the circulating inactive metabolite (GS-331007). (50, 53) Due to its pharmacokinetic profile, few clinically relevant interactions with the SOF are expected, although it is recommended that concomitant use with strong Gp-p inducers such as RFP and some natural products such as St. John's wort be avoided. On the other hand, SOF can be safely administered with immunosuppressants. (50) In combination with LDV, SOF can be used safely with most ARVs although there is some risk of hyperbilirubinemia when administered with ATV. (37)

The results of this review suggest that clinically relevant interactions with DAAs can be related to multiple mechanisms. Among them, interactions between DAAs with certain morbidities of clinical interest such as cirrhosis, renal failure and inflammatory infectious processes are evident. (32, 65) Liver and kidney damage alters the metabolism and excretion of drugs and their metabolites. This can lead to accumulation of the metabolites in the bloodstream and to possible unwanted toxic effects. Therefore, it is important to constantly monitor therapy and promote rational use of drugs to ensure the best possible health outcomes.

CONCLUSIONS

According to the results obtained, more than 99% of the drug interactions of clinical relevance in HCV patients receiving pharmacological therapy are pharmacokinetic and are associated with either induction or inhibition of liver metabolism and changes in the bioavailability of drugs due to inhibition and/or induction of Gp-p, OATP and BCRP. Clinically relevant interactions may occur frequently in polymedicated patients who receive concomitant therapy for treatment of other associated diseases when they are also receiving SIM or therapies such as 2D and 3D enhanced with RTV. Plasma concentrations of concomitant drugs can be altered in HCV patients being treated with these drugs and drugs for other associated diseases. This situation is more likely in cases where DAAs are administered simultaneously with ARVs, tuberculosis treatments, lipid lowering agents, antiarrhythmic agents, immunosuppressants and anticonvulsants. We recommend looking for the most appropriate therapeutic alternative for each patient's health condition to guarantee effectiveness and safety.

LIMITATIONS

The main limitation of this study was its restricttion to the PubMed/MedLine database. However, this effect was lessened because the review was complemented by a search for bibliographic references found in the 90 articles reviewed.

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