

Effectiveness and potential drug interactions in antiviral therapy for the treatment of chronic hepatitis C: real-life data from a specialized center in southern Brazil

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Direct-acting antivirals used in the treatment of hepatitis C have demonstrated high rates of efficacy, are well tolerated and considered safe. However, they are not free of drug interactions. To describe the effectiveness of hepatitis C treatment and the incidence and severity of potential drug interactions between drugs used during this treatment. A cross-sectional study with 148 patients who began treatment for hepatitis C between April and June 2016 in a specialized center in Brazil. Drug interactions were identified in the Truven Health Analytic/DynaMed Plus and Hep-C Interactions databases. Regarding treatment outcome, 93.9% of patients achieved SVR, 2.7% relapsed and 3.4% did not return after the end of the follow-up period. A total of 328 chronic diseases were identified (71 different diseases), and 88.5% of the patients had at least one chronic disease. The patients reported the use of 474 drugs (121 different drugs), with 3.2 drugs per patient on average. We identified 265 potential drug interactions, classified as important (6.0%), with clinical significance (20.7%) and without clinical significance or with insufficient data (69.4%). Cirrhotic patients had a higher average number of potential drug interactions than non-cirrhotic patients (2.51 x 0.79, p = 0.000). Hepatitis C treatment with direct-acting antivirals are effective and safe for most of patients.

Keywords: Hepatitis C. Drug interactions. Direct-acting antivirals. Safety. Real-world data.

INTRODUCTION

Hepatitis C affects about 185 million people worldwide and is a serious public health problem (Messina *et al.*, 2015). The chronic form of the disease can progress to cirrhosis, liver cancer and death. The treatment of hepatitis C has evolved in recent years, mainly due to the development of direct-acting antiviral drugs (DAAs) (WHO, 2017; Castro *et al.*, 2015).

It is estimated that from 1.4 to 1.7 million people are infected with the hepatitis C virus in Brazil (Mesquita

et al., 2016). Treatment for hepatitis C has been offered by the public health system since the 1990s and care protocols are continuously reviewed and updated based on scientific evidence. In 2015, the drugs of the new generation of direct-acting antivirals were incorporated: sofosbuvir, simeprevir and daclastavir (Mesquita *et al.*, 2016; Brasil, 2015).

The new direct-acting antivirals have shown high rates of efficacy, are well tolerated and considered safe (Binda *et al.*, 2017; WHO, 2017). In spite of this, the DAAs are not free from drug interactions, since people who use them may exhibit comorbidities, which may be treated with the concomitant use of other medications (Binda *et al.*, 2017; Deming *et al.*, 2016). These situations were not considered in the clinical trials, so it is necessary to evaluate the clinical importance of these interactions in patients from real-

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life studies, who use polypharmacy, suffer the impact of chronic diseases, or may develop special conditions such as liver and kidney damage (Binda *et al.*, 2017; Scavone *et al.*, 2016).

The prevalence of potential drug interactions is usually studied in particular groups of patients like older people and hospitalized patients due to the large number of drugs prescribed to these patients. There are few studies on ambulatory care and especially with patients with chronic hepatitis C (Melo, Storpitis, Ribeiro, 2018; Teotonio *et al.*, 2017; Pinto *et al.*, 2013).

The aim of this study is to describe the incidence and severity of potential interactions between drugs used in the treatment of hepatitis C, sofosbuvir, daclatasvir, simeprevir, ribavirin and alfapeginterferon-2a, and other medicines used by patients treated at a specialized center for treatment of hepatitis C in Porto Alegre/RS.

METHODS

A cross-sectional study was conducted with patients who started the treatment of hepatitis C in a *Serviço de Atendimento Especializado* - SAE (Specialized Care Service) for viral hepatitis, located in the city of Porto Alegre, RS.

The sample consisted of all patients who started treatment for hepatitis C between April and June 2016 (148 patients), of both sexes, residents of the city of Porto Alegre. The drugs used to treat hepatitis C were direct-acting antivirals (DAAs) sofosbuvir, simeprevir and daclastavir in different combinations, which could include or not alfapeginterferon and ribavirin, according to the current Brazilian Guidelines (Brasil, 2015).

The data were collected in medical records, using a data collection tool, validated in a pilot study. The variables analyzed were gender, age, genotype, presence or absence of cirrhosis, treatment outcome, medications used to treat hepatitis C, presence of comorbidities, use of prescribed and non-prescribed medications, including medications used to treat other chronic diseases, treatment of acute diseases and management of adverse effects resulting from the treatment of hepatitis C.

Patients with advanced fibrosis (stage 4) diagnosed via biopsy or hepatic elastography and patients with clinical signs and/or ultrasonographic findings related to liver cirrhosis were considered cirrhotic patients (Brasil, 2015). The Brazilian Guidelines in force in the study period included only patients with fibrosis stage 3 or over. Another condition for receiving treatment is

being coinfecting with HIV and extra-hepatic disease (Brasil, 2015).

Regarding the outcomes, the Sustained Virological Response (SVR) characterized the eradication of HCV, having been verified with the undetectable HCV-RNA result at the 12th week of the post-treatment follow-up. Patients that had undetectable levels of HCV-RNA at the end of treatment and return of detectable HCV-RNA levels during follow-up were considered as relapsing (Brasil, 2015). Data pertaining to patients who did not return at the end of the follow-up period were reconsidered as lost.

The comorbidities were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (Cid 10, 2018).

The number and medications used were collected from the patients' medical records. It should be noted that drug use is registered by the pharmacist on the patient's chart during the initial interview and in the monthly pharmaceutical consultations during treatment, including medical prescriptions of long-term medications. The patients were questioned about the use of non-prescription drugs, supplements and herbal medicines.

The drugs consumed were classified based on the Anatomical Therapeutic Chemical (ATC) system of the Nordic Council of Medicines, which corresponds in increasing order to the anatomical, therapeutic and pharmacological spheres (WHO, 2018). The first classification level was use, which corresponds to the anatomical subgroup to which the drug is related.

For the identification of potential interactions between sofosbuvir, daclatasvir, simeprevir, ribavirin and alfapeginterferon and other medicines when used concomitantly, monographs of the drugs were consulted in the Truven Health Analytics database – DynaMed Plus (Truven Health Analytics, 2017) and in the HEP Drug Interactions database of the University of Liverpool (HEP Drug Interactions, 2018), available on www.hep-druginteractions.org. The interactions were classified according to risk categories or pharmacological importance in: *major interactions, interaction with potential clinical significance, potential weak interaction, interaction without clinical significance or insufficient data, and non-clinically significant interaction* (HEP Drug Interactions, 2018).

The management of the interactions followed the guidelines of the same databases (Truven Health Analytics, 2017; HEP Drug Interactions, 2018). The number and type

of interactions identified were compiled using descriptive statistics (simple and relative frequencies, measures of central tendency). The average number of drugs and of interactions were analyzed using Student's t-test for independent samples, with different variances.

The study was approved by the Research Ethics Committee of the Federal University of Health Sciences of Porto Alegre and by the Ethics Committee of the Presidente Vargas Maternal and Child Hospital, under legal opinion number 1,899,407.

RESULTS

In the study period, of the 148 patients who started treatment for hepatitis C, most (68.2%) were carriers

of genotype 1 and two individuals were concomitantly infected by genotypes 1 and 2. Other risk factors identified were: coinfection with HIV (9.4%) and coinfection with the hepatitis B virus (0.7%); prior use of alcohol (61.5%), current use of alcohol (6.7%).

Regarding treatment outcome, 93.9% of patients achieved SVR, 2.7% relapsed and 3.4% did not return at the end of the follow-up period. The characterization of the patients, hepatitis C treatments and outcomes are presented in Table I.

TABLE I – Characteristics of the patients from a specialised center in Hepatitis C treatment, Porto Alegre/RS, April to June 2016, distributed according to cirrhosis presence

Patient's characteristics	Without cirrhosis n=62	With cirrhosis n=86	Total n=148
Age (median, range, in years)	56 (33 to 73)	61 (28 to 86)	58 (28 to 86)
Male gender	54.8%	51.2%	52.7%
HCV genotype			
1	82.3%	58.2%	68.2%
2	1.6%	4.6%	3.4%
3	12.9%	39.0%	26.3%
4	0.0%	1.2%	0.7%
1 e 2	3.2%	0.0%	1.4%
Individual with at least one co morbidity	83.9%	91.8%	88.5%
Number of drug use*			
0	22.6%	5.8%	12.8%
1	24.2%	11.6%	16.9%
2	11.3%	19.7%	16.2%

(continuing)

TABLE I – Characteristics of the patients from a specialised center in Hepatitis C treatment, Porto Alegre/RS, April to June 2016, distributed according to cirrhosis presence

Patient's characteristics	Without cirrhosis n=62	With cirrhosis n=86	Total n=148
3	9.7%	18.6%	14.8%
4	12.9%	10.5%	11.5%
5	6.4%	12.8%	10.2%
>5 (6 a 10)	12.9%	20.9%	17.6%
Hepatitis C treatment			
SOF+DAC	53.2%	16.3%	31.7%
SOF+DAC+R	27.4%	67.5%	50.7%
SOF+PEG+R	4.8%	7.0%	6.1%
SOF+R	1.6%	4.6%	3.4%
SOF+SIM	11.3%	0.0%	4.7%
SOF+SIM+R	1.6%	4.6%	3.4%
Outcomes			
SVR	93.5%	94.2%	93.9%
Relapse	1.6%	3.5%	2.7%
Loss of follow-up	4.8%	2.3%	3.4%

SOF: sofosbuvir, SIM: simeprevir, DAC: daclastavir, PEG: alfapeginterferon, R: ribavirina

SVR: sustained viral response

**excluded the drugs used for treatment of Hepatitis C.*

Among the individuals evaluated, 88.5% reported at least one other chronic disease besides HCV, totaling 328

diseases, 71 being different. Figure 1 shows the distribution of comorbidities reported according to ICD-10.

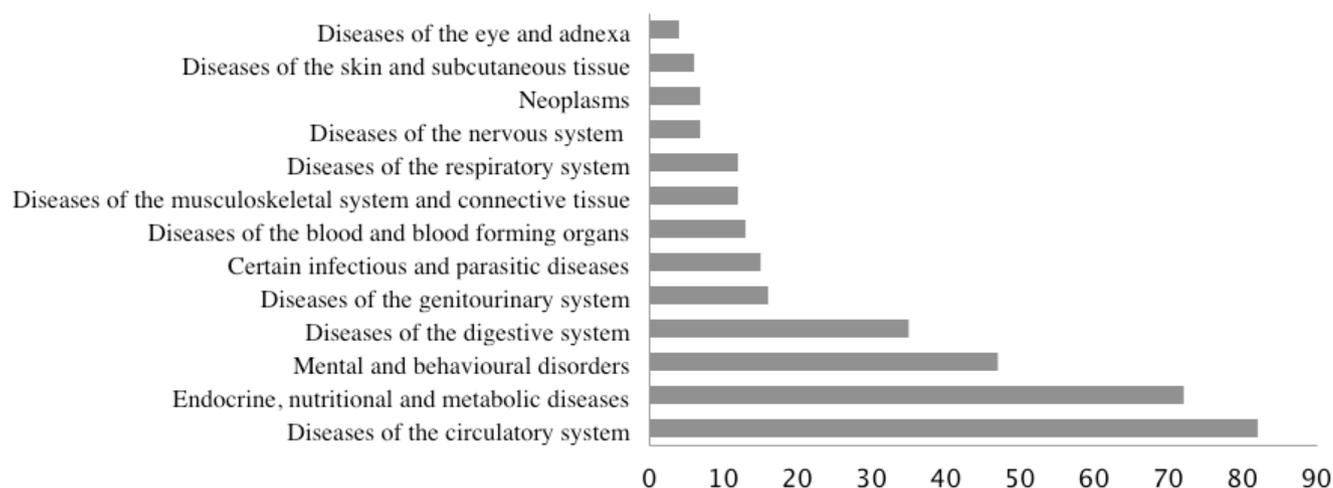


FIGURE 1 – Percentage distribution of co morbidities (n = 328), according to the ICD-10, presented by patients undergoing treatment for Hepatitis C in a specialised center in Porto Alegre/RS, from April to June 2016.

Regarding drugs used concomitantly with the hepatitis C treatment, 474 were reported, 121 being different, with 3.2 drugs per patient on average. The frequency of drugs and therapeutic groups is described in Table II.

For the 474 mentioned drugs, 265 potential interactions with the medicines used to treat hepatitis C were identified, with 1.79 drug interactions per patient on average. Table III present the drug interactions identified according to classification, degree of hepatic impairment of the patients and suggested recommendations for management.

Table IV shows the distribution of potential interactions according to the severity of hepatic damage and the total number of medications used concomitantly. The total number of drugs and the total number of drug interactions were shown to be superior and significant in the group of patients with cirrhosis when compared to those without cirrhosis. All patients undergoing antiretroviral therapy for the treatment of HIV had their regimen assessed and, if necessary, adjusted prior to the initiation of the treatment of hepatitis C.

TABLE II – Frequency of the drugs utilized (n=474) according to Anatomical Therapeutic Classification (ATC) used by patients undergoing treatment for hepatitis C. Porto Alegre/RS, April to June, 2016

Therapeutic subgroup ATC classification	Drug	Use frequency [n(%)]
A02B -Drug for acid related disorders	Omeprazole	39 (8,23)
C03A-Diuretic	Hydrochlorothiazide	37 (7,81)
N02B-Analgesic	Paracetamol	35 (7,38)
C09A-Agent acting on the renin-angiotensin system	Enalapril	26 (5,48)
A10B-Drug used in diabetes	Metformin	26 (5,48)

(continuing)

TABLE II – Frequency of the drugs utilized (n=474) according to Anatomical Therapeutic Classification (ATC) used by patients undergoing treatment for hepatitis C. Porto Alegre/RS, April to June, 2016

Therapeutic subgroup ATC classification	Drug	Use frequency [n(%)]
C09A-Agent acting on the renin-angiotensin system	Losartan	20 (4,22)
C07A- Beta blocking agent	Propranolol	17 (3,58)
N02B- Analgesic	Dypiron	15 (3,16)
A10B-Drug used in diabetes	Glibenclamide	14 (2,95)
H03A- Thyroid therapy	Levothyroxine sodium	13 (2,74)
B01A- Antithrombotic agent	Acetylsalicylic	12 (2,53)
C09A-Agent acting on the renin-angiotensin system	Captopril	12 (2,53)
SC07A- Beta blocking agent	Atenolol	11 (2,32)
N03A- Antiepileptic	Clonazepam	11 (2,32)
C10A-Lipid modifying agent	Simvastatin	11 (2,32)
C08C- Calcium channel blocker	Amlodipine	10 (2,11)
N06A - Psychoanaleptic	Fluoxetine	8 (1,69)
R06- Antihistamine for systemic use	Loratadine	8 (1,69)
N02B-Analgesic	Dorflex®*	7 (1,48)
N06A - Psychoanaleptic	Amitriptyline	6 (1,26)

*Association of dypirone, orphenadrine citrate and caffeine.

TABLE III – Potential drug interactions classified according risk categories, samples and recommendations to management according to DynaMed Plus and HEP Drug Interactions databases

Severity	Drug for hepatitis C treatment	Potencial Drug Interaction/ Use frequency (n)	Recommendation
Major interactions	R	dipyron (15)	Should not be co-prescribed
	DAC	dexamethasone (1)	

(continuing)

Severity	Drug for hepatitis C treatment	Potencial Drug Interaction/ Use frequency (n)	Recommendation
Interactions with clinical significance	SIM	dipyron (2) hydroxizyne (1) tamsulosin (1) dutasterida (1) glibenclamide (1)	Additional monitoring recommended, dosage or intake time adjustment
	R	levothyroxine (8) lamivudine (3) abacavir (2) tenofovir (1)	
	DAC	dipyron (17) amlodipine (10) simvastatin (9) ritonavir (5) pravastatin (2) verapamil (1) digoxin (1) nifedipine (1)	
Weak potential interaction	DAC	levothyroxine (10)	Might need monitoring or dosage adjustment
Interaction without clinical significance or with insufficient data		123	Might need monitoring or dosage adjustment

SIM: simeprevir, DAC: daclastavir, R: ribavirina.

TABLE IV – Number and average number of drugs and potential drug interactions identified by patients on hepatitis C treatment with or without cirrhosis, Porto Alegre/RS, April to June, 2016

	Cirrhotics (n=86)	Non cirrhotics (n=62)	p-value
Number drugs	319	155	0.002953*
Number of drug interactions	216	49	0.000000*
Average number of drugs per patient	3.71	2.50	
Average number of drug interactions per patient	2.51	0.79	

* p-value <0.05; t test for independent samples.

DISCUSSION

Among the patients included in this study, SVR rates reached 93.9% and are in accordance with data from clinical trials and real-life studies (Sette-Jr *et al.*, 2017; Flisiak, Pogorzelska, Flisiak-Jackiewicz, 2017; Bansal *et al.*, 2015; Sulkowski *et al.*, 2014). Considering the results obtained with the new DAAS, the World Health Organization (WHO) proposed, in 2016, the “Global Health Sector Strategy on Viral Hepatitis 2016-2021: Towards Ending Viral Hepatitis”, aimed at establishing global strategies capable of achieving the goal of elimination of viral hepatitis as a public health problem by 2030 (WHO, 2017).

The most common regimen for HCV treatment was SOF + DAC + R. With the new DAA, many patients who were previously ineligible for the treatment of comorbidities, with the publication of the Brazilian Guidelines in 2015, have been granted access to hepatitis C treatment (Brasil, 2015). Although DAAs are considered safe and well tolerated (Scavone *et al.*, 2016; Umar, Akhter, Osama, 2016), patients use other drugs, making it difficult and complex to evaluate all potential drug interactions (Umar, Akhter, Osama, 2016).

Other studies have evaluated the potential interactions between drugs used to treat hepatitis C and other medications used concomitantly with them. Proton pump inhibitors and beta-blockers were the most frequent drugs, in a study conducted in Italy with 449 patients and 15 treatment centers between March 2015 and March 2016 (Kondili *et al.*, 2017). The study pointed out that of the 142 drugs used by patients with mild degrees of hepatic impairment, 20% require dose adjustment or monitoring. Of the 322 drugs used in critically ill patients, 25% require dosage adjustment or monitoring and 3% are contraindicated. The study found that 30-44% of patients are at risk of potential drug interactions (Kondili *et al.*, 2017). Some drugs are used by patients with liver cirrhosis to treat complications of the disease. Proton pump inhibitors prevent the bleeding of esophageal varices and beta blocking agents treat portal hypertension (Weersink *et al.*, 2016).

Besides the risk of drug interactions, a cohort analysis of an HCV-infected veterans database identified 11,526 individuals who were exposed to proton pump inhibitors. The increasing use of proton pump inhibitors was associated with dose-dependent risk of progression of chronic liver disease into cirrhosis, as well as with increased risk of hepatic decompensation and

hepatocellular carcinoma (Li *et al.*, 2018). In these cases, it is necessary to evaluate the risk-benefit relationship for the patient.

In the USA, in a study with 664 patients, vitamins, herbal supplements, antacids and anti-secretors were the most commonly-used drugs. In another study in the USA (Ottman *et al.*, 2018), with 300 patients, the most commonly-used drugs were proton pump inhibitors, histamine receptor antagonists and statins.

Most of the potential drug interactions identified in this evaluation (66.8%) were classified as having no clinical significance or with insufficient data. The suggested management was monitoring and adjusting the dose if necessary. The potential drug interactions considered more severe were related to dipyron, except for one case related to dexamethasone. The use of dipyron and alfapreginterferon and/or ribavirin is contraindicated because it increases the risk of developing anemia (HEP Drug Interactions, 2018). It should be noted that dipyron is a widely used analgesic in Brazil, including as self-medication (Arrais *et al.*, 2016), and its occasional use may explain the fact that there were no complications during treatment. This fact highlights the importance of previous counselling for the treatment of hepatitis C and the importance of pharmaceutical evaluation throughout treatment. Knowledge about comorbidities and use of drugs allows the team to follow the most appropriate management of possible clinical complications during the treatment of hepatitis C.

In this study, the use of dipyron was reported by 14 patients and 10 of them used ribavirin. Other 8 people reported associations between the use of dipyron and muscle relaxants or antispasmodics, and 5 of them used ribavirin. Dipyron, alone or in combination, is a nonprescription drug in Brazil. It was not possible to identify whether the use was by prescription or by self-medication. Nonetheless, its clinical occurrence was not observed in this study. Also resulting in severe interaction, the use of daclatasvir and dexamethasone to decrease the concentration of daclastavir is contraindicated due to the induction of CYP3A4 by dexamethasone, which may decrease the efficacy of daclastavir (HEP Drug Interactions, 2018; Binda *et al.*, 2017; Scavone *et al.*, 2016). A patient was referred to a specialized service for the use of injectable dexamethasone in combination with analgesics and vitamin B complex.

Knowledge of the drugs' pharmacokinetic mechanisms is essential for the management of drug interactions (Pons *et al.*, 2017). Most interactions are

linked to hepatic metabolism (induction or inhibition of cytochrome P450-3 A4 [CYP3A4]) and/or intestinal transporters (anion-carrying polypeptide and P-glycoprotein) (Pons *et al.*, 2017; Kondili *et al.*, 2017). Sofosbuvir has lower chances of interactions, since its metabolization does not depend on cytochromes (Pons *et al.*, 2017).

As an example of interaction with potential clinical significance, we can mention the use of dutasteride and daclatasvir. Dutasteride is metabolized by CYP3A4/5 and its concentrations may be increased due to the moderate inhibition of intestinal CYP3A4 by simeprevir. Close monitoring is recommended because of the heightened adverse effects like impotence, decreased libido and dizziness. A 48-hour dose interval may be suggested if the adverse effects are severe. Dutasteride is also contraindicated in patients with severe hepatic impairment (HEP Drug Interactions). In combination with daclatasvir and simvastatin, an increased concentration of simvastatin may occur due to the inhibition of OATP1B1 and BCRP by daclatasvir; therefore, reducing the dose of simvastatin and monitoring serum lipid levels as well as the adverse effects of this drug, such as muscle pain, is recommended (Binda *et al.*, 2017; Pons *et al.*, 2017).

The use of levothyroxine and daclatasvir has a weak potential for interaction. The mechanism of thyroid hormones is complex. T3 and T4 can be transported by OATP1B1, which is inhibited by daclastavir, but it is not clear whether this has clinical significance. Therefore, monitoring the thyroid function is recommended (HEP Drug Interactions, 2018).

Important interactions may occur between all 2nd generation DAAs that act as strong or moderate inducers or inhibitors of CYP 3A4, such as anticonvulsants, antibiotics, systemic dexamethasone, cisapride, herbal medicines and antiretrovirals. Inducers of P-glycoprotein (P-gp) may also trigger interactions, such as rifampicin, carbamazepine, phenytoin and St. John's wort (Scavone *et al.*, 2016). These interactions are all foreseen in the DAAs' package inserts (Gilead, 2015; Bristol-Myers Squibb, 2015; Janssen-Cilag, 2015).

An important drug interaction already foreseen in the package leaflet is that of sofosbuvir and amiodarone. The combination of amiodarone with other DAA may result in severe symptomatic bradycardia, the mechanism of which is unknown. Coadministration of these drugs is contraindicated, but if necessary, then cardiac monitoring is recommended (Truven Health

Analytics, 2017; Binda *et al.*, 2017; Pons *et al.*, 2017; Gilead, 2015). None of the patients who were followed-up used amiodarone.

Ribavirin does not inhibit cytochrome P450 enzymes; therefore, the potential for the occurrence of interactions triggered by this pathway is minimal. On the other hand, the potential for interactions may persist for up to 2 months (5 times the half-life of ribavirin) following the completion of the ribavirin treatment due to its long half-life (Binda *et al.*, 2017; Farmanguinhos, 2017; Truven Health Analytics, 2017).

In our study, patients with cirrhosis, on average, used more drugs than patients without this condition, a result similar to other international studies' (Kondili *et al.*, 2017; Langness *et al.*, 2017). Many medicines are metabolized by CYP 450 and this pathway is impaired in patients with cirrhosis, increasing the risk of toxicity for individuals exposed to drug interactions (Ottman *et al.*, 2018; Kondili *et al.*, 2017). Pharmacokinetic changes occur in patients with cirrhosis, like hypoalbuminemia, ascite and impairment of renal excretion. These changes can reduce drug clearance; cause the upregulation of drug receptors and changes in the receptors' sensitivity. Lower doses are recommended for the use of several drugs in patients with cirrhosis, especially those who undergo first-pass metabolism or are metabolized by the CYP3A enzymatic pathway. Despite this, the data are limited in terms of correlating pharmacodynamic effects with the degree of liver impairment (Lewis, Stine, 2013).

Three times more interactions between DAAs and other drugs were identified among patients with cirrhosis. In the study by Kondili *et al.* (2017), drug interactions were primarily identified in the ombitasvir regimen, veruprevir/ritonavir regimen and dasabuvir regimen because of ritonavir, but no significant clinical outcomes were reported during the study. These conditions were not evaluated in our study.

Other studies evaluated interactions of hepatitis C treatment with use of other medicines. Langness *et al.* (2017) evaluated the ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, simeprevir/sofosbuvir and sofosbuvir/ribavirin combinations, having analyzed 664 patients, and a total of 5,217 drugs (7.86 drugs per patient on average) were reviewed, for which 781 potential drug interactions (1.18 drug interactions per patient) were identified. Among the patients with cirrhosis (51.5%), the average number of drugs per patient was 8.99 and the average number of potential interactions was 1.25 per patient. Differently from our results, where more

interactions were identified in severely ill patients, the number of interactions was similar among people with different stages of liver disease. Ottman *et al.* (2018) identified 554 potential interactions in a retrospective study with 300 patients in the United States. The mean number of interactions per patient was 1.85, 8.8% being considered severe and 67.0% with potential clinical significance. This mean is similar to that found in our study, which corresponded to 1.79 potential drug interactions per patient. In relation to the classification, in our study, most of the interactions identified (69.4%) were classified as having no clinical significance. On the other hand, the most commonly used hepatitis C treatment regimens in Ottmann's study were ledispavir/sofosbuvir and ombistavir/paritaprevir/ritonavir + dasabuvir, which were not evaluated in our study.

In addition to the interactions considered, the use of other medications may generate non-clinically significant interactions. Considering the general health of the patient, some medications may require dose adjustment in patients with hepatic or renal impairment (Binda *et al.*, 2017).

Drug interactions are common and management requires adjustment of drugs or increased monitoring. However, there are still few data on interactions between the drugs used to treat hepatitis C and other drugs (Langness *et al.*, 2017; Scavone *et al.*, 2016). The work of a multidisciplinary team, including pharmacist, optimizes patient care (Ottman *et al.*, 2018; Langness *et al.*, 2017; Deming *et al.*, 2016). This care includes education, monitoring and management of therapy and adverse effects. Also, the team can develop adherence promotion strategies and thus increase the chances of success (Mohammad *et al.*, 2014; Walters-Smith, Marshall, 2009; Kolor, 2005). The treatment selected should be periodically reviewed by the pharmacist to propose alternatives and thus minimize the risk of potential drug interactions. For this, the available online tools, such as those used in this evaluation, can be useful (Pons *et al.*, 2017). Pharmacovigilance is known to improve patient care. Because of the limitations of pre-marketing data, real-life scenario data are important for assessing therapy outcomes (Pons *et al.*, 2017).

This study had some limitations, including retrospective data collection in a single care center and non-randomization of the groups of patients. Patients with impaired renal function and co-infected with HIV, who may need further monitoring of drug use, were also not evaluated separately. Patients may not

report all the medicines they take, especially in cases of self-medication, over-the-counter medicines and herbal medicines, although the full report is requested. In addition, many mechanisms involved in drug interactions are complex and not yet fully elucidated.

In the present study, the patients treated exhibited several stages of liver damage, in addition to chronic comorbidities. All patients underwent pharmaceutical and medical evaluation, and adjustments were made prior to the beginning of the hepatitis C treatment, both in relation to possible drug interactions and adequacy of therapy to comorbidities and severity of liver disease. Preventing adverse events caused by potential drug interactions and managing them are central to clinical pharmacy practice. The involvement of the pharmacist in the multidisciplinary team allows it to identify these interactions, thus optimizing care, in addition to contributing to the monitoring and possible adjustments of the drug therapy.

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CONFLICTS OF INTEREST

There are no conflicts of interest declared by any of the authors.

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