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Impact of Pharmacist Interventions on Direct-Acting Antivirals Sustained Virologic Response and Drug-Drug Interactions

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Abstract

Infection by HCV is a growing global concern, given its effect on the mortality rate [1]. It is an important cause of cirrhosis, hepatocellular carcinoma, and liver transplant [2, 3]. In 2015, 71 million people were living with HCV. Several studies have shown that the number of new cases declined from the second half of the twentieth century. However, the incidence rate in 2015 was 23.7

Index terms—

1 Introduction

nfection by HCV is a growing global concern, given its effect on the mortality rate [1]. It is an important cause of cirrhosis, hepatocellular carcinoma, and liver transplant [2,3]. In 2015, 71 million people were living with HCV. Several studies have shown that the number of new cases declined from the second half of the twentieth century. However, the incidence rate in 2015 was 23.7% (1.75 million new infections by HCV). This increase is related to different mechanisms of transmission. Besides the growing number of young injecting drug users in rural areas, there are reports of HCV transmission among men who have sex with men (MSM) infected with HIV. **??**4]. In 2016, the World Health Organization (WHO) showed overall goals for the elimination of HCV infection by 2030. This include a 90% reduction in new cases of chronic hepatitis C, a reduction of 65% of deaths, and treatment of 80% of eligible patients [5]. The old therapy in chronic hepatitis C has been a challenge because of the adverse events related to the use of oral ribavirin (RBV) and subcutaneous administration of peginterferon (PEG-IFN). This old therapy had low rates of SVR. In 2015, direct-acting antivirals (DAAs) were incorporated in Brazil. DAAs shows a better efficacy and safety profile, and has a better tolerability for patients [6]. The Brazilian Ministry of Health has issued a protocol with the criteria for eligible patients and guidelines for the treatment of chronic hepatitis C. DAAs such as sofosbuvir (SOF), daclatasvir (DCV) and simeprevir (SMV) have been made available. In the second half of 2017, 3D (ombitasvir/paritaprevir/ritonavir+dasabuvir)(OBV/PTV/r +DSV) were included into this protocol [7]. Despite the aforementioned benefits over the old therapy, DAAs therapy presents a high risk of drug-drug interactions (DDIs) [7], [8]and there are some contraindications for all DAAs regimens [9]. The use of cytochrome P450 (CYP)/P-glycoprotein (P-GP) inducers (such as carbamazepine and phenytoin) are contraindicated, because of the risk of reduced concentrations of DAAs and high risk of virological failure [9]. Thus, it is essential to evaluate the continuous-use medication before starting treatment. DAAs have interactions with many

Author: e-mail: marcelnogueira7@gmail.com drugs, especially in HCV-HIV co-infected patients in antiretroviral therapy [7]. CYP3A4 is the metabolic pathway for protease inhibitors such as SMV and NS5A inhibitor (DCV). These drugs can interact with enzyme inhibitors such as ketoconazole [10], [11], and inducers of CYP3A4, such as dipyrone and phenobarbital [12]. Similarly, daclatasvir (DCV) acts as a substrate and an inhibitor of P-glycoprotein (P-GP). Moreover, DCV is a weak inhibitor of organic anion transporters (OAT1B1/OATP1B3) and breast cancer resistance protein (BRCP) [11]. Sofosbuvir (SOF) is less involved in this, but it is as P-GP substrate and concomitant use of P-GP inducers should be avoided [10].

As a specialist in the management of pharmacotherapy, clinical pharmacist contributes to patient care by promoting the rational use of drugs and providing pharmacotherapy services [13]. A clinical pharmacist can identify cases of medication nonadherence, and provides support to hepatologists, optimizing patient care [14]. As well as encourages prevention measures, contributes to the reduction of HCV transmission, increases

adherence to treatment and monitors adverse reactions [15]. Thereby, patient understands risks and benefits of pharmacotherapy, improving adherence and treatment outcome [16]. The involvement of the clinical pharmacist is beneficial forhepatology team because DDIs are a common event in the treatment of chronic hepatitis C. The identification and management of this is an intensive resource that requires adjustments to pharmacotherapy, in addition to continuous monitoring of patients. The assessment of DDIs in DAAs therapy and pharmacist interventions was recently published in the scientific literature [15], [17]. Nevertheless, in these studies, it was unclear whether the medical staff approvesthe pharmacist interventions.

2 II.

3 Aim of the Study

Our primary objective was to evaluate the impact of pharmacist interventions related to DDIs on SVR. As secondary objectives: 1) to quantify DDIs identified by drug class and drug interaction potential; 2) to quantify pharmacist interventions recommended to medical staff and patient.

4 III.

5 Ethics Approval

Research Ethics Committee (Plataforma Brasilprotocol number 81497617.1.0000.0068) approved this retrospective study conducted under the STROBE Initiative. Informedconsentwasnotethicallyrequired for thisresearch.

IV.

6 Method a) Participants

We included patients with chronic hepatitis C, with DAAs prescription (SOF/DCV/SMV) with or without RBV or PEG-IFN, that received medication counseling by the Clinical Pharmacy of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP). We excluded patients who died, who had DAAs therapy suspended or without the final hepatitis C virus RNA-polymerase chain reaction test(HCV RNA-PCR).

7 b) Setting

We assessed data tabulated in Microsoft Excel between December 2015 and June 2017, collected from patients of infectious disease, liver transplantation, and gastroenterology services of HCFMUSP, a public tertiary teaching hospital. Before starting DAAs therapy, all patients were referred for Clinical Pharmacy of HCFMUSP and received medication counseling. This service promotes the rational use of medicines, patient care, and recommends conducts for medical staff to optimize pharmacotherapy. Concomitant use of drugs was analyzed by the electronic prescription system or by manual prescriptions. All included patients have received medication counseling by Clinical Pharmacy as established by the following steps: 1) individual or group counseling supported by an information leaflet that addresses issues such as chronic hepatitis C, HCV transmission, prevention, medication, adherence and patient care during DAAs therapy; 2) DDIs analysis on the HEP Drugs Interactions [8] and as necessary, pharmacist intervention addressed to medical staff, for management of DDIs; 3) Individualized guidance to facilitate medication administration times, according to routine of each patient; 4) tabulation of baseline characteristics, DDIs and pharmacist interventions on the database. By identifying DDIs, Clinical Pharmacy staff performed management of DDIs according to the clinical experience of each pharmacist and severity of interaction. Discussions were conducted with medical staff to solve this, in addition to sending letters when face-to-face contact was not possible. 5) DAAs dispensation. After these steps, all patients were referred for medical staff to authorize starting treatment. We performed the acceptance of pharmacist interventions accessing electronic medical records, new medical prescriptions, and by telephone follow-up.

Hence, we divided patients into three different groups: 1) Drug Interaction Avoided (DIA), those with pharmacist interventions approved, 2) Drug Interaction Persisted (DIP), those pharmacist interventions not accepted for any reason; 3) no drug interaction (NDI).

8 c) Variables

The primary endpoint was SVR, defined as an undetectable viral load, three months after completion of DAAs therapy [7]. Among the secondary endpoints are: 1) number of DDIs (identified by drug or drug class); 2) severity of each DDIs according to HEP Drug Interactions -weak interaction, potential interaction and do not coadminister [8]

9 d) Data sources/measurement

For the primary outcome, we used logistic regression to compare SVR rates between DIA, DIP and NDI groups. The results were collected from electronic hospital records and recorded on the database. To minimize the risk of bias, three authors (MSN, NLL, and GDRS) performed double-checking of all collected data presented in this study.

10 e) Study sample size

No sample size calculation was done before the conduction of this study. We recruited all patients from December 2015 to June 2017, who met the inclusion criteria. A post-doc analysis was conducted with G*Power [18]to estimate the achieved power of the primary outcome (association between SVR and groups of intervention by logistic regression), considering ?=5% and observed effect size (OR), sample size and two-tailed regression model R 2 .

11 f) Quantitative variables

The baseline characteristics include gender distribution, age, ethnic origin, DAAs regimen, treatment duration, HCV genotype, and presence of cirrhosis. We used frequency and percentage for categorical variables (total sample and for each group: DIA, DIP, NDI). We defined the continuous variables as mean and standard deviation.

12 g) Statistical methods

We compared the baseline characteristics between groups by the chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables. We used intention-to-treat (ITT) for missing data of SVR and obtained the odds ratio (OR) was obtained by a logistic regression model, including SVR as a dependent variable, groups (DIA, DIP and NDI) as independent variable and age, sex, genotype, and presence of cirrhosis as control variables. We considered the level of statistical significance to be 5%, and performed all analyses using STATA 13 (Stata Corp, Texas, USA).

V.

13 Results

14 a) Participants

We included 1046 patients with chronic hepatitis C, with DAAs prescription. After Clinical Pharmacy guidance, patients were divided into groups DIA (n=273), DIP (n= 26), and NDI (n=747). In total, we excluded 74 patients (74/1046, 7.7%). Of these patients, ten had suspended treatment by adverse events, and 64 did not present the final HCV RNA-PCR test. No information was found about the death of patients on the electronic medical records.

15 b) Descriptive data

Overall, there was a ratio of 48.9% men, 51.0% women and mean age of 58.0 ± 11.42. A statistically significant difference of mean age was found between DIA and NDI groups. The ethnic majority consisted of Caucasians in all groups. The most common DAAs regimen was SOF + DCV + RBV (48.4%) and the overall treatment duration was 12 weeks (84.7%). We observed a higher frequency of genotype 1b (37.0%), followed by 1A (32.9%). Cirrhotic corresponded to 49.5% of overall patients, with statistically significant difference among the three groups. The baseline characteristics are available in table 1.

16 c) Outcome data

Our data showed a total of 299 patients (28.5%) identified with DDIs. In this group of patients, 273 had pharmacist intervention approved by the medical staff (DIA), and 26 were not approved (DIP). The total number of DDIs was 464, and 286 (61.6%) were identified only with DCV. For DCV interactions, identified drugs were composed of calcium channel blockers such as amlodipine, diltiazem and verapamil (n=85, 29.7%), followed by levothyroxine (n=59, 20.6%) and statins (n =46, 16.0%) (Table **??**). The clinical pharmacists performed one hundred thirty-four interventions, such as alter administration time and 261 monitoring for side effects. Given the DDIs between DAAs and levothyroxine or warfarin, the medical staff accepted 54 interventions for laboratory monitoring tests (52.4%), and thirty-five alternative medication interventions (34.0%) because of contraindicated interactions between SOF, DCV, SMV, RBV, and drugs such as dipyrone (metamizole), anticonvulsants (phenobarbital, phenytoin, primidone, carbamazepine), amiodarone and dexamethasone. Paracetamol was recommendedfor medical staff to replace dipyrone. Drugs such as valproicacid, ethosuximide, lamotrigine and levetiracetam were recommended (after withdrawal) for patients with anticonvulsants prescription.

Propafenone and prednisone were recommended to replace amiodarone and dexamethasone, respectively. Dosing adjustment (n=7, 6.7%) was requested for daclatasvir 90 mg and daclatasvir 30 mg (as a resultof CYP3A4 inducerefavirenz and CYP3A4 inhibitor such as ritonavir, respectively). Moreover, dosing adjustments for amlodipine (10 mg to 5 mg/day), atorvastatin and simvastatin (both to 20 mg/day) because of potential interaction with DCV, were requested. In seven cases (n=7, 6.79%), discontinuation of drugs such as dipyrone, dexamethasone, orlistat, and colestyramine, was suggested for patients with no treatment indication. In the DIP group, 16 interventions for laboratory monitoring tests (61.5%), eight for the alternative medication (30.7%) -given the use of contraindicated drugs such as dipyrone, anticonvulsants, and dexamethasone, and two for DCV dosing adjustment were not approved. The acceptance rate of pharmacist interventions was 79.8% (Table **??**). Our team identified three hundred thirteen drugs (68%) as potential interaction, 103 (23%) weak interaction,

and 43 (9%) as "do not coadminister" (Figure **??**). All identified DDIs by group (DIA and DIP) are available in Appendix A and B.

17 d) Main results

Intention-to-treat analysis (ITT) revealed an overall SVR rate of 80.1% (n=838/1046). In the DIA and DIP groups, SVR rates were 86.1% (n=235/273) and 57.7% (n=15/26), respectively. In the NDI group, 78.7% of patients (n=588/747) achieved SVR. The logistic regression compared SVR rates among the three groups.The results demonstrate that the DIA group had a greater probability of SVR compared to the NDI group (OR: 1.51; 95% CI 1.00 -2.28; p=0.048). The DIP group had lower probability of SVR compared to DIA group (OR: 0.26; 95% CI 0.10 -0.62; p=0.003) and NDI group (OR: 0.39; 95% CI 0.17 -0.90; p=0.029) (Table **??**). The post-doc analysis resulted in an estimated achieved power of 99%, considering ?=5%, effect size=1.51, sample size=1046, and R 2 =0.0361.

18 VI.

19 Discussion

Our study shows the impact of pharmacist interventions related to DDIs on the clinical outcome of DAAs therapy in 1046 patients. Although we emphasize that our findings reveal an overall SVR of 80.1%, we present a larger sample of patients comparing to others real-life studies of Cheinquer et al. (n=219) [19], Ferreira et al. (n=296) [20]and AI444040 [21](n=211). Cheinquer demonstrated the effectiveness of DAAs (SOF/DCV/SMV), 3D therapy (OBV/PTV/r + DSV) and SOF/ledipasvir (LDV), with or without RBV, and showed a higher SVR rate (>90%). Ferreira aimed to evaluate the effectiveness of (SOF/DCV/SMV/LDV/PEG-IFN) with or without RBV, while the clinical study AI444040assessed the effectiveness of SOF+DCV with or without RBV [21]. Both presented higher SVR rates (>90%). Despite this, samples of real-life studies were composed of 89 cirrhotic patients (42.7%) -Cheinquer,99 patients (38.8%) -Ferreira, and 30 patients (14.2%) -AI444040. In our analysis, 513 patients (49.5%) had cirrhosis. In Brazil, only patients with advanced liver disease (fibrosis and cirrhosis) or hepatitis B virus/HIV co-infected are given DAAs therapy [7]. Possibly, this is related to the results of the overall SVR rate in our findings. Nevertheless, in our data, patients have made use of concomitant drugs (n=299). Only Ottman, Townsend, Hashem, DiMondi, and Britt assessed the impact of DDIs on SVR in 300 patients [17]. This study evaluated patients on DAAs regimen (SOF, DCV, SMV, LDV, 3D, and elbasvir / grazoprevir), with or without RBV. In comparison to our results, a higher SVR rate was observed (95.6% vs, 80.1%). Ottman et al. did not found no statistically significant difference in SVR among patients who had at least one DDI compared with those who had not identified DDIs (94.8% vs, 95.8%; 169 had advanced fibrosis or cirrhosis. However, the authors did not compare SVR rates in pharmacist intervention groups, as we presented, our logistic regression showed a higher probability of SVR in the DIAgroup, in comparison to DIP and NDI (Table **??**). Possibly, this is related to the alternative medication (34.0%) in the DIA group, because interactions between DAAs and contraindicated drugs were solved. Likewise, there was a statistically significant difference of cirrhotic patients between the three groups. Regardless, our result highlights the role of the clinical pharmacist in the effectiveness of chronic hepatitis C treatment. This demonstrates that DDIs in DAAs therapy should not be neglected by the medical staff to avoid virological failure [9]. DDIs are also common in therapy with other DAAs. Maasoumy et al. demonstrated that 49% of patients were affected by DDIs with protease inhibitors (boceprevir and telaprevir), and management is required [6]. Other data suggest that the management ofDDIs can be performed by laboratory monitoring tests, dosing adjustment, alternative medication, or discontinuation, when necessary [6,15,17,22]. Langness et al. [15] observed DDIs frequency with DAAs such as SOF/LDV, 3D, SMV/SOF, and SOF/RBV. Commonly recommended interventions for the management of each interaction were discontinuation (for contraindicated drugs, supplements, and herbal products), as well as monitoring for side effects. In our retrospective cohort study, the risk of self-medication and the use of supplements or herbal products (such as St. John's wort) were part of medication counseling for all patients. Therefore, we only consider the discontinuation intervention to those with DDIs in prescriptions. Besides Ottmanassess SVR, the author identified and quantified a total of 554 DDIs in 300 patients on DAAs therapy [17].

Ottman's study presented a greater focus on LDV/SOF and 3D. Only nine patients (3.0%) used SOF + DCV + RBV and of those, six had 11 DDIs identified (n=11/554 2.0%). Among the drug classes involved in DDIs, there are statins (n=87, 15.7%), calcium channel blockers (n= 63, 11.4%) and analgesics (n=48%, 8.6%). The most commons pharmacist interventions were dosing adjustment (29.6%), alternative medication (6.9%), and discontinuation (4.5%). Overall, 191 interventions were accepted (84.1%). We can compare our results of identified DDIs and the acceptance rate of pharmacist interventions. Our data present a higher frequency of laboratory monitoring tests (n=54, 52.4%) and alternative medication (n=35, 34%) approved interventions than dosing adjustment. This is explained by a higher proportion of patients using LDV/SOF or 3D scheme in Ottman's study. These DAAs act as inhibitors of various transporters (OATP1B1/3 OATP2B1, P-gp, BCRP) and different metabolic pathways (CYP3A4/5, UGT1A1, CYP2D6) in addition to inducing CYP2C19 [22].

Our study has some limitations. We instructed patients to do not start DAAs therapy until receive medical authorization (after medication counseling by Clinical Pharmacy), but we cannot guarantee that all patients followed this conduct. Probably, some have started treatment after medication counseling and dispensation.

We advised patients about DDIs and several pharmacist interventions were performed by sending letters to the external medical staff. Possibly, some of them did not handed it to the medical staff and therefore, were included in DIP group. The clinical pharmacy staff advised all patients about the risks of self-medication and herbal product consumption. We told to avoid dipyrone during DAA therapy, because of the risk of interaction [8,12]. Dipyrone is one of the most consumed over-the-counter drugs in Brazil [23], and we must consider the hypothesis that not everyone followed these advices.

Because of methodological limitations of a retrospective cohort study, we did not classify cirrhotic patients according to the Child-Pugh score. Probably, this would make it possible to understand SVR rates showed in our findings.

20 VII.

21 Conclusion

Although the overall rate of SVR was lower than other real-life studies, our results indicate that the DIA group had a significant probability of SVR compared to DIP and NDI groups. Furthermore, this in DAA therapy are common and the medical staff should not neglect it. Pharmacist interventions may contribute to the effectiveness of DAAs therapy and makes it possible to avoid treatment failures caused by DDIs.

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