BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e19925

Article

Direct-acting antivirals for chronic Hepatitis C are effective and safe: an observational study in Londrina/PR

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This study aimed to evaluate the effectiveness and safety of direct-acting antivirals in a Unified Health System pharmacy of Londrina, Brazil. A descriptive observational study was performed from June 2017 to June 2018. Sociodemographic, clinical, and therapeutic variables of patients were collected from secondary data sources. Effectiveness was evaluated by sustained virologic response (SVR) and safety was evaluated by adverse events (AEs) and drug interactions (DIs). The mean population (N = 30) was 56.6 ± 11.3 years old and almost all patients had comorbidities (93.3 %) and concomitant drugs (96.7 %). Effectiveness evaluation was possible in 17 patients, and all of them (100.0 %) achieved SVR. Eighteen patients (60.0 %) reported 38 AEs, mostly mild, such as stomach symptoms and headache. No statistical relation was found between AE occurrence and treatment duration, Ribavirin use, number of comorbidities or number of concomitant drugs. A total of 48 DIs were reported, 18 being severe, and were managed by the pharmacist. The study indicates that the treatment was effective and safe.

Keywords: Hepatitis C. Drug therapy. Effectiveness. Safety.

INTRODUCTION

Hepatitis C is an infectious disease of significant morbidity and mortality. About 3 % of the world population is infected by the Hepatitis C virus (HCV), whose transmission occurs predominantly by infected blood. The treatment of Hepatitis C has had a worldwide revolution over the last decade. Until 2011, the only available and nonspecific treatment was the association of Interferon (IFN) and Ribavirin (RBV), with low effectiveness rates and low tolerability and safety profiles. In 2011 direct-acting antivirals (DAAs) were launched, and in 2013 the second generation DAAs arrived, with cure rates above 90 % and mild adverse reactions: Simeprevir (SIM), Sofosbuvir (SOF) and Daclatasvir (DCV) and, after a few years, Ombitasvir, Paritaprevir and Dasabuvir (in fixed association with Ritonavir known as 3D) (Ferreira, Pontarolo, 2017).

In Brazil, the Unified Health System (SUS) provides the treatment for Hepatitis C through the Clinical Protocol of the Ministry of Health. It defines the cure as the sustained virologic response (SVR), in other words, the non-detection of HCV ribonucleic acid (HCV-RNA) after 12 or 24 weeks of treatment completion (Brasil, 2015, 2018). DAAs are among the highest cost drugs of the SUS. As DAAs are new and expensive drugs, post-marketing studies are essential for evaluating their performance under actual conditions of use. Thus, the aim of the present study was to evaluate the effectiveness and safety of the pharmacological antiviral treatment for Hepatitis C in a SUS public pharmacy.

MATERIAL AND METHODS

A descriptive observational study was performed at a SUS public specialized pharmacy in Londrina, Paraná, from June 2017 to June 2018. All patients receiving pharmaceutical care during the period were included. Sociodemographic, clinical, and therapeutic variables were collected from three secondary sources

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at the Pharmacy: pharmaceutical records, treatment solicitation processes, and computerized systems. Independent variables were gender, age, lifestyle habits, pre-treatment HCV tests (genotype, quantifying, biopsy, elastography, liver markers, others), antiviral and concomitant drugs, year of diagnosis, health history, and comorbidities and laboratory tests in general. Dependent variables (outcomes) were effectiveness of treatment (post-treatment viral quantifying) and safety of treatment (adverse events (AEs), and drug interactions (DIs)).

The patient's hepatic disease was described by HCV genotype (1 to 7) and fibrosis staging (F0 to F4, according to the Metavir score from the results of hepatic biopsy, hepatic elastography, Aspartate Transaminase to Platelet Ratio Index and/or Fibrosis-4 Score).

Outcomes of effectiveness and safety were evaluated. HCV treatment is considered effective when an SVR is achieved, i.e., the HCV-RNA is no longer detected in blood quantifying performed after 12 or 24 weeks since the last dose of medication (Brasil, 2018). Patients were contacted by telephone to present this test report.

Safety of treatment was evaluated by the assessment of AEs and DIs. AEs were classified according to causality following Naranjo's algorithm as definite, probable, possible, or doubtful (Naranjo *et al*., 1981), and according to severity following World Health Organization (WHO) classification as mild, moderate, severe, or fatal (WHO, 2000). DIs were classified following the *HEP Drug Interactions* tool as severe, potential, or potential weak (University of Liverpool, 2019).

Data were collected and assessed using Microsoft Excel® and Statistical Package for Social Sciences® for Windows®. The Mann-Whitney nonparametric test ($p < 0.05$) was used to compare means and the Spearman nonparametric test ($p < 0.05$) was used to evaluate the correlation between discrete variables. All results were presented anonymously and statistically. The study was authorized by the institution and was approved by Research Ethics Committees of the State University of Londrina (CAAE no. 95054318.0.0000.5231) and the State University of Maringá (CAAE no. 95054318.0.3001.0104).

RESULTS AND DISCUSSION

The majority of the study population (N = 30) was composed of men (N = 17; 56.7 %), which agrees with the national incidence proportion (57.7 % of men, 42.3 % of women) (Brasil, 2019). The mean age was 56.6 ± 11.3. Most patients were between 30 and 59 years old (N = 20; 66.7 %) and 10 patients (33.3 %) were elderly (60 years or older). Patients were diagnosed at 47.7 ± 16.8 years old, and all of them were in the chronic phase of Hepatitis C. Regarding lifestyle habits, most of the population was sedentary (N = 17; 56.7 %), 10 patients (33.3 %) consumed alcohol and 5 individuals (16.7 %) were smokers.

As occurs in Brazil and worldwide (Brasil, 2018), the most prevalent genotype was type 1 (N = 19; 63.3 %), followed by type 3 (N = 10; 33.3 %) and type 2 (N = 1; 3.3 %). Most patients were at advanced stages (F3/F4) of hepatic fibrosis (N = 14; 46.7 %), but in nine cases (30.0 %) there was no staging information. Staging is recommended by the Clinical Protocol and helps in choosing the pharmacotherapy (Brasil, 2015, 2018) but since it is not obligatory, many physicians do not register staging. The most prescribed treatment regimen was SOF + DCV + RBV (Table I). Four patients (13.3 %) had previously tried IFN + RBV, and all of them had relapsing results.

TABLE I – Prescribed therapeutic regimens for Hepatitis C treatment of patients attended by the Specialized Pharmacy of Londrina between June 2017 and June 2018 (N = 30)

Therapeutic Regimen		Patients (%)
Drugs	Sofosbuvir + Daclatasvir + Ribavirin	15 (50.0 %)
	Sofosbuvir + Daclatasvir	8 (26.7 %)
	Sofosbuvir + Simeprevir	4 (13.3 %)
	Sofosbuvir + Simeprevir + Ribavirin	1 (3.3 %)
	Ombitasvir + Paritaprevir + Dasabuvir + Ritonavir	1 (3.3 %)
	Sofosbuvir + Interferon alfa-2a + Ribavirin	1 (3.3 %)
Duration	12 weeks	25 (83.3 %)
	24 weeks	5 (16.6 %)

Source: author.

Twenty-eight patients (93.3 %) had comorbidities, of which the most prevalent were systemic arterial hypertension (N = 10; 33.3 %), orthopedic diseases (N = 10; 33.3 %), co-infection with HIV viruses (N = 8; 26.7 %) and digestive disorders (N = 6; 20.0 %). No patient was co-infected with the Hepatitis B virus. Almost the entire population (N = 29; 96.7 %) had concomitant drugs (mean 7.2 ± 3.6 drugs per patient), which was expected due to the high prevalence of comorbidities. Regarding prescription and self-medication drugs, a mean of 4.5 (± 3.1) and 2.6 (± 2.2) drugs per patient were observed, respectively. In addition, nine patients (30.0 %) reported taking homemade preparations such as teas and homemade syrups.

Evaluation of SVR according the Clinical Protocol criteria was possible in 17 patients, and treatment was effective in all of them (100.0 %). Three patients related cure but did not have the test result because they left this to the physician. One patient performed the test before the time established by the Clinical Protocol, which makes it impossible to guarantee SVR. Two patients died before SVR evaluation. There were seven events of loss of patient follow-up after treatment completion. The patient's link with the specialized pharmacy is objectified through the medication, and this explains the difficulty in maintaining the link with the individual after treatment completion.

The high effectiveness matches other post-marketing observational studies in the literature. Regarding SOF + DCV regimens, Margusino-Framiñán *et al.* (2019), Ridruejo *et al.* (2019) and Pin-Nan *et al.* (2018) observed SVR rates of 94.6 %, 96.1 % and 100 %, respectively. Regarding SOF + SIM regimens, Bruno *et al.* (2017) and Alam *et al.* (2016) observed SVR rates of 93.2 % and 92.4 %, respectively. Concerning 3D regimens, Leventer-Roberts *et al.* (2017) and Chen-Hua *et al.* (2018) observed SVR rates of 98.8 % and 98.1 %, respectively.

Because of these good results, DAAs improve the patient's quality of life. Without intervention, chronic liver inflammation advances to progressive stages of fibrosis (Goldman, Schafer, 2014), and nearly 20 % of patients progress to cirrhosis and 1 % to 5 % develop hepatocellular carcinoma (Brasil, 2018). In Brazil, Hepatitis C causes the most deaths among all viral hepatitis: from 2000 to 2017, there were 53,715 deaths associated with Hepatitis C (Brasil, 2019). It is also important to mention that the untreated disease, especially at advanced and cirrhotic stages, demands high costs from the health system with hospitalizations, medical consultations, medications, exams and even liver transplantation (Souza Jr *et al*., 2019).

Regarding treatment safety, 18 patients (60.0 %) reported possible AEs. There were 38 reports (1.3 ± 1.6 AEs per patient): 8 moderate AEs, 30 mild AEs and no severe or fatal AE (Table II). The most prevalent causality being described as possible (60.5 %). The good

safety profile of DAAs allows a wide range of patients to be treated. AEs were similar to those reported in the literature. Chen-Hua *et al.* (2018) most frequently observed events such as headache, fatigue, nausea, and insomnia. Bruno *et al.* (2017) related pruritus, fatigue, rash and anemia, especially in patients using Ribavirin. Margusino-Framiñán *et al.* (2019) reported fatigue/asthenia, headache, insomnia and gastrointestinal symptoms. In all of these studies, discontinuation of treatment due to AEs was rare or zero.

Seventeen patients (56.7 %) used RBV. They had more AEs (mean 1.5 ± 1.8 AEs per patient) than patients who did not use RBV (mean 1.0 ± 1.1 AE per patient), but without statistically significant difference (p = 0.650). There was also no statistically significant difference (p = 0.957) in the number of AEs per patient regarding treatment duration (means 1.2 ± 1.3 for 12 weeks and 1.8 ± 2.4 for 24 weeks). No statistical correlation was found between the number of AEs and the number of patient comorbidities (p = 0.177) or the number of concomitant drugs (p = 0.792). It is possible that the small size of the population contributed to these statistical results, but this small size characteristic of the object of the study does not constitute methodological failure.

TABLE II – Classification of adverse events of Hepatitis C treatment of patients attended by the Specialized Pharmacy of Londrina between June 2017 and June 2018 (N = 30)

		Adverse Events	**Patients (%)**
Severity[a]	Moderate (N = 8; 21.1 %)	Anemia	6 (20.0 %)
		Bacterial infection	1 (3.3 %)
		Fever	1 (3.3 %)
	Mild (N = 30; 78.9 %)	Stomach Symptoms[b]	7 (23.3 %)
		Headache	6 (20.0 %)
		Fatigue	5 (16.7 %)
		Diarrhea	2 (6.7 %)
		Others	10 (33.3 %)
			Adverse Events (%)
Causality[c]	Definite		1 (2.6 %)
	Probable		14 (36.8 %)
	Possible		23 (60.5 %)
			Adverse Events per Patient
Therapeutic Regimen	Sofosbuvir + Interferon alfa-2a + Ribavirin		5.0
	Sofosbuvir + Daclatasvir + Ribavirin		1.3
	Sofosbuvir + Daclatasvir		1.1
	Ombitasvir + Paritaprevir + Dasabuvir + Ritonavir		1.0
	Sofosbuvir + Simeprevir + Ribavirin		1.0
	Sofosbuvir + Simeprevir		0.7

[a]Severity was evaluated following World Health Organization classification (WHO, 2000). [b]Stomach symptoms include nausea, burning, pain and others (often the patient could not exactly define the stomach symptom). [c]Causality was evaluated following Naranjo's algorithm (Naranjo *et al.*, 1981). **Source:** author.

Forty-eight DI events were reported in pharmaceutical records. Regarding concomitant prescribed drugs, there were seven severe interaction events: Zidovudine + RBV (N = 5), Carbamazepine + SOF (N = 1) and Carbamazepine + DCV (N = 1). Regarding concomitant self-medication drugs, there were 11 severe interaction events: Metamizole + RBV (N = 10) and Dihydroergotamine + SIM (N = 1) (University of Liverpool, 2019). DIs were managed by the pharmacist to ensure the success of pharmacotherapy.

Results indicated that the treatment with DAAs was effective, with a high SVR rate, and safe, with predominantly mild adverse reactions, which shows that they are a powerful resource to improve patients' quality of life and to help eradicate Hepatitis C from the world. On the other hand, DAAs are new drugs. They have been marketed for less than a decade and have very high cost. In addition, new drugs of this class are being developed and integrated into national and international protocols, including the possibility of retreating patients who have already experienced DAAs who have not been cured, or even patients reinfected with HCV. Therefore, further post-marketing studies are needed to ratify the effectiveness and safety of different treatment regimens for Hepatitis C.

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Received for publication on 08th March 2020
Accepted for publication on 16th August 2020