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The benefits of a public pharmacist service in chronic hepatitis C treatment: The real-life results of sofosbuvir-based therapy

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ABSTRACT

Background: In Brazil, the sofosbuvir-based therapy was introduced in the public health system (SUS) in 2015 to treat Chronic Hepatitis C (CHC). This drug and other direct-acting antiviral agents (DAAs) represent a major advance in the HCV-infection treatment due to their high effectiveness and tolerability. However, the drug safety profile is limited by significant drug interactions and its use is restricted for their high cost. Pharmacists have the opportunity to improve patient care by monitoring the therapy, recommending strategies to guarantee treatment adherence, effectiveness and safety, preventing complications of the disease, and drug-related problems, thus reducing the cost for patients and payers.

Objective: This study aimed to assess the results of the one of the first patient group treated with sofosbuvir in Brazil and their opinions about the benefits of clinical pharmacist services in the achievement of the cure for CHC and in the management of their therapy difficulties.

Methods: This cohort study (November 2015–January 2017) enrolled 240 patients followed up by the clinical pharmacists at the University Pharmacy (UPh) of the Federal University of Santa Catarina, Brazil, during the CHC treatment. The therapeutic schemes used were sofosbuvir + daclatasvir or + simeprevir associated or not with ribavirin. At the end of the therapy, the patients provided qualitative feedback about the clinical pharmacist services.

Results: The study demonstrated high levels of treatment adherence (99.2% of completion rates) and effectiveness rates (Sustained Virological Response rates) (92.1%). Patients reported high levels of satisfaction with the care provided on account of the good rapport built with their pharmacist, the counseling and education on HCV-infection and on sofosbuvir-based therapy utilization, motivation for adherence, and convenient access to the pharmacist.

Conclusions: The clinical pharmacist services provided by the UPh was beneficial to patients treated for CHC with the sofosbuvir-based therapy.

Introduction

Chronic Hepatitis C (CHC) is a major public health problem, considered the leading cause of cirrhosis and liver failure. According to the World Health Organization (WHO), about 130–150 million people have CHC, which represents approximately 2.25% of the world's population.[1] The treatment of CHC has changed rapidly after sofosbuvir (SOF) discovery and other direct-acting antivirals (DAAs) regimens. DAAs offer better cure rates and side-effect profiles, and shortened treatment courses. However, new drugs are much more expensive than previous treatments.[2,3]

In Brazil, between 1999 and 2017, 331,855 cases of CHC were reported and the disease led 75% of them to death due to viral hepatitis.[4,5] In 2015 the Brazilian Ministry of Health incorporated SOF and others such new DAAs, daclatasvir (DCV), simeprevir (SIM) into the Clinical Protocol and Therapeutic Guidelines (CPTG) for Hepatitis C. The new drugs are provided free of charge to the patients assisted by the public health services.[6]

Irrespective of DAAs' high efficacy and safety profile, it is known that numerous cofactors exist, which can affect the progression of CHC and therapy effectiveness and safety, such as end-stage liver failure (decompensated cirrhosis), adverse lifestyle choices (alcohol, substance abuse,

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and smoking), co-morbidities and comedications.[4] Furthermore, there are several limitations associated with the use of DAAs, such as significant adverse events (AE), mainly when associated with ribavirin (RBV) (e.g. hemolytic anemia) and complicated drug-drug interactions (DDI).[5,7]

These particularities underscore how crucial effective treatment and patient support are in the management of hepatitis C virus (HCV) infection. Recommendations to guide the establishment and maintenance of clinical pharmacy services for patients infected with HCV have been published and have contributed to defining areas of clinical pharmacist involvement in the treatment and management of HCV infection.[8–11] Recent studies have reported pharmacists' contributions to the management of CHC in terms of optimizing the utilization of HCV therapies.[12–15] Pharmacists are well equipped to assist the medical team and the patients with comprehensive management of the HCV treatment.

In various settings, the pharmacist can promote education about reducing HCV transmission, facilitate access to the HCV treatment, improve adherence to medication, detect DDI, assist in monitoring AE and recommend strategies to minimize it. The clinical pharmacist can manage the drug therapy for all chronic HCV patients, including those with comorbid conditions (e.g., congestive heart failure, cardiovascular disease, diabetes mellitus, hypertension) and those who are coinfected with the human immunodeficiency virus (HIV).[8–11]

This study shows results of one of the first patient groups treated with sofosbuvir-based therapy in Brazil and their opinions about the benefits of the clinical pharmacist services to their therapy results.

Methods

Local

The study was developed at the University Pharmacy (UPh) of the Federal University of Santa Catarina (UFSC) in Florianopolis, Brazil. The UPh is responsible for dispensing high-cost drugs for the treatment of chronic diseases, provided free of charge by the public health system. The UPh was one of the first specialty pharmacies in the country to deliver sofosbuvir-based therapy. Since 2015, SOF, DCV and SIM have been dispensed at the UPh.

Access to medicines

Before the drug can be delivered, prior authorization from the Brazilian public health system is required. Patients are referred to the pharmacy by a clinician to initiate the pre-authorization. The UPh pharmacists are responsible for the paperwork necessary to appeal for free-of-charge access to high-cost drugs via the public health system. They assist patients to organize whichever baseline laboratory test values required for the prior-authorization request. After the patient is deemed a candidate, the pharmacy team is notified and the patients are called for an appointment for the first drug dispensing.

Patient recruitment and data collection

This cohort study enrolled 240 HCV-infected patients assisted by the UPh team from November 2015 to January 2017. All patients included in the study were treated with the scheme containing SOF + DCV or + SIM associated or not with RBV. Data were collected during the clinical interview by means of a standardized form including demographics (age, sex, race/ethnicity), medical history (HCV genotype, prior HCV treatment history, history of cirrhosis, HIV coinfection and comorbidities. The data related to outcomes of treatments encompassed Sustained Virological Response (SVR) (defined as the maintenance of negative HCV RNA 12 weeks after the end of treatment), non-response, relapse (collected from patients' laboratory exams). Dropout was reported to the pharmacists by the patients themselves and death by their relatives. The AE reported by the patients during the treatment were also collected.

Clinical pharmacy service: practice description

Building a good rapport

The first meeting of the pharmacist with the patient at the UPh aims to establish a relationship of trust. The building of a good rapport is always based on active listening and empathy, which for patients with CHC is especially important. Even after seeing the physician before the first drug dispensing, many patients have questions, fears and expectations about the therapy. For patients with CHC, many concerns stem from misinformation obtained from the Internet and from bad experiences with a previous therapy, mainly due to occasional AE. Additionally, patients often read about complementary and alternative drugs touted to cure HCV infection. The pharmacist team provides honest feedback about the patient's issues focusing on individual characteristics.

First appointment

To help conduct the first appointment, the UPh pharmacist completes a pharmaceutical care form in order to include the various aspects of clinical care during the therapy management, which contains patient screening criteria, inclusion and exclusion criteria, recommended sofosbuvir-based regimens for specific HCV genotypes and fibrosis levels, and recommended monitoring.

In the first appointment, the pharmacist interviews each new patient and gathers information about the patient's demographics, social history (alcohol consumption, drug abuse, smoke) eating routine, medical history, therapy regimen selection (indication is evaluated according to the national clinical guidance), and pharmacoterapy (current prescription and nonprescription medications).

Each medication in use is reviewed to provide proper instructions about handling, storage, administration, AE and DDI. When a DDI is detected, the relevant physician is contacted, and the medicines are dispensed only after review and adjustment of the therapy.

After the medication counseling, all patients receive a card with general use recommendations according to patient routine (dosage, frequency). Other ways to support adherence are recommended based on individual needs, including the use of diaries, timers, pillboxes or other devices. Also, a guide developed by the pharmacists to manage AE is handed to the patients. The document is prepared based on the most common AE reported in primary literature and medicine leaflets. Patients are advised to give preference for non-pharmacological strategies to manage AE. Furthermore, patients are asked to take notes about any discomfort experience during the treatment. Patients using the sofosbuvir-based scheme + RBV are advised to monthly monitor the risk of anemia by blood count.

All patients with hepatitis C are asked about past or current drug and alcohol use. The pharmacist provides basic factual information about medical consequences of drug and alcohol use, ascertains the patient's attitudes toward his or her drug use, and helps him or her to identify and focus on health behavior changes that he or she feels motivated to make. When patients disclose illicit drug use, pharmacists collaborate with them in order to assess their drug use profile and the impact it has on their health and other areas of functioning. In such cases, patients are informed about public health centers that could support their decision on discontinuing the use of those substances.

At the end of the first drug dispensing session, a follow-up appointment is scheduled to 28 days later for supply (refill) of the drug and monitoring of the therapy safety and effectiveness.

Follow-up – adherence, effectiveness and safety monitoring

Patients are asked in the meantime to report the drug utilization process so that missed doses or difficulties to adherence could be identified. Specific questions are also asked to monitor occasional AE and initiation of new medications. If AE are reported, the pharmacist provides counseling, gives suggestions on how to monitor and manage them, thereby preventing therapy dropout. The CHC therapy

effectiveness is assessed through SVR, however, during the treatment, viral load is monitored as well as the improvement of liver function with laboratory tests.

Patient satisfaction: qualitative feedback

For the purpose of this study, the patients' opinions about the clinical pharmacists' service was assessed qualitatively. After the end of treatment, patients received a questionnaire with the question: *"What was the importance of the clinical pharmacists' service during your treatment?"*. The answers were analyzed using the content analysis method.[16] First, a pre-analysis of the material was carried out with the aim of systematizing the initial ideas. From the pre-analysis, the material was explored, that is, submitted to an in-depth study, guided by hypotheses and theoretical references. The data were coded, classified and categorized.[16]

Ethics statements

The study was approved by the Human Research Ethics Committee of the authors' institutions (Protocol Number: 27185514.3.1001.0121).

Statistical methods

A unified database comprising the collected data was created using the Excel software. The statistical analysis was performed using the STATA software version 14 - License 301406276417 - (Stata Corp, College Station, USA).

Results

Table 1 shows the demographics and clinical characteristics of the 240 patients enrolled in the study. Most patients were males (68.3%) and Caucasians (92.1%). The mean age was 57 years (SD = 0.5). Regarding clinical characteristics, the main comorbidities observed were diabetes mellitus (20.0%) and hypertension (20.4%). HCV genotype 1 was the most common one (62.1%). More than half the patients (51.2%) had experienced previous treatments. Most of the patients were treated during 12 weeks (78.3%) and used the scheme containing SOF + DCV + RBV (59.5%).

Table 1
Baseline characteristics of the 240 patients enrolled in the study.

Sociodemographic characteristics	N (240)	%
Age, mean 57; SD 0.5		
Sex		
Male	164	68.3
Female	77	32.1
Race		
Caucasian	221	92.1
Not Caucasian	19	7.9
Clinical Characteristics		
Genotype		
1	149	62.1
2	5	2.1
3	86	35.8
Cirrhosis	85	35.4
HIV	33	13.7
Diabetes Mellitus	48	20.0
Hypertension	49	20.4
Obesity	2	0.8
Dyslipidemia	4	1.7
Steatosis	5	2.1
Previous Treatment	123	51.2
Therapeutic Scheme		
SOF + DCV	66	27.5
SOF + DCV + RBV	143	59.5
SOF + SIM	26	10.8
SOF + RBV	5	2.1
Treatment Duration		
12 weeks	188	78.3
24 weeks	52	21.6

SOF: sofosbuvir; DCV: daclatasvir; SIM: simeprevir; RBV: ribavirin.

Table 2
Outcomes and adverse events of patients followed during DAAs use (sofosbuvir with daclatasvir or simeprevir ± ribavirin).

Outcomes	N (240)	%
SVR	221	92.1
No response	3	1.2
Relapse	9	3.7
Dropout	2	0.8
Death	5	2.1
Adverse events most often reported		
Fatigue	133	55.4
Headache	128	53.3
Mood changes	114	47.5
Skin reactions [a]	114	47.5
Body pain, painful joints	100	41.6
Nausea	85	35.4

[a] Skin reactions considered: rush, pruritus and dry skin.

Most of the patients (99.2%) completed the treatment. The study had an overall cure rate (SVR) of 92.1%, excluding patients who discontinued the therapy. The AE most often reported were fatigue, headache, mood changes, skin reactions, body pain, painful joints, and nausea. However, none of the patients discontinued the therapy due to AE (see Table 2).

Patient satisfaction: qualitative feedback

The qualitative data were categorized as follows: (1) the importance of building a good rapport; (2) counseling and education, motivation to adherence; and (3) convenient access to the pharmacist.

The feedback obtained from the patients assisted at the UPh was overwhelmingly positive. Patients reported high levels of satisfaction with the care provided on account of the good rapport built with their pharmacist, the counseling and education offered, motivation to adherence, and the convenient access to the pharmacist. Chart 1 describes the qualitative analysis of the patients' reports.

Discussion

CHC is a severe and silent disease. For a long time, its treatment was restricted to therapies that produced poor therapeutic response and serious AE. The development of sofosbuvir-based therapy has changed rapidly the epidemiological landscape of the disease worldwide and patient's perspectives of cure.[4–7] These changes increased the demand for CHC services providing an opportunity for pharmacist involvement in the HCV management. This study shows the successful experience of a clinical pharmacy service directed to patients using sofosbuvir-based therapy. The patients' reports evince the importance and benefits of the service for the therapeutic outcomes achieved.

The overall cure rate (SVR) in this study was high (92.1%). However, despite of the remarkable DAAs efficacy, it is known that medication effectiveness is often associated with patient adherence to treatment.[17] Regarding the aim of CHC therapy, this issue has always been a common concern, mainly due to significant pill burden and complex dosing regimens of the schemes containing interferon, for example the first generation of DAAs (boceprevir or telaprevir) associated with pegylated interferon and RBV.[18] Although current treatments are easier, concerns still exist about patients taking medications for multiple comorbidities. In our study, almost half of the patients presented diabetes mellitus and or hypertension, and most of them underwent a previous therapy. In this sense, pharmacists can provide information not only about HCV treatments, but also about other

Categories	Patient's report
The importance of building a good rapport	*"The pharmacist offers attention and friendliness. Sometimes the patients are feeling discouraged, nervous and upset about their disease, thinking they're going to die. That's when all the care and dedication of the pharmacists make a difference!"*
Counseling, education and motivation to adherence	*"Having the pharmacist around was very important because you always end up having some questions about the treatment, then you have a professional that can help you out. It was excellent!"* *"The presence of a pharmacist was extremely important, giving you the necessary and relevant information about the treatment itself and about the medication, warning you about keeping regular times of taking your medications, in addition to the open channel provided to contact them when necessary. In my case, I received the care, friendliness and attention from the professionals with whom I was in contact."* *"Without him, I wouldn't have taken the situation and my state of health so seriously"* *"It's so important! The pharmacist answers your questions, gives instructions about*

Chart 1. Qualitative analyses of the patient's reports about the clinical pharmacy services at the UPh.

medications that patients utilize for comorbidities, preventing and managing DDIs.

Through the clinical pharmacy service, the patients were counseled to incorporate the HCV therapy into their daily activities and use the tools available to assist in achieving compliance. In the follow-up visits, the UPh pharmacists are also supposed to assess whether the patients used the medication properly. Thus, the pharmacist contributes to higher effectiveness rates. The patients enrolled in the study reported the importance of the counseling, education and motivation to adherence provided by the UPh pharmacists.

Furthermore, patients who had negative experiences with previous treatments are generally more reluctant to new therapies, mainly due to the possibility of new severe AE.[19,20] In the study, most of the patients were experienced. In this sense, the pharmacists reassured the patients by telling them about the AE that might arise during the therapy, giving them strategies to manage such AE. In this study, none of the patients discontinued the therapy due to AE. The treatment completion rates were high (99.2%). Similar results were also demonstrated in other studies showing the effects of pharmacist-led DAAs utilization management.[12–15] The patients reported the importance of pharmacist instructions about AE and the encouragement not to quit in case of AE.

Low levels of linkage to care and limited access to specialists who treat CHC has been related to patient perceptions of tolerability and reasons to defer treatment.[19–21] Clinical pharmacists at the point of care can collaborate with other health care providers to identify AE early and initiate appropriate strategies to minimize complications and treatment discontinuation.[8–11,22] Furthermore, during the treatment it is not unusual that patients have easier access to the pharmacist rather

	dosage and side effects, and any further assistance necessary. It goes beyond emotional support. The pharmacist is a psychologist for the patient. I really appreciated that. They're very humane, and this helps a lot. They're key elements in the treatment." *"The pharmacist is of paramount importance, and so it was with regard to my treatment. I was well advised and encouraged not to give up in case of adverse and unfavorable reactions."*
Convenient access to the pharmacist	*"It was extremely important, as the pharmacist represented an extension of the medical care, and I had easy and direct contact with them."* *"He was always available. He is so supportive. Every time I needed, I reached him directly through his personal contact number."*

Chart 1. (*continued*)

than to the physician. In our study, most of the patients reported seeing the physician only at the outset of therapy and then at the end thereof. Thus, every dispensing pharmacist has the opportunity to assess the patients' medication needs. In this study, patients reported that the convenient access to the pharmacist was crucial during the treatment.

The high cost of DAAs is also of concern to the health systems, requiring therapy monitoring to avoid overall health care costs.[21,23,24] Clinical pharmacy services improve the patients' access to the therapy and ensure enhanced monitoring, thus leading to positive patient outcomes avoiding disease progression and subsequent hospitalization.[12–15]

Even the roles and responsibilities of the clinical pharmacist may vary, and depending on the health care setting, the involvement of a clinical pharmacist in the management of HCV therapy can positively affect patient outcomes. This is reinforced by the results pointed out in this article. The absence of a control group is a limitation of the present study. With no control group, it is not possible to determine whether the management strategies provided by the clinical pharmacy service had a direct effect on cost or cure rate. However, despite these limitations, patient outcomes and satisfaction were demonstrated, validating the benefits of the service. The UPh team provide key strategies to manage the CHC treatment that may prove beneficial to others looking to initiate or expand the existing HCV pharmacist services.

Conclusions

This article shows positive outcomes of CHC therapy led by clinical pharmacists, mainly to patients who had negative experiences with previous treatments. The UPh pharmacist team ensured appropriate support to patients with HCV infection during the therapy. All the patients were thoroughly counseled and were given access to the pharmacist, who answered their questions, which resulted in less stress for patients and better attitudes toward the treatment, thus leading to successful therapy outcomes.

Declaration of interest

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2019.02.008.

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