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Hepatitis C: sociodemographic and clinical profile of patients treated with direct-acting antivirals in a pharmaceutical office

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ABSTRACT. To report the sociodemographic and clinical profile of patients treated with direct-action antivirals (DAAs). Patients infected with hepatitis C virus in current treatment were followed up in a pharmaceutical office. Sociodemographic, clinical and medicines uses characteristics were obtained. A total of 62 patients were enrolled, with a higher proportion of men, aged between 40 and 69 years, low schooling, and workers. Were predominant the HCV virus genotype 1 (45.2%) and 3 (48.4%), and 19.4% were cirrhotic. Of the referred comorbidities, stood out those diseases related to the cardiovascular system (19.8%), psychiatric disorders (17.6%), endocrine and metabolic disorders (14.5%). Co-infections represented 5.2%, and were distributed between acute hepatitis A (1.0%), chronic viral hepatitis B (2.1%), and HIV (2.1%). Previous or current use of licit / illicit substances was reported by 33.9% of patients. A significant difference was identified in the youngest age group (25 to 39 years, $p = 0.02$), with a lower average viral load compared to the other age groups. The pharmacotherapeutic follow-up carried out in the period resulted in 157 pharmaceutical consultations. Patients with hepatitis C using DDAs were mostly men, aged between 40 and 69 years. Type 3 HCV genotype was most frequently identified. The presence of cirrhosis and other comorbidities serves as an alert for health professionals in the implementation of public health policies.

Keywords: HCV; antivirals agents; direct-acting antivirals; pharmaceutical services; genotype.

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Introduction

Hepatitis C represents one of the main causes of liver transplants and deaths in the world (WHO, 2018), which may result in liver cirrhosis and hepato cellular carcinoma (Khalili & Burman, 2016). The disease is characterized by an acute or chronic condition, leading to asymptomatic primary complications, mild or severe, which can progress to spontaneous cure (around 15% of cases), or to chronic infection (in up to 85% of cases) (Khalili & Burman, 2016).

Several factors such as diabetes mellitus, obesity, old age of the patient, and coinfection by the human immunodeficiency virus or by the hepatitis B virus are indicative of worst prognosis and influence the rate of disease progression (Lingala & Ghany, 2015). Behavioral factors, such as consumption of legal and illegal drugs, also contribute to a progressive worsening of liver fibrosis (Lingala & Ghany, 2015).

Laboratory diagnosis of chronic hepatitis C usually occurs in two stages (World Health Organization, 2017). The first step is the investigation of antibodies against the virus (anti-HCV), which may indicate previous or current infection with seroconversion. The confirmatory step corresponds to the performance of molecular tests by means of reverse transcription followed by polymerase chain reaction (RT-PCR) to detect the circulating HCV-RNA in the patient and, therefore, confirm the presence of active infection. Molecular tests are also called viral load tests and are quantitative (Applegate, Fajardo & Sacks, 2018).

The new treatments against HCV, the direct-acting antivirals (DAAs), constitute a great advance in the fight against the disease (Brasil, 2019), and its effectiveness in eliminating the hepatitis C virus (HCV) in the human body is firmly established (Ioannou & Feld, 2019). The DDAs present cure rates above 90%, ease of dosing, low intercurrence of serious adverse effects, short treatment period (Taherkhani & Farshadpour, 2017), and excellent patient safety profile, contributing to the success of the therapy (Ioannou & Feld, 2019).

Virological results can be optimized through adherence to DAAs, and the presence of the clinical pharmacist, in a multiprofessional care model, contributes to high adherence rates (Slevinet al., 2019). The work of the multidisciplinary team guarantees diagnosed patients access to treatment, information, and support for its conclusion, resulting in the cure of the disease and preventing the transmission of the virus (Yamamoto et al., 2018).

The importance of updated studies on hepatitis C in Brazil is justified by the number of reported cases. In the period from 1999 to 2017, more than 330 thousand cases were detected, affecting more men (58%), and individuals aged 60 years or older. Hepatitis C represents the third leading cause of liver transplants, accounting for approximately 70% of deaths from viral hepatitis in Brazil (Brasil, 2019). Considering the probable sources or mechanisms of infection, the use of injectable drugs (13.2%), blood transfusion (11.4%), and unprotected sexual intercourse (8.9%) stand out (Brasil, 2018). However, in the majority of reported cases (53.7%), the source of infection has not been identified (Brasil, 2018), reinforcing the need to expand research on the topic to fill the existing gaps about the disease.

Considering the complications of hepatitis C and the burden it causes in patients, the objective of this study was to describe the sociodemographic and clinical profile of patients treated with DAAs, providing greater knowledge about the disease and prevention.

Material and method

Study design and data collection

This study was carried out at the Pharmacy of Paraná of the 20th Regional Health of the Government of the State of Paraná, located in the city of Toledo, which covers an estimated population of 358,000 inhabitants (Instituto Brasileiro de Geografia e Estatística, 2011).

The DAAs used in this study are those provided for in the Clinical Protocol and Therapeutic Guidelines (CPTG) for Hepatitis C and Coinfections of the Ministry of Health of Brazil and its updates (Brasil, 2019), including ombitasvir, veruprevir, ritonavir, and dasabuvir (3D); daclatasvir (DAC), sofosbuvir (SOF); ledipasvir (LED); simeprevir (SIM); velpatasvir (VEL); glecaprevir (GLE), and pibrentasvir (PIB) – all associated or not to ribavirin (Brasil, 2019).

The inclusion criteria for patients were as follows: age over 18 years, confirmed HCV infection, and prescribed treatment of DAAs, according to the CPTG for hepatitis C and Coinfections (Brasil, 2019). The selection and data collection of patients chronically infected with HCV were carried out from January 2019 to May 2020.

The research instrument used was composed of open and closed questions about the sociodemographic characteristics of the patients (sex, age, education, and occupation); clinical characteristics (virus genotype, liver staging, initial viral load, use of licit/illicit drugs, cirrhosis, time of diagnosis, and comorbidities); the patient's knowledge about the disease and treatment; previous and current treatments (prescribed and non-prescribed); and drug interactions and adverse events.

Information was also obtained through access to the medical request to release the treatment.

For hepatic staging data, we used the results of elastrography tests, liver biopsy or, in their absence, abdominal ultrasound, and APRI and FIB4 data (Brasil, 2019).

Comorbidities were classified according to ICD-11 (World Health Organization, 2020).

The implementation of pharmaceutical care service followed a standard of care in which all patients should receive education and advice on the treatment to be started.

Genotypes and HCV RNA levels were measured using the *real time polymerase chain reaction* (RT-PCR) methodology, performed by the Central Laboratory of Paraná State (LACEN/PR) or private laboratories. Data were obtained by accessing the patient's medical record.

Ethical aspects

This study was approved by the Standing Committee for Ethics in Research Involving Human Beings (*Comitê Permanente de Ética em Pesquisa Envolvendo Seres Humanos*, COPEP), under the number 3,794,273. Patients who agreed to participate in the study received a Free and Informed Consent Term.

Statistical analysis

The information obtained was recorded in Excel® spreadsheets. Sociodemographic, clinical, and medication use variables were represented by their absolute and relative frequencies through descriptive analysis. Subsequently, using the supplement Real Statistics Using Excel (Zaiontz, 2021), Mann Whitney and

Kruskal-Walis tests, with p-value = 0.05, were carried out to investigate if the viral load of each patient could be conditioned by factors such as hypertension, diabetes, psychiatric disorders, use of licit/illicit substances, presence of cirrhosis and genotype of the virus (Mello, 2014).

Results and discussion

Sociodemographic characteristics

The total sample of this study was composed of 62 patients with hepatitis C using DAAs. The pharmacotherapeutic follow-up carried out in the period resulted in 157 pharmaceutical consultations. There was a greater participation of men than women (56.5% vs. 43.6%). The mean age of the patients was 53 years, and the median was 53.5, ranging from 25 to 88 years. The predominant age group was 40 to 69 years old (74.2%), with less frequency among individuals aged 70 years or older. As to schooling, was observed that the frequency was higher among patients with primary and secondary education (43.6% and 40.3%, respectively). Regarding occupation, there was a predominance of workers (61.3%) in the study sample and a small proportion of students (1.6%) (Table 1).

Table 1. Sociodemographic characteristics of patients infected with the hepatitis C virus, at the Pharmacy of Paraná of the 20th Regional Health, from January 2019 to May 2020.

Variables	N = 62	%
Sex		
Female	27	43.6
Male	35	56.5
Age group (years)		
25 to 39	11	17.7
40 to 49	15	24.2
50 to 59	17	27.4
60 to 69	14	22.6
⩾70	05	8.1
Education		
Illiteracy	01	1.6
Primary education	27	43.6
Secondary education	25	40.3
Higher education	09	14.5
Occupation		
Retiree	17	27.4
Unemployed	06	9.7
Student	01	1.6
Primary- and secondary-level workers	25	40.3
Informal workers	08	12.9
Higher-level workers	05	8.1

Clinical features

According to the evaluated tests, there was a predominance of HCV genotype 1 (45.2%) and 3 (48.4%). Regarding hepatic staging, 19.4% of patients were cirrhotic (Table 2).

As to the estimated time of diagnosis, there was a high frequency of patients diagnosed in the period of 1 to 2 years (33.9%), followed by patients with more than 10 years of diagnosis (22.6%). Patients diagnosed over a 10-year period include those who used Interferon (IFN) and Ribavirin, and those who were being monitored and awaiting more effective treatment options. Patients with a diagnosis of less than 1 year represented 11.3% of the sample (Table 2).

Considering the previous treatment, 93.5% were treatment-free (Table 2).

Immunization against other viral hepatitis was also researched in this study. Only 29.0% of patients were immunized against the hepatitis A and B virus (HAV + HBV). Against hepatitis B virus (HBV), immunization was confirmed in 38.7% of the sample (Table 2).

The average viral load resulted in 5.6 log10 IU/mL, with values not exceeding 7.04 log10 IU/mL (data not shown).The difference in viral load between the groups is available in the table 4.

Among the reported comorbidities (n=96), diseases related to the cardiovascular system (19.8%), psychiatric disorders (17.6%), endocrine and metabolic disorders (14.5%), and diseases related to the gastrointestinal tract (12.4%) stood out. Although less frequent, coinfections (5.2%) were distributed among acute

hepatitis A (1.0%), chronic viral hepatitis B (2.1%), and HIV (2.1%) (Table 3). Previous or current use of licit/illicit substances was reported by 33.9% of patients.

Table 2. Initial clinical characteristics of the 62 patients infected with the hepatitis C virus, at the Pharmacy of Paraná of the 20th Regional Health, before starting treatment with DAAs[a], from January 2019 to May 2020.

Variables	N=62	%
Genotype		
1	28	45.2
2	04	6.4
3	30	48.4
Liver Staging		
Cirrhotics	12	19.4
Non-cirrhotic	51	82.3
Estimated diagnosis time		
1 year	07	11.3
1 to <2 years	21	33.9
2 to <4 years	05	8.1
4 to <6 years	11	17.7
6 to <10 years	04	6.4
> 10 years	14	22.6
Previous treatment		
Yes	04	6.5
No	58	93.5
Immunization against other viral hepatitis		
No	20	32.3
HAV + HBV[b]		29.0
HBV[c]		38.7

[a]DAAs: Direct-acting antivirals. [b]HAV: Hepatitis A Virus. [c]HBV: Hepatitis B Virus.

Table 3. Description of the most relevant comorbidities, reported by the 62 patients, at the Pharmacy of Paraná of the 20th Regional Health, undergoing Direct-acting Antivirals against hepatitis C, from January 2019 to May 2020.

Variables	N=96	%
Diseases related to the cardiovascular system		
Arterial hypertension	16	16.7
Cardiac insufficiency	03	3.1
Psychiatric disorders		
Bipolar Affective Disorder	01	1.0
Depressive Episodes	08	8.3
Anxious disorders	08	8.3
Endocrine and metabolic disorders		
Hypothyroidism	04	4.2
Non-insulin-dependent diabetes mellitus	08	8.3
Insulin-dependent diabetes mellitus	01	1.0
Dyslipidemia	01	1.0
Diseases related to the gastrointestinal tract		
Gastritis and Duodenitis	06	6.3
Other liver diseases	03	3.1
Hepatomegaly	01	1.0
Jaundice	01	1.0
Other Abnormalities of Plasma Proteins	01	1.0
Neurological disorders		
Epilepsy	04	4.2
Migraine	02	2.1
Coinfections		
Acute Hepatitis A	01	1.0
Chronic viral hepatitis B	02	2.1
Human Immunodeficiency Virus (HIV) disease	02	2.1
Diseases related to blood and hematopoietic organs		
Hereditary Factor VIII Deficiency	01	1.0
Purpura and other hemorrhagic conditions	04	4.2

Musculoskeletal diseases		
Other muscle disorders	04	4.2
Respiratory system diseases		
Asthma	03	3.1
Neoplasms		
Breast	01	1.0
Uterus	01	1.0
Diseases related to the renal system		
Chronic renal failure	01	1.0
Other diseases[a]	08	8.3

[a]Other diseases include post-transplant immunosuppression condition, prostate hyperplasia, glaucoma, inner ear disorders, malaria, and psoriasis.

Using Mann Whitney and Kruskal-Walis statistical tests, (p-value = 0.05), we evaluated whether the viral load can be influenced by the group of patients with or without a diagnosis of hypertension, diabetes, psychiatric disorders, substance use licit / illicit, presence of cirrhosis and genotype of the virus. Although the average viral load is different between groups, there was no statistical significance.

According to the Mann-Whitney test, we identified a significant difference only in the youngest age group (25 to 39 years, p = 0.02), whose average viral load of 4.66 was lower when compared to the other age groups (Table 4).

Table 4. Risk factors related to the possible action on viral load, reported by the 62 patients, at the Pharmacy of Paraná of the 20th Regional Health, undergoing direct-acting antivirals against hepatitis C, from January 2019 to May 2020.

Variables	Total sample (n,%)	Average/SD	Test
Age group (years) versus Initial Viral Rate			Mann-Whitney (P)
25 to 39	11 (17.7)	4.66 + - 1.02	154.5 (0.02)
40 to 49	15 (24.2)	5.29 + - 1.05	346.5 (0.12)
50 to 59	17 (27.4)	5.14 + - 1.13	200.0 (0.74)
60 to 69	14 (22.6)	5.12 + - 0.84	175.0 (0.71)
⩾70	05 (8.1)	5.26 + - 1.01	285.0 (0.80)
Age over 40 years			Mann-Whitney (P)
No	11 (17.7)	4.82 + - 1.11	200.00 (0.08)
Yes	51 (82.3)	5.21 + - 0.99	
Hypertension			Mann-Whitney (P)
No	56 (93,5)	5,09 +- 1,00	
Yes	4 (6,5)	5,84 +- 1,08	74 (0,23)
Diabetes			Mann-Whitney (P)
No	55 (88,7)	5,11 +- 1,02	
Yes	7 (11,3)	5,34 +- 1,08	170,5 (0,63)
Psychiatric disorders			Mann-Whitney (P)
No	45 (72,6)	5,30 +- 0,98	
Yes	17 (27,4)	4,71 +- 1,03	283,5 (0,12)
Use of legal / illegal substances			Mann-Whitney (P)
No	47 (75,8)	5,20 +- 0,97	
Yes	15 (24,2)	4,93 +- 1,16	316,5 (0,56)
Cirrhosis			Mann-Whitney (P)
No	50 (80,6)	5,17 +- 1,02	
Yes	12 (19,4)	4,99 +- 1,02	279 (0,71)
Genotype			Kruskal-Walis
1	28 (45,2)	5,31 +- 0,93	
2	4 (6,4)	5,45 +-1,16	
3	30 (48,4)	4,93 +- 1,07	4,18 (0,12)

[a]The age group over 40 is in the Clinical Protocol and Therapeutic Guidelines (CPTG) as a priority group to be tested, at least once in a lifetime, due to biosafety failures that occurred in the past.

Hepatitis C patients using DAAs face daily challenges that include disease control, prevention of complications, as well as medication-related issues, including continued access to treatment, prevention and management of adverse reactions and drug interactions, and adherence to treatment.

The cases reported and treated for chronic hepatitis C in our study were more frequent in men than in women. The predominance of men in our sample is consistent with similar studies (Brasil, 2019, Oliveira-filho et al., 2019; Gomes et al., 2020), and may be related to greater exposure to risk factors (Jin et al., 2020).

Patients aged 40 to 69 years were frequent in this study. Oliveira et al. (2019) demonstrated in a study carried out in the Amazon, a greater proportion of individuals with HCV over the age of 40 years.

The greater proportion of workers found in our study has also been demonstrated by other researchers. Oliveira et al. (2019) cited the source of income obtained by most individuals with active infection from regular or irregular work – but there were also individuals who received social or pension benefits, and even from criminal activity. For the authors, the association between HCV infection and involvement with illegal activities may represent an example of socioeconomic marginalization, contributing to increasing health risks.

The frequency of patients with type 3 genotype was slightly higher than HCV genotype 1 in this sample. However, worldwide HCV virus genotype 1 has been prevalent over genotype 3 (Petruzziello, Marigliano, Loquercio, Cozzolino, & Cacciapuoti, 2016; Campos Fernández de Sevilla, et al., 2019a, , Slevin et al., 2019; Gomes et al., 2020) as well as in the southern region of Brazil (Campiotto, et al., 2005, Lampe et al., 2013).

Advanced disease, defined as the presence of liver cirrhosis, was recorded in 19.4% of patients. Higher values were found by Keast, Holderread, Cothran, and Skrepnek (2019) (22.0%), Yamamoto et al. (2018) (22.2%), Slevin et al. (2019) (36.2%), and Gomes et al. (2020) (35.4%). On the other hand, the predominance of non-cirrhotic patients in the study reveals important achievements in the early detection and treatment of the disease, with possible minimization of the occurrence of complications related to the time of exposure to the virus.

Patients with time between 1 and 2 years between diagnosis and treatment, comprised the largest group and this shows us agility in the early detection of cases of hepatitis C in our health system. The importance of an early diagnosis of hepatitis C is necessary to avoid the deleterious effects of the virus, which manifest themselves 10 to 20 years after infection (Razavi, 2020), as well as it should be a priority to identify patients with advanced fibrosis who are at low enough risk to dispense Hepatocellular Carcinoma after the sustained virological response (Ioannou & Feld, 2019).

A considerable portion of the patients did not have previous immunization against the HBV and HAV. This finding contradicts the current guidelines of the CPTG, which states that all patients with diagnoses must be immunized against HVA and HBV (Brasil, 2019). The verification of immunization can be done in the pharmaceutical office, which is a health screening action (Conselho Federal de Farmácia, 2013).

The average viral load found in this study was considered intermediate. The youngest age group (25 to 39 years) had a significantly lower viral load. Some researchers suggest that viral load is significantly associated with the virus genotype, elevated serum ALT levels, thrombocytopenia, arthralgia, fever, vomiting, and dizziness (Basharkhah et al., 2019). Although viral load is considered an important prognostic factor in determining treatment, the relationship between viral load, genotype, and disease progression remains controversial (Basharkhah et al., 2019). Factors related to treatment failure in CHC are related to older age, high hepatitis C viral load, and impaired glucose tolerance at the start of treatment (Ghenea et al., 2020).

Among the comorbidities found in this study, those related to the cardiovascular system, mental health and endocrine, and metabolic disorders stood out. Arterial hypertension and diabetes mellitus are common comorbidities reportedin other pharmaceutical care studies in hepatitis C (Campos Fernández de Sevilla et al., 2019b; Gomes et al., 2020).Still, the presence of psychiatric disorders was less than that reported by Spanish researchers (20.3%) (Campos Fernández de Sevilla et al., 2019b) and Americans (48.3%) (Slevin et al., 2019). For Kyuregyan et al. (2020), chronic hepatitis C can present extrahepatic manifestations, such as cryoglobulinemia, insulin resistance, type 2 diabetes mellitus, neurological disorders, and lymphomas. The presence of comorbidities (hypertension, diabetes, and psychiatric disorders) may be related to less adherence to treatment, as well as the use of legal/illegal substances, and it will be the subject of future research.

The importance of the pharmaceutical clinic is evidenced in this study through the large number of information and advice provided to each patient at the beginning and during the treatment. In the study by Gomes et al. (2020), patients reported high levels of satisfaction with the care provided due to the good relationship built, the counseling and education offered, motivation for adherence, and convenient access to the pharmacist. Pharmacists play an important role in the proper use of medications, helping to identify and reduce morbidity and mortality for patients, in addition to reducing costs with healthcare services(Watanabe, Mcinnis, & Hirsch, 2018).

The lack of access to education as a vulnerability factor for infection was identified in our sample. Gheorghe et al. (2020) also demonstrated that education was relevant in their study, being a risk factor that makes individuals more susceptible to chronic HCV infection.

The education of the patient in the knowledge of the objectives of the treatment becomes a determining factor for the good therapeutic follow-up. Health care delivery and education has become a challenge for providers. Nurses and other professionals are challenged daily to assure that the patient has the necessary information to make informed decisions. Patients and their families are given a multitude of information about their health and commonly must make important decisions from these facts. Obstacles that prevent easy delivery of health care information include literacy, culture, language, and physiological barriers (Beagley, 2011). Education provided by healthcare professionals should also consider raising awareness of HCV, the different routes of transmission and ways to avoid infection or reinfection. It should also clarify the right to testing and treatment (Brunner & Bruggmann, 2021).

According to the findings of the present study, patients with hepatitis C using DAAs were mostly men, aged between 40 and 69 years, with a low level of education, and workers. The frequency of patients with type 3 genotype was slightly higher than HCV genotype 1.

Although simple detection methods, highly effective and easy-to-administer therapies, and efficient preventive measures are available to combat hepatitis C, most countries in the world will not reach the World Health Organization's goal of eliminating this infectious disease and its consequences by 2030.(Brunner & Bruggmann, 2021). Based on the results presented, it is suggested the implementation of public policies for integral care. The offer of diagnosis, treatment and follow-up by the clinical team must be available together, avoiding the segmentation of services, which can lead to the loss of patient follow-up.

Persons who inject drugs (PWIDs), as well as those deprived of their liberty, sex workers, indigenous people and migrants face high incidence of HCV, high prevalence of HCV infection, stigma, discrimination, criminalization and difficulties in accessing services (WHO, 2018). The testing of these groups should be prioritized, as well as the follow-up of therapy, in cases of need. On the other hand, the heterogeneity of the sample presented in the results, with a considerable number of young adults, suggests that mass testing against the HCV Antigen (rapid tests) could contributeto early detection and treatment, with a consequent decrease in the transmissibility of the virus.

Conclusion

The identification of patients with cirrhosis and other comorbidities serves as a warning in the implementation of public health policies. Patient follow-up with the construction of a care plan contributes to the success of therapy. The importance of this study was to demonstrate the real life of a pharmacist's office in the follow-up of patients undergoing treatment against the hepatitis C virus. The individualization of care is necessary, as the sample of patients is heterogeneous. Young to elderly patients are affected by the disease and the patients' comorbidities and frailties must be considered.

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