Treatment of chronic Hepatitis C with daclatasvir, sofosbuvir and simeprevir in patients from the reference hospital of infectology in central Brazil

Tratamento da Hepatite C crônica com daclatasvir, sofosbuvir e simeprevir em pacientes do hospital de referência de infectologia do centro do Brasil

DOI:10.34117/bjdv7n4-045

Recebimento dos originais: 07/03/2021
Aceitação para publicação: 03/04/2021

Bruna Menêzes Gonçalves
Infectious Diseases Clinical Care Specialist
Municipal Hospital of Flores de Goiás
Address: Av. Bahia, Q. D, L. 10, Vila Israelândia - Pontalina - Goiás
E-mail: brunamenego@gmail.com

Symone Coelho Galvão Sirqueira
Pharmaceutical Care Specialist
Tropical Diseases Public Hospital - Dr. Anuar Auad
Address: Rua Turiaçu Qd D6 Lt 4 residencial Araguaia-Alphaville Flamboyant - Goiânia - Goiás
E-mail: symone_sirqueira@yahoo.com.br

Rodrigo Sebba Aires
PhD, Tropical Medicine
Federal University of Goiás
Address: Rua 34, nº 157, Setor Marista - Goiânia - Goiás
E-mail: rsaires@uol.com.br

Mara Cristina Nolasco Sampaio
Clinical Pharmacology Specialist - UFG
Tropical Diseases Public Hospital - Dr. Anuar Auad
Address: Avenida Rochedo qd. 22 lt 03 Jardim Califórnia - Goiânia - Goiás
E-mail: marakris@gmail.com

Jakeline Ribeiro Barbosa
PhD, Tropical Medicine
Center for Strategic Studies, Oswaldo Cruz Foundation - Fiocruz
Address: Av. Brasil, 4.036 - Expansion Building - Room 1004 - Manguinhos - Rio de Janeiro
Email: jakeline.barbosa@fiocruz.br

Angela Ferreira Lopes
PhD, Tropical Medicine and Public Health
Pharmacy College - Federal University of Goiás
Address: Pharmacy College - Federal University of Goiás - Rua 240 corner with 5th Avenue, Room 209 - Leste Universitário - Goiânia - Goiás
E-mail: angela_lopes@ufg.br

Danillo Rodrigues de Sá Godoi
MD, Health Care
Pontifical Catholic University of Goiás
Address: Rua 21, nº 342 - Vila Jaraguá - Goiânia - Goiás
E-mail: danillogodoi@gmail.com

ABSTRACT
The drug treatment of hepatitis C represents a great therapeutic advance in favor of the elimination of the virus. The present study assessed the efficacy of treatment regimens involving direct action antivirals (DAAs), given to patients with chronic hepatitis C, attended at a referral hospital of infectology, central Brazil. This is a descriptive and cross - sectional study, based on the electronic database of the outpatient pharmacy, that evaluated the characteristics of patients and drug regimens involving DAA, from November 2015 to June 2017. Among 717 patients enrolled in this study, most of them had advanced liver fibrosis, were treatment naïve and HCV genotype 1 infected almost 80% of participants. A high efficacy of HCV treatment was achieved with 97% (95% CI: 94.9-98.2%) of SVR among the 431 patients who presented the results of viral load tests (HCV-RNA) at 12 weeks post-treatment. Patients infected with genotype 3 and who were cirrhotic had a lower SVR rate (87%). Treatment efficacy was not associated with age or sex among participants. The results of this study corroborate the findings in literature that showed a high efficacy of DAAs in the treatment of chronic hepatitis C, implemented through the clinical protocol and therapeutic guidelines for hepatitis C of the Ministry of Health in 2015. Many challenges must be overcome in order to combating viral hepatitis. In this context, the efficacy of HCV treatment it is an important issue to achieve the HCV elimination as a public health threat.

Keywords: Chronic Hepatitis C, Drug Therapy, Sustained Virologic Response.

RESUMO
O tratamento medicamentoso da hepatite C representa um grande avanço terapêutico em prol da eliminação do vírus. O presente estudo avaliou a eficácia de regimes de tratamento envolvendo antivirais de ação direta (AAD), administrados a pacientes com hepatite C crônica, atendidos em hospital de referência em infectologia, região central do Brasil. Trata-se de um estudo descritivo e transversal, com base no banco de dados eletrônico da farmácia ambulatorial, que avaliou as características dos pacientes e dos regimes medicamentosos envolvendo DAA, no período de novembro de 2015 a junho de 2017. Dentre os 717 pacientes cadastrados neste estudo, a maioria deles tinham fibrose hepática avançada, eram virgens de tratamento e o genótipo 1 do HCV infectou quase 80% dos participantes. Uma alta eficácia do tratamento do HCV foi alcançada com 97% (IC 95%: 94,9-98,2%) de RVS entre os 431 pacientes que apresentaram os resultados dos testes de carga viral (HCV-RNA) 12 semanas após o tratamento. Pacientes infectados com o genótipo 3 e que eram cirróticos tiveram uma taxa de RVS mais baixa (87%). A eficácia

do tratamento não foi associada à idade ou sexo entre os participantes. Os resultados deste estudo corroboram os achados da literatura que evidenciam uma elevada eficácia dos AAD no tratamento da hepatite C crônica, implementados por meio do protocolo clínico e das diretrizes terapêuticas para hepatite C do Ministério da Saúde em 2015. Muitos desafios devem ser superados em a fim de combater a hepatite viral. Nesse contexto, a eficácia do tratamento do HCV é uma questão importante para se conseguir a eliminação do HCV como uma ameaça à saúde pública.

Palavras-chave: Hepatite C crônica, Terapia medicamentosa, Resposta Virológica Sustentada.

1 INTRODUCTION

Hepatitis C, caused by the Hepatitis C Virus (HCV), is considered a public health problem, affecting 2.5% of the global population[1]. According to estimates by the World Health Organization (WHO) approximately 71 million people are chronically infected with the virus[2]. This viral infection stands out as being the predominant cause of cirrhosis and, consequently liver transplantation both in Brazil and worldwide[1-4]. It is estimated that in Brazil there are about 1.7 million people with the disease[5-8].

The drug treatment of hepatitis C represents a great therapeutic advance in favor of the elimination of the virus. The Clinical Protocol and Therapeutic Guidelines, prepared by the Brazilian Ministry of Health, has undergone some changes since its implementation[6]. Initially, in 2011, treatment was based on peg alpha-interferon (PEG) and ribavirin (RBV)[7]. In 2013, first generation protease inhibitors (PIs), boceprevir (BOC) and telaprevir (TEL) were used for the treatment of patients with HCV genotype 1[8].

This therapy has faced some challenges, such as adverse effects and difficulty in patient adherence to treatment, among others[10]. In 2015, new guidelines were implemented, including direct action antivirals (DAA); sofosbuvir (nucleotide analogue); simeprevir (second generation PI); and daclatasvir (non-structural protein 5A inhibitor). The use of first-generation PIs was discontinued, and the efficacy and safety of disease management was improved[6].

This treatment mainly seeks to eliminate the hepatitis C virus, which is attested by sustained virological response (SVR), evidenced by undetectable levels of viral RNA (HCV-RNA) after three months of treatment[6]. A decrease in the incidence of chronic liver complications and consequent reduction of HCV transmission is a contributing factor in the improvement of expectation and quality of life of the infected individual[6,11].

Despite the feasibility of new drug treatments in Brazil, the data on their effectiveness, in different epidemiological scenarios, are still scarce[12,13]. In this context, this article presents an evaluation of the efficacy of combination therapies of daclatasvir, sofosbuvir and simeprevir, used by patients with chronic hepatitis C at the hospital of reference of infectology in central Brazil.

2 METHODS

Design, location and duration of study

This is a cross-sectional study, based on information from antiviral treatment with sofosbuvir, daclatasvir and/or simeprevir in patients with chronic hepatitis C, performed at the outpatient pharmacy service, at the reference hospital of infectology in central Brazil, during November 2015 to July 2017.

This study included patients who started treatment for hepatitis C according to the criteria established in the 2015 guidelines[6] by Brazilian Ministry of Health and who presented the viral load test result after 12 weeks of treatment, regardless of the clinical follow-up performed in public or private services.

The case definition of chronic hepatitis C is characterized by anti-HCV positive result and viral RNA detectable (HCV-RNA) for more than six months[4].

Data analysis

Sociodemographic, clinical-laboratory data and the type of antiviral treatment for hepatitis C were analyzed in Microsoft Excel programs (Microsoft Office® 2016) and Openepi version 3.01 (2013).

Frequencies and prevalences were calculated by comparing the patients' response to antiviral treatment using Fisher's exact test. Results with values of p (two-tailed) <0.05 were considered statistically significant, with a Confidence Interval of 95% (CI 95%).

Ethical aspects

This study was approved by the Research Ethics Committee, linked to the State Health Department of Goiás, Brazil, under CAAE nº 64167617.0.0000.0034.

3 RESULTS

Among 717 chronic hepatitis C patients attended at the reference infectious diseases hospital during study period, a total of 431 (60%) individuals, that presented the results of viral load test (HCV-RNA) after 12 weeks of treatment, were eligible for this

study (Figure 1). The median age was 55 years old (ranged, 19-84), with a male:female ratio of 1.3:1. Approximately 80% of the participants lived in the metropolitan region and about 50% self-reported as brown race / skin color (Table 1). No statistically significant difference was observed between the 717 patients attended at hospital and the 431selected participants (p> 0.05).

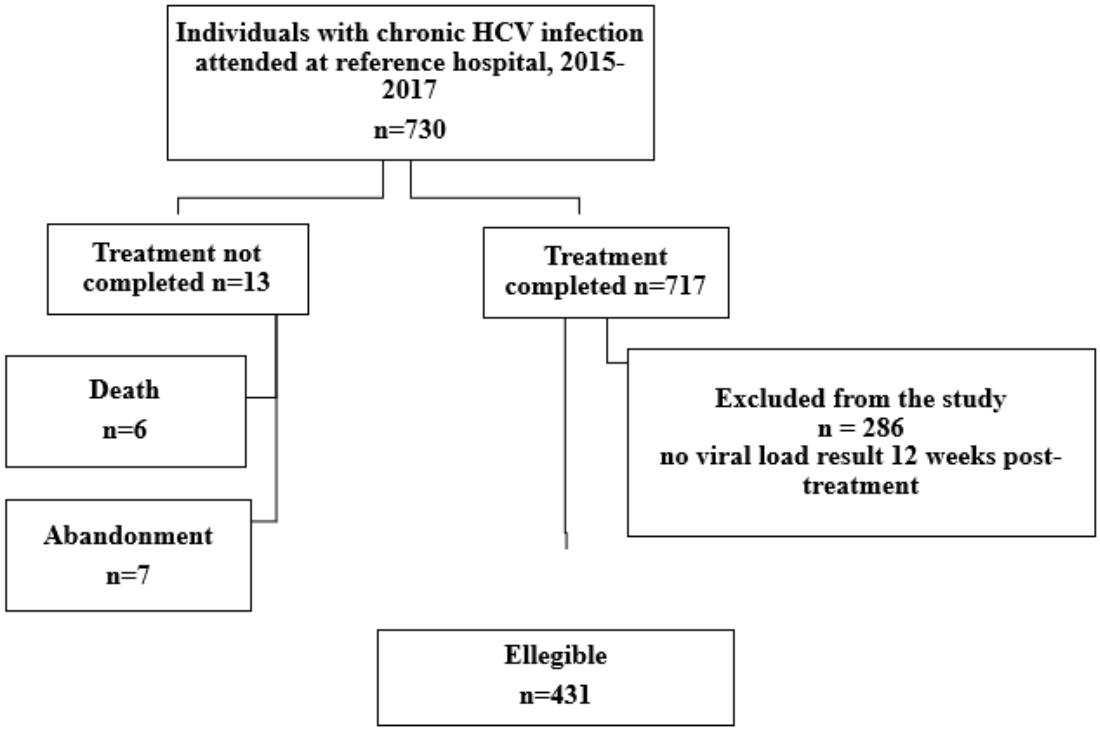

Figure 1. Flow diagram of chronic HCV patients selected at the reference hospital of infectology, central Brazil, 2015-2017.

Table 1. Socio-demographic characteristics, second result of viral load test, of patients with chronic hepatitis C treated with DAA at the reference hospital of infectology, Goiás, 2015-2017

VARIABLE	PATIENTS TREATED FOR HCV [1] Treatment completed N=717 n (%)	With Result of LR[2] N=431 n (%)	*P*
GENDER			
FEMALE	284 (39,6)	184 (42,6)	0,152
MALE	433 (60,4)	247 (57,4)	
AGE GROUP, YEARS			
≤ 20	1 (0,1)	0 (0)	0,586*
21 ┤ 29	8 (1,1)	2 (0,4)	
30 ┤ 59	477 (66,4)	289 (66,9)	
≥ 60	231 (32,4)	140 (32,7)	
RACE / COLOR			
WHITE	278 (38,7)	159 (36,8)	0,558*
BLACK	35 (4,9)	23 (5,3)	
BROWN	346 (48,1)	211 (48,8)	

OTHERS[A]	58 (8,3)	38 (9,1)	
CITY OF RESIDENCE			
GOIÂNIA AND METROPOLITAN REGION[B]	570 (79,5)	340 (78,8)	0,401
OTHERS[C]	147 (20,5)	91 (21,2)	

[a] Yellow, Indigenous or Unspecified. [b]Abadia de Goiás, Aparecida de Goiânia, Aragoiânia, Bela Vista de Goiás, Bonfinópolis, Brazabrantes, Caldazinha, Caturaí, Goianápolis, Goianira, Guapó, Hidrolândia, Inhumas, Nerópolis, Nova Veneza, Santo Antônio de Goiás, Senador Canedo,Terezópolis de Goiás, Trindade (Source: IBGE,2013).[c]Formosa, Formoso do Araguaia, Goianira, Goiatuba, Guapó, Inaciolândia, Iporá, Itaberaí, Itapuranga, Itumbiara, Jaraguá, Luziânia, Mara Rosa, Minaçu, Morrinhos, Mundo Novo, Nazário, Orizona, Piracanjuba, Pires do Rio, Pontalina, Porangatu, Rio Verde, Santa Helena de Goiás, São Luís dos Montes Belos, Silvânia, Uruaçu, Uruana, Urutaí.[*]*p* with three degrees of freedom.[1]HCV = hepatitis C Virus.[2]LR= Viral Load.

HCV genotypes 1 to 4 were identified, with a predominance of genotype 1 and 3 in 80% and 18.5% of cases, respectively. The quantitative HCV-RNA at the beginning of treatment showed a variation of 244 to 22.757.5 IU/mL, with a median of 1.054.1 IU/mL. Advanced fibrosis (stages F3 or F4) and liver cirrhosis were the most prevalent hepatic events. The HIV coinfection was detected among 11.6% of the participants (Table 2).

Table 2. Clinical-laboratory characteristics of patients with chronic hepatitis C, central Brazil, 2015-2017.

VARIABLE	FREQUENCY N=431 n (%)	*P*
HCV GENOTYPE		
1	341 (79,1)	
1 WITHOUT SUBTYPE	59 (13,6)	
1A	163 (37,8)	
1B	119 (27,1)	1
2	7 (1,6)	
3	80 (18,5)	
4	3 (0,7)	
VIRAL LOAD, INITIATION OF TREATMENT UI/ML		
≤ 600.000	162 (37,6)	
600.000 ┤ 800.000	32 (7,4)	1
> 800.000	237 (55)	
COMORBIDITIES		
NONE	366 (84,9)	
HIV	50 (11,6)	1
TRANSPLANTED	10 (2,3)	
OTHERS*	5 (1,2)	
**STAGING OF FIBROSIS ** **		
F0-F1	2 (0,4)	
F2	53 (12,3)	
F3	124 (28,8)	1
F4	152 (35,3)	
UNINFORMED[A]	100 (23,2)	
CLINICAL CARE PROCEDURE		
Public (SUS)	329 (76,3)	0,0000001
Private	102 (23,7)	
Previous treatment		
None	300 (69,6)	1
Experienced	131(30,4)	

IFN-based regimens[1]	73 (16,9)
BOC-BASED REGIMENS[2]	30 (7)
TEL-BASED REGIMENS[3]	17 (4)
NO INFORMATION	11 (2,5)

* Peripheral nervous system disorders, lichen planus, vasculitis, glomerulonephritis. ** Staging classified by Metavir scale, where F0 characterizes liver without fibrosis and F4 severe fibrosis or cirrhosis. [1]IFN= interferon alfa or peginterferon alfa.[2]BOC=boceprevir.[3]TEL=telaprevir. [a] Patients with clinical signs or ultrasound evidence suggestive of hepatic cirrhosis without evaluation of fibrosis.

Most patients underwent a clinical follow-up in the public health service (p=0.0000001) and 70% of the study population were treatment naïve for chronic hepatitis C. Approximately 12% of individuals had experienced previous treatment with protease inhibitors (boceprevir and/or telaprevir). All the six regimens used to treat the study participants involved DAA: 83.8% (n=361/431) used sofosbuvir and daclatasvir; 13.9% (n=60/431) sofosbuvir and simeprevir; 2.3% (n=10/431) sofosbuvir solely (Table 3). In addition, DAA treatment regimens also included ribavirin in 52.6% (n=227/431) and peg alpha-interferon in 0.7% (n=3/431) of patients.

Table 3. Antiviral therapy schemes used by patients with chronic hepatitis C, central Brazil, 2015-2017

REGIMENS	GENOTYPE				TREATMENT WEEKS		SVR**** (%)
	1	2	3	4	12	24	
RIB+SOF+DAC* (N=203)	152	-	50	1	159	44	98
SOF+DAC (N=158)	129	-	27	3	125	33	95
RIB+SOF+SIM (N=14)**	14	-	-	-	14	-	100
SOF+SIM (N=46)	46	-	-	-	46	-	98
RIB+SOF (N=7)	-	7	-	-	7	-	100
RIB+SOF+PEG* (N=3)**	-	-	3	-	3	-	66

Treatment time was 12 weeks for 82% (n=354) of participants and 24 weeks for 77 individuals, among those: 58% used boceprevir or telaprevir previously; 41% were Child-Pugh B or C; 1% HIV / HCV coinfected.

Overall SVR rate of more than 90% was observed in the study participants. The SVR ranged, according to the treatment regimen used, from 66 (for those with PEG regimen) to 100%. Patients without SVR were older than 30 years and no significant statistical difference was observed between SVR and sex (Table 4). The therapeutic failure was observed in 13 patients infected by HCV 1A (n=6), HCV 1B (n=2) and HCV 3 (n=7) (p=0.01). All patients infected by genotypes 2 or 4 presented SVR.

Table 4. Characteristics of patients with chronic hepatitis C, according to sustained virological response, Goiás, 2015-2017.

VARIABLES	FREQUENCY		Total	*P*
	SVR n (%)	Without SVR n (%)		
SEX				
FEMALE	181 (98,3)	3 (1,7)	184	0,078
MALE	237 (95,9)	10 (4,1)	247	
AGE GROUP, YEARS				
≤ 20	0 (0)	0 (0)	0	0,38
21 ┤ 29	2 (100)	0 (0)	2	
30 ┤ 59	278 (96,1)	11 (3,9)	289	
≥ 60	138 (98,5)	2 (1,5)	140	
HCV GENOTYPE				
1	335 (98,2)	6 (1,8)	341	0,01
2	7 (100)	0 (0)	7	
3	73 (91,3)	7 (8,7)	80	
4	3 (100)	0 (0)	3	
STAGING OF FIBROSIS				
F0-F1	2 (100)	0 (0)	2	0,15
F2-F3	175 (98,8)	2 (1,2)	177	
F4	147 (96,7)	5 (3,3)	152	
UNINFORMED[A]	94 (94)	6 (6)	100	

[a]Patients with clinical signs or ultrasound evidence suggestive of hepatic cirrhosis without evaluation of fibrosis. * SVR= Sustained Viral Response.

All patients with F0 to F2 hepatic fibrosis achieved SVR. However, among those with more advanced fibrosis (F3 or F4), 2,5% did not present SVR. It is worth noting that of the 131 patients previously experimented, one patient (infected with genotype 1) did not present SVR after being submitted to a new treatment.

4 DISCUSSION

In the present study, we analyzed data on patients with chronic viral hepatitis C treated with antiviral therapy schemes involving direct action antivirals (DAAs) at the reference hospital of infectology, Goiás State, 2015 to 2017. There are no data regarding the subject in the central region of Brazil. Our results are in line with other national studies that have previously analyzed the therapeutic efficacy of treatments in patients with chronic hepatitis C[14-16].

The participants were predominantly male, older than 40 years of age and brown race / skin color. The epidemiology of hepatitis C in Brazil indicates that men are more frequently affected in this age group[17]. The race / color characteristics may be related to the researched region. Studies conducted by Rosa[16] and Teixeira[15] identified most of

chronic HCV cases among white population in the South of Brazil. However, in the central Brazil region the population is predominantly of brown race / skin color, according national data[18].

The hospital outpatient pharmacy, setting for this study, is based in the capital of Goiás and is one of the three treatment centers for chronic hepatitis C in the State. Consequently, we believe that the location of the health unit explains the fact that most of patients lived at the metropolitan region.

Regarding the clinical and laboratory characteristics of the patients, a predominance of HCV genotype 1 (subtypes A and B) was observed, followed by genotype 3. This is in line with the worldwide distribution characteristics of the virus according to WHO[11], both genotypes are the most prevalent in Brazil. In a survey developed at the referral hospital in the study, Oliveira[19] found that 77% of HCV patients were infected by genotype 1 and 20% of genotype 3.

The hepatic impairment of the patients is evidenced by the presence of fibrosis of different degrees, besides cirrhosis. Thus, most patients treated had advanced fibrosis (stages F3 or F4). Its severity is generally related to the age and duration of infection[20].

A large proportion (62.4%) of patients had viral load (HCV-RNA) values above 600,000 IU / mL. In the literature studies have demonstrated different relations among degrees of fibrosis and viral load. Although Vieira[21] affirmed a significant correlation between advanced fibrosis and high HCV-RNA indices in the treatment outcome, other studies did not find this correlation[22,23].

This study showed that 11.3% of participants were coinfected with HIV. According Brazilian official data[17] in 2016, among individuals infected by HCV, 9.3% were coinfected with HIV. It is worth emphasizing that this coinfection condition promotes a rapid progression of chronic hepatitis C[24,25].

Studies have shown that chronic hepatitis C patients naïve of treatment are more likely to achieve SVR compared to those that had already treated with other therapies[14,26]. In this study most patients were naïve and they were treated by therapeutic regimens according the Ministry of Health[6], therefore, the predominance of these schemes is proportional to the genotypes and comorbidities present in this study population.

The efficacy of the treatment (greater than 95%) detected in this study corroborates the findings of previous literature, which demonstrated in patients undergoing DAA regimens an SVR with a range of 85% to 97%[6,14]. The results of SVR in relation to the different therapeutic schemes and to the infecting genotype, also

corroborate the findings of other studies[27,28]. There were no associations between the SVR results and the age or sex of the participants.

Among the three patients with HCV genotype 3, treated with a regimen including sofosbuvir, peg alpha-interferon and ribavirin, the SVR rate was 66% (2/3), while one who presented with decompensated cirrhosis and previous treatment did not present SVR. However, a phase 3[29] clinical trial demonstrated SVR of 91% in a setting involving patients with the same clinical characteristics. Perhaps this divergence of results can be explained by the small sample size employed in our study.

For the 50 HCV / HIV coinfected patients, only three did not present SVR after treatment, despite being treatment-naïve for Hepatitis C. Of these, one patient was non-cirrhotic and infected by HCV genotype 3, while the other two were HCV / HIV coinfected, cirrhotic and infected by genotype 1A. Only the former patient was treated for 12 weeks, while the latter two had treatment lasting 24 weeks, according to the current protocol[6].

There is also a significant relationship between a lower rate of SVR, cirrhotic patients and infection by genotype 3 (n = 6/7). Studies have observed that infection with this genotype and the presence of hepatic cirrhosis may be associated with a lower SVR in the treatment of chronic hepatitis C compared to the other genotypes, regardless of the treatment regimen[30,31]. Therefore, in 2015, Brazilian Ministry of Health recommended that chronic HCV patients with decompensated cirrhosis, should have your treatment time extend to 12 to 24 weeks, except for those infected by genotype 3, which did not present a satisfactory response [6].In this line, another change in official guidelines occurred in 2017[30] However, patients with such genotype did not present satisfactory responses. Thus, despite little evidence available in the literature on the efficacy of treatment in patients with genotype 3 with duration of therapy for 24 weeks, in 2017 there was a change in PCDT[30] aimed at improving the response to treatment in this group of patients.

The limitations of this study were inherent to those that involve secondary data, mainly related to the database with information incomplete or mistakenly filled in. Thus, it was not possible to analyze the treatment efficacy of the 717 patients treated at the unit during the study period, since it was only possible to obtain a viral load test result after 12 weeks of treatment in 60% (n=431) of cases. These 431 patients had their data analyzed in full. Nevertheless, the results obtained here may be useful for analysis and management of hepatitis C treatment in populations with a similar profile.

The results of this study have shown the efficacy of the direct action antivirals selected by the Ministry of Health for the treatment of chronic hepatitis C, as stated in the Brazilian Ministry of Health 2015 guidelines[6] and, therefore, these results may contribute to future analysis of these drugs, both in Goiás and in Brazil, and thus improve clinical protocols.

ACKNOWLEDGEMENTS

We are grateful to the Pharmacy staff, especially the Ambulatory Pharmacy, the Reference Hospital of Infectology of Goiás and the State Technical Advisory Committee of Hepatitis C of Goiás.

REFERENCES

1. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: an up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016;22(34):7824-40.

2. World Health Organization - WHO. Hepatitis C. Updated July 2018. Available online: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-c. (accessed on 05 february 2019).

3. Chalupa P, Holub M, Davidová A, Arientová S, Beran O. Immune response in the pathogenesis of hepatitis C virus infection. Epidemiol Mikrobiol Imunol. 2015 Oct;64(4):198-203.

4. Brazil. Ministry of Health. Secretariat of Health Surveillance. General Coordination of Development of Epidemiology in Services. Health Surveillance Guide. Brasília, DF: volume 2 / Ministry of Health - 1. ed. Current, 2017.

5. Ministry of Health (BR). Ministry of Health Surveillance. Department of STD, AIDS and Viral Hepatitis. The technical manual for the diagnosis of viral hepatitis [Internet]. Brasília: Ministry of Health; 2015 [quoted 2017 Nov 25]. 68 p. Available in: http://www.aids.gov.br/pt-br/pub/2015/manual-tecnico-para-o-diagnostico-dashepatites-virais

6. Ministry of Health (BR). Ministry of Health Surveillance. Department of STD, AIDS and Viral Hepatitis. Clinical Protocol and Therapeutic Guidelines for Hepatitis C and Coinfections. Brasília: Ministry of Health; 2015. 101 p.

7. Ministry of Health (BR). Ministry of Health Surveillance. Department of STD, AIDS and Viral Hepatitis. Clinical Protocol and Therapeutic Guidelines for Hepatitis C and Coinfections. Brasília: Ministry of Health; 2011. 106 p.

8. Ministry of Health (BR). Ministry of Health Surveillance. Department of STD, AIDS and Viral Hepatitis. Clinical Protocol and Therapeutic Guidelines for Hepatitis C and Coinfections: management of patients chronically infected by HCV genotype 1 and advanced fibrosis. Brasília: Ministry of Health; 2013. 52 p.

9. American Association for the Study of Liver Diseases (US). Hepatitis C guidance: AASLD-IDSA recommendations of testing, managing, and treating adults with hepatitis C virus. Hepatol. 2015 ago; 62(3): 932-954.

10.Ministry of Health (BR). Department of Epidemiological Surveillance. Viral Hepatitis: Brazil is aware [Internet]. Brasília: Ministry of Health; 2008 [quoted 2017 Nov 25]. 60 p. Available in: http://bvsms.saude.gov.br/bvs/publicacoes/hepatites_virais_brasil_atento_3ed.pdf

11. World Health Organization. Guidelines for the screening and treatment of persons with chronic hepatitis C infection [Internet]. Geneva: World Health Organization; 2016 [quoted 2017 Nov 25]. 140 p. Available in: http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

12. Sirqueira EN. Evaluation of the therapeutic response rates of patients with hepatitis C undergoing therapies with new generation direct acting antivirals: a systematic review. Savior. Monografia [Graduation in Medicine] - Federal University of Bahia; 2016. 48p.

13. Ferreira VL. Free therapies for chronic hepatitis C: systematic review and meta-analysis. Curitiba. Dissertation [Master's Degree in Pharmaceutical Sciences] - Federal University of Paraná; 2016. 121p.

14. Cheinquer HH, Coelho HSM, Aires RS, Quintela ED, Lobato CO, Medeiros Filho JM et al. New direct action antivirals containing regimes to treat patients with hepatitis C chronic infection: first results from a national real-world registry of the Brazilian Hepatology Society. J Hepatol. 2017 abr; 66(1): S508.

15. Teixeira MA. Analysis of the safety and effectiveness of the treatment of chronic hepatitis C with protease inhibitors boceprevir and telaprevir in a reference center. Florianópolis. Dissertation [Master's Degree in Pharmacy] - Federal University of Santa Catarina; 2017. 112 p.

16. Rosa JA. Treatment of patients with chronic viral hepatitis C: experience of the application and monitoring of injectable drugs at Nereu Ramos Hospital, from 2005 to 2008. Florianópolis. Dissertation [Master's Degree in Pharmacy] - Federal University of Santa Catarina; 2009. 136 p.

17. Ministry of Health (BR). Ministry of Health Surveillance. Department of STD, AIDS and Viral Hepatitis. Epidemiological Bulletin: Viral Hepatitis [Internet]. Brasília: Ministry of Health; 2017 [quoted 2017 Nov 25]. 68 p. Available in: https://central3.to.gov.br/arquivo/387533/

18. Brazilian Institute of Geography and Statistics (BR). Demographic Census 2010 [Internet]. Brasília: Brazilian Institute of Geography and Statistics; 2011 [quoted 2017 Nov 25]. 270 p. Available in: https://biblioteca.ibge.gov.br/visualizacao/periodicos/93/cd_2010_caracteristicas_populacao_domicilios.pdf

19. Oliveira TJB. Epidemiological profile of hepatitis C cases in a referral hospital in infectious diseases in the State of Goiás, Brazil. Goiânia. Course Completion Work [Multiprofessional Residency in Infectology] - Secretary of Health of the State of Goiás; 2017. 12 p.

20. Omland LH, Krarup H, Jepsen P, Georgsen J, Harritshoj LH, Riisom K et al. Mortality in patients with chronic and cleared hepatitis C viral infection: nationwide cohort study. J Hepatol. 2010 jul; 53(1): 36-42.

21. Vieira AM, Freire R, Mangualde C, Pinho V, Fernandes AL, Alves F et al. Hepatitis C: casuistry of the consultation of hepatology of a district hospital. J Port Gastrenterol. 2007 may; 14 (1): 134-140.

22. Al-Khurri LE, Al-Khafaji KR, Al-Salihi SA, Alwaysi SA, Al-kayshi RJ. Serum HCV-RNA levels in patients with chronic hepatitis C: correlation with histological features. Arab J Gastroenterol. 2009 mar; 10(1): 10-13.

23. Shahid M, Idrees M, Nasir B, Raja AJ, Raza SM, Amin I et al. Correlation of biochemical markers and HCV RNA titers with fibrosis stages and grades in chronic HCV-3a patients. Eur J Gastroenterol Hepatol. 2014 jul; 26(7): 788-794.

24. Silva ACM, Barone AA. Risk factors for HIV infection in patients with hepatitis C virus Rev Saude Publica. 2006 Feb; 40 (3): 482-488.

25. Strauss E. Hepatitis C. Journal of the Brazilian Society of Tropical Medicine. 2001 jan-fev; 34 (1): 69-82.

26. Hézode C, Fourati S, Chevaliez S, Scoazec G, Soulier A, Varaut A et al. Sofosbuvir-daclatasvir-simeprevir plus ribavirin in direct-acting antiviral-experienced patients with hepatitis C. Clin Infect Dis. 2017 jun; 64(11): 1615-1618.

27. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015 Apr; 61(4):1127-1135.

28. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. LO8: Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: Phase 3 ALLY-1 study. J Hepatol. Elsevier; 2015 Jun 15;62(Supplement 2): S261–S262.

29. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology. 2015 nov; 149(6): 1462-1470.

30. Ministry of Health (BR). Secretariat of Science, Technology and Strategic Inputs. National Commission of Incorporation of Technologies in SUS. Recommendation Report: Extended treatment time HCV - Genotype 3 with Cirrhosis, for 24 weeks. Brasília: Ministry of Health; 2017 [quoted 2017 Nov 25]. 36 p.

31. Callefi LA. Effectiveness and safety of triple therapy with boceprevir or telaprevir in the treatment of chronic hepatitis C genotype 1 in patients attended at referral centers in Brazil. Sao Paulo. Thesis [PhD in Sciences] - University of São Paulo; 2017. 118 p.