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Original Article

National Brazilian survey on the outcomes of hepatitis c retreatment in patients non-responders to direct antiviral agents

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ABSTRACT

Background and aims: Treatment of hepatitis C with direct antiviral agents (DAA) is associated with almost 95% of sustained virological response. However, some patients need retreatment. In Brazil, it should be done according to the Ministry of Health guidelines, frequently updated to include newly available drugs. This study aimed to conduct a national survey about the characteristics and outcomes of retreatment of hepatitis C in previously non-responders to DAAs.

Patients and methods: Institutions from all over the country were invited to participate in a national registry for retreatment, including information about clinical and epidemiological characteristics of the patients, type and outcomes of retreatment regimens. Only patients previously treated with interferon-free regimens were included.

Results: As previous treatments the distribution was: SOF/DCV (56%), SOF/SIM (22%), 3D (11%), SOF/LED (6%) and SOF/RBV (5%). For retreatment the most frequently used drugs were SOF/GP (46%), SOF/DCV (23%) and SOF/VEL (11%). From 159 patients retreated, 132/159 (83%) had complete information in the registry and among them only seven patients were non-responders (SVR of 94.6%). All retreatments were well tolerated, without any serious adverse events or interruptions.

Conclusion: The retreatment of patients previously non-responders to DAAs was associated with high rate of SVR in this sample of Brazilian patients. This finding allows us to conclude that the retreatment options available in the public health system in Brazil are effective and safe and are an important component of the strategy of elimination of hepatitis C in our country.

Introduction

Hepatitis C virus (HCV) infection still affects almost 57 million people globally.[1] Cirrhosis and hepatocellular carcinoma (HCC) can occur in infected patients and were associated with death in approximately 290,000 patients in the year of 2019, mostly in those not submitted to treatment.[2]

Fortunately, the advent of direct antiviral agents (DAAs) heralded a remarkable revolution on the treatment of hepatitis C, leading to very high rates of cure, ranging from 85 to 100% of cases.[3]

However, despite the high rates of sustained virological response (SVR), a considerable number of patients (1%-15%) was not capable to eliminate the virus after an initial treatment even with the interferon-free regimens. The factors associated with treatment failure with DAAs include variables related to adherence, occurrence of resistant variants, presence of advanced grades of fibrosis, drug-drug interactions, and genetic characteristics of the host.[4–6]

The knowledge of the characteristics of patients not responding to treatment with DAAs and the results of retreatment with therapies available for the whole population is of great importance to establish strategies for hepatitis C elimination in our country.

The aim of this study was to conduct a registry of retreatment outcomes in patients previously non-responders to DAA therapy in Brazil.

Patients and methods

Reference centers on hepatitis C treatment from the whole country of Brazil were invited to participate in the National Registry of Hepatitis C Retreatment, coordinated by IBRAFIG (Instituto Brasileiro do Fígado – ibrafig.org.br), during the years of 2020 and 2021.

Centers accepting to participate were asked to fulfill a standardized web-based database with login and password provided by the coordinator center. Data included clinical and laboratory features as well as treatment outcomes of patients retreated for hepatitis C after failing a first interferon-free treatment.

The variables collected in the registry were: sex, age, genotype, grade of fibrosis, HIV coinfection, prior liver transplantation (LT), type and duration of the first treatment, and type and duration of retreatment.

Retreatment was done according to the guidelines established for the Brazilian public system (PCDT - Clinical Protocol for the Treatment of Hepatitis C and Coinfections), that were constantly updated during the years (PCDT, 2017; 2018; 2019),[6] or according to medical decision in the case of private medicine.

Statistical analysis included descriptive data expressed as numbers and percentages for categorical variables and as means and standard deviation for continuous variables.

The study was approved by the Ethical Committee of the Federal University of Sao Paulo, Sao Paulo, Brazil (number 4.199.479).

Results

Twenty centers participated in the study, from the various regions of the country. The centers were: Serviço Municipal de Infectologia de Caxias do Sul, RS (n = 19), Faculdade de Medicina de Ribeirão Preto - USP, SP (n = 21), Universidade Federal de São Paulo, SP (n = 17), Ambulatório de Hepatites Virais de Criciuma, SC (n = 11), Hospital Moinhos de Vento, Porto Alegre, RS (n = 11), Universidade Estadual Paulista Julio de Mesquita Filho, Botucatu, SP (n = 10), Hospital Clementino Fraga Filho, Rio de Janeiro, RJ (n = 9), Universidade Estadual de Campinas, SP (n = 7), Hospital Portugues, Salvador, BA (n = 7), Secretaria Municipal de Saúde de Curitiba, PR (n = 7), Hospital Geral de Bonsucesso, Rio de Janeiro, RJ (n = 6), Universidade Federal do Triângulo Mineiro, Uberaba, MG (n = 6), Universidade de São Paulo, SP (n = 5), Serviço de Atendimento Especializado/SAE hepatites, Canoas, RS (n = 5), Universidade Federal de Sergipe, SE (n = 4), Hospital Nossa Senhora das Graças, Curitiba, PR (n = 3), Fundação de Medicina Tropical do Amazonas, AM (n = 1), Universidade Federal de Minas Gerais, MG (n = 1).

Hence, 159 patients, non-responders to a first treatment with DAAs were included in the registry (70.4% men, mean age of 58.7 ± 9.3 years). Of these, nine (5.7%) had undergone LT and nine (5.7%) were HIV co-infected.

Regarding genotype (GT) distribution, 86 patients were GT1 (54.1%), 66 were GT3 (41.5%), six were GT2 (3.8%) and one was GT4 (0.6%).

The grade of fibrosis was determined by elastography in 73 patients, by clinical and/or image characteristics in 32, by liver biopsy in 25, and by FIB-4 in two patients. Liver fibrosis showed the following distribution: 10 patients were F0 (6.2%), 15 F1 (9.4%), 24 F2 (15.9%), 22 F3 (13.8%) e 87 were cirrhotic (54.7%).

The general characteristics of the patients included for retreatment are shown in Table 1.

The first treatment with DAAs, leading to failure, had the following distribution: sofosbuvir plus daclatasvir (SOF/DCV) in 97 cases (61%), sofosbuvir plus simeprevir (SOF/SIM) in 29 cases (18.2%), veruprevir/ritonavir plus ombitasvir plus dasabuvir (3D combo) in 17 cases (10.7%), sofosbuvir plus ledipasvir (SOF/LED) in 10 cases (6.3%), and sofosbuvir plus ribavirin (SOF/RBV) in six cases (3.8%).

The duration of the first treatment was 12 weeks in 138 patients (86.8%) and 24 weeks in 20 patients (12.6%). Only one patient was treated for eight weeks, with the combination SOF/LED. Seventy-one patients (44.6%) received RBV in the first treatment (Table 2).

Among 159 patients submitted to retreatment and included in the study, 132 had data available concerning SVR and 125 (94.7%) achieved SVR after retreatment.

The type of retreatment more frequently prescribed was SOF plus glecaprevir/pibrentasvir (SOF/GP) combination, prescribed for 69 (52.3%) subjects followed by SOF/DCV in 23 (17.4%), SOF plus velpatasvir (SOF/VEL) in 14 (10.6%) and SOF/LED for 11 (8.3%) patients. Other regimens less frequently prescribed were GP (n = 4), SOF/SIM (n = 5), SOF/VEL/SIM (n = 3), and SOF/VEL/VOX (n=3). Seventy-one (53.7%) subjects also received RBV in association with DAAs. The treatments used in the first and in the retreatment are showed in Table 2.

Table 3 shows the characteristics of patients retreated according to the variables evaluated and SVR associated to type of treatment. All patients treated with triple combination (SOF/GP, SOF/VEL/SIM and SOF/VEL/VOX) responded to retreatment, as well as GT1 non-responders to SOF/SIM treated with SOF/LED (n = 11), and GT1 non-responders to SF/DCV treated with SOF/SIM (n = 5).

Among the seven non-responders, six were male, all of them cirrhotic, five had GT3 and two GT1. None was transplanted or HIV coinfected. Four were treated with SOF/DCV, two with SOF/VEL and one with GP. The small number of

Table 1 – General characteristics of the 159 HCV-patients included in the Brazilian registry for retreatment.

Characteristic	N = 159
Age, years ± SD	58.7 ± 9.3
Sex, n (%)	
Male	112 (70.4)
Female	
Genotype, n (%)	
GT1	86 (54.1)
GT2	6 (3.8).
GT3	66 (41.5)
GT4	1 (0.6)
Grade of fibrosis, n (%)	
F0	10 (6.2)
F1	15 (9.4)
F2	24 (15.9)
F3	22 (13.8)
F4	87 (54.7)
Anti-HIV reactive, n (%)	9 (5.7)
Liver transplant, n (%)	9 (5.7)

HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Table 2 – Drugs used on the first treatment and on retreatment of hepatitis C patients.

First treatment, n (%)	n = 159
SOF/DCV	97 (61.0)
SOF/SIM	29 (18.2)
3D	17 (10.7)
SOF/LED	10 (6.3)
SOF/RBV	6 (3.8)
Retreatment, n (%)	N = 132
SOF/GP	69 (52.3)
SOF/DCV	23 (17.4)
SOF/VEL	14 (10.6)
SOF/LED	11 (8.3)
SOF/SIM	5 (3.8)
GP	4 (3)
SOF/VEL/SIM	3 (2.3)
SOF/VEL/VOX	3 (2.3)

SOF, sofosbuvir; DCV, daclatasvir; SIM, simeprevir; 3D, paritaprevir/ombitasvir/ritonavir plus dasabuvir; LE, Ledipasvir; RBV, ribavirin; GP, glecaprevir plus pibrentasvir; VEL, velpatasvir; SIM, simeprevir; VOX, voxilaprevir.

Table 3 – SVR and characteristics of patients submitted to retreatment according to the type of retreatment.

Type of retreatment	Men, n (%)	Age, years	GT1/non1	Cirrhosis	Ribavirin	SVR
SOF/GP (n = 69)	50 (72.4)	58.6±10.1	34/35	28 (40.5)	34 (49.2)	**100%**
SOF/DCV (n = 23)	13 (56.5)	58.7±11.0	18/5	16 (69.5)	14 (60.8)	**82.6%**
SOF/VEL (n = 14)	11 (78.5)	58.6±9.9	2/12	7 (50)	4/10	**85.7%**
SOF/LED (n = 11)	7 (63.6)	58.5±9.8	11/0	7 (63.6)	7 (63.6)	**100%**
SOF/SIM (n = 5)	3 (60.0)	54.0±8.8	5/0	4 (80)	4 (80)	**100%**
GP (n = 4)	3 (75.0)	59.4±9.8	4/0	1 (25)	0 (0)	**75%**
SOF/VEL/SIM (n = 3)	3 (100)	56.5±8.2	3/0	3 (100)	3 (100)	**100%**
SOF/VEL/VOX (n = 3)	2 (66.6)	61.5±9.7	1/2	2 (66.6)	2 (66.6)	**100%**

GT, genotype; SVR, sustained virological response; SOF, sofosbuvir; DCV, daclatasvir; SIM, simeprevir; 3D, paritaprevir/ombitasvir/ritonavir plus dasabuvir; LE, Ledipasvir; RBV, ribavirin; GP, glecaprevir plus pibrentasvir; VEL, velpatasvir; SIM, simeprevir; VOX, voxilaprevir.

retreatment non-responders did not allow statistical analysis between responders and non-responders.

Adverse events were reported in only 17 patients (12.9%), were of mild intensity and did not require treatment interruption or suspension. The most frequently reported were anemia (n = 5), related to the use of RBV, and pruritus associated or not with rash (n = 2).

Discussion

The prevalence of HCV infection in Brazil is estimated in 0.7%.[7] Since the year of 2015 the country started to count on the possibility to treat HCV-infected patients with interferon-free regimens, based on the combination of DAAs. At the beginning, this type of treatment was offered to the public health system only for patients with advanced fibrosis, but beyond 2017 interferon-free therapies were available to all patients infected with HCV.[8]

Despite the high rates of SVR obtained with DAAs, literature data report 1% to 15% of non-response to a first course interferon-free treatment.[9] A Brazilian study including 3,989 patients treated with several DAAs combinations showed 96% of SVR, therefore resulting in 4% of non-responders in our country.[10] These patients ought to be retreated to achieve the cure of the infection.

In the present study we report the data from a national registry conducted in Brazil, involving the five regions of the country, with information about characteristics of patients submitted to retreatment of hepatitis C who had failed interferon-free regimens and the outcomes of the new treatment.

It was observed that among 159 non-responder patients initially included most were male (70,4%), infected with GT1 (54,1%) and cirrhotic (54,7%). These findings are in accordance with other study that evaluated 172 non-responders to DAAs, comparing them to 5,063 responders.[11] In this study non-responders were also more frequently male and cirrhotic.

It is interesting to note that the vast majority of cirrhotic non-responder patients in our study had been submitted to a first treatment including RBV (71/87, 81.6%). The design of the study, that included only non-responders to a previous treatment, did not allow to analyze the impact of RBV on SVR, but since RBV had been used in most patients we can suggest that its use has not avoided treatment failure in cirrhotic patients, in contrast to other studies.[12]

Regarding the type of first treatment with DAAs, there was a predominance of SOF/DCV combination, used in 61% of the cases. This combination, when administered to 152 patients for 12 weeks, was associated with 9% non-response in naïve patients and 14% in those previously treated with interferon.[13] When the same combination was evaluated for 24 weeks of treatment, in a study of 211 patients infected by genotypes 1, 2, or 3, SVR occurred in 98% of the GT1 patients, 92% of GT2, and 89% of GT3, inducing a non-negligible number of non-responders, mainly in GT3 positive patients (11%).[14] Different rates of treatment failure with other combinations used as first treatment (SOF/SIM, 3D, SOF/LED and SOF/RBV) were reported, ranging from 3 to 21%.[15-18]

The global SVR rate in the present study for retreatment was 94.7%. The most frequent type of retreatment used, regardless of genotype, was the SOF/GP combination, nowadays the first line interferon-free regimen recommended for retreatment of HCV in Brazil.[8] This type of treatment is based on the combination of three drugs that are directed to different steps of viral replication, similar to the combination SOF/VEL/voxilaprevir, the most internationally used combination for treatment failure after DAA treatment.[19] There are few studies evaluating SOF/GP combination.[20] However, this regimen is included in international guidelines for treatment of patients who failed after various types of treatment and with complex resistant variants.[21]

The combination SOF/DCV, reported in 17.4% of cases, was prescribed to GT1 patients non-responders to SOF/SIM, as well as in GT3 non-responders to the combination SOF/NS5A for 12 weeks in whom the treatment was repeated with the same combination for 24 weeks, in association with RBV, according to the 2018 Brazilian guidelines.[8] Some studies had demonstrated the efficacy of the retreatment of GT3 patients failing SOF/DCV with the same therapy for 24 weeks and with the addition of RBV.[22] The lower rate of response to SOF/DCV retreatment obtained in the present study (SVR 82.6%) can be attributed to the presence of almost 70% of cirrhotic patients in this group, corresponding to patients with more advanced grades of fibrosis that were treated at the beginning of DAA era in Brazil.

The present study has some limitations. The type of treatment was not uniform in all reference centers since the guidelines were updated frequently. Furthermore, the treatment could be different from the national guidelines for public health in the case of private practice. Another limitation

was the small number of non-responders to retreatment, not allowing for identification of factors associated with non-response. However, this was inherent to the excellent rates of response to the various types of therapies available for retreating the patients.

In conclusion, patients retreated for hepatitis C after a failure to previous DAA therapies can achieve high rates of response (94.7%) with the regimens of therapy recommended in current national guidelines, favoring the Brazilian Hepatitis C Elimination Plan [7] and leaving no one behind.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Polaris Observatory HCV Collaborators. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. Lancet Gastroenterol Hepatol. 2022;7:396–415.
2. World Health Organization. Hepatitis C key facts. July 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c Accessed in 24 Feb 2022.
3. Stanciu C, Muzica CM, Girleanu I, et al. An update on direct antiviral agents for the treatment of hepatitis C. Expert Opin Pharmacother. 2021;22:1729–41.
4. Costilla V, Mathur N, Gutierrez JA. Mechanisms of virologic failure with direct-acting antivirals in Hepatitis C and strategies for retreatment. Clin Liver Dis. 2015;19:641–56.
5. Shousha HI, Saad Y, Saleh D, et al. Simple predictors of nonresponse to direct-acting antivirals in chronic hepatitis C patients. Eur J Gastroenterol Hepatol. 2020;32:1017–22.
6. Sarrazin C. The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hepatol. 2016;64:486–504.
7. Benzaken AS, Girade R, Catapan E, et al. Hepatitis C disease burden and strategies for elimination by 2030 in Brazil. A mathematical modeling approach. Braz J Infect Dis. 2019;23:182–90.
8. Ministério da Saúde, Brazil. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite C e Co-infecções. http://www.aids.gov.br/pt-br/pub/2017/protocolo-clinico-e-diretrizes-terapeuticas-para-hepatite-c-e-coinfeccoes. (Accessed in 2 Mar 2022).
9. Pawlotsky JM. Retreatment of hepatitis C virus-infected patients with direct-acting antiviral failures. Semin Liver Dis. 2019;39:354–68.
[10]. Lobato CMO, Codes L, Silva GF, et al. Direct antiviral therapy for treatment of hepatitis C: a real-world study from Brazil. Ann Hepatol. 2019;18:849–54.
[11]. Kassas ME, Alboraie M, Badry ME, et al. Retreatment of chronic hepatitis C patients who failed previous therapy with directly acting antivirals: A multicenter study. Int J Infect Dis. 2020;96:367–70.
12. Buti M, Riveiro-Barciela M, Esteban R. Management of direct-acting antiviral agent failures. J Hepatol. 2015;63:1511–22.
13. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase 3 study. Hepatology. 2015;61:1127–35.
14. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370:211–21.
15. Ferenci P, Bernstein D, Lalezari J, et al. PEARL-III study ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370:1983–92.
16. Lawitz E, Matusow G, DeJesus E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: a phase 3 study (OPTIMIST-2). Hepatology. 2016;64:360–9.
17. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med. 2014;370:222–32.
18. Jang ES, Kim K, Kim YS, et al. Real-life effectiveness and safety of sofosbuvir-based therapy in genotype 2 chronic hepatitis C patients in South Korea, with emphasis on the ribavirin dose. Gut Liver. 2020;14:775–82.
19. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med. 2017;376:2134–46.
20. Martin MT, Patel S, Kulik L, Chan C. Glecaprevir/pibrentasvir + sofosbuvir + ribavirin offers high cure rate for hepatitis C virus retreatment in real-world settings. J Hepatol. 2021;75:251–4.
21. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. J Hepatol. 2020;73:1170–218.
22. Lionetti R, Piccolo P, Lenci I, Siciliano M, Visco-Comandini U, De Santis A. Daclatasvir, sofosbuvir with or without ribavirin for 24 weeks in hepatitis C genotype 3 cirrhosis: a real-life study. Ann Hepatol. 2017;18:434–8.