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ORIGINAL PAPER

Safety and Efficacy of Direct-Acting Antivirals in the Treatment of Hepatitis C in Transplant Recipients

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ABSTRACT

Objectives: To perform a comparative analysis, evaluating the efficacy and safety profiles discerningly in a cohort of liver transplant recipients and non-liver transplant recipients infected with hepatitis C and treated with direct-acting antivirals (DAA). **Methods:** This study is a real-life retrospective, observational analysis of individuals with chronic hepatitis C who were treated with DAA. During this period, 990 patients diagnosed with hepatitis C received DAA therapy, 165 of whom had undergone liver transplantation. Exclusion criteria included HIV-positive patients and those without a sustained virologic response (SVR) assessment. **Results:** The SVR was 95.8 and 95.6% in liver transplant recipients and nonrecipients, respectively (p = 0.94). The majority of patients were treated with sofosbuvir (SOF) in combination with daclatasvir, simeprevir, and ledipasvir. Ribavirin (RBV) was co-administered to 43.2% of patients, resulting in no improvement in SVR and an increase in adverse events. Treatment of genotype 2 patients with SOF and RBV and genotype 3 patients with SOF, interferon, and RBV for only 12 weeks showed suboptimal efficacy (89.5 and 83.3%), respectively. **Conclusion:** The treatment of hepatitis C with DAA is as effective and safe in liver transplant patients as in non-liver transplant patients, and the prescription of RBV is inadvisable due to the increase in serious adverse events without improvement in SVR.

Descriptors: Hepatitis C; Liver Transplantation; Biological Treatment; Direct-Acting Antivirals.

Segurança e Eficácia dos Antivirais de Ação Direta no Tratamento da Hepatite C em Transplantados

RESUMO

Objetivos: Realizar uma análise comparativa, avaliando cuidadosamente os perfis de eficácia e segurança em uma coorte de receptores de transplante de fígado e não receptores de transplante de fígado infectados com hepatite C e tratados com antivirais de ação direta. **Métodos:** Este estudo é uma análise observacional retrospectiva da vida real de indivíduos com hepatite C crônica que foram tratados com antivirais de ação direta. Durante esse período, 990 pacientes diagnosticados com hepatite C receberam terapia com antivirais de ação direta, 165 dos quais foram submetidos a transplante de fígado. Os critérios de exclusão incluíram pacientes HIV positivos e aqueles sem avaliação de resposta virológica sustentada. **Resultados:** A resposta virológica sustentada foi de 95,8 e 95,6% em receptores e não receptores de transplante de fígado, respectivamente (p = 0,94). A maioria dos pacientes foi tratada com sofosbuvir (SOF) em combinação com daclatasvir, simeprevir e ledipasvir. A ribavirina (RBV) foi administrada a 43,2% dos pacientes, resultando em ausência de melhora na resposta virológica sustentada e aumento de eventos adversos. O tratamento de pacientes do genótipo 2 com SOF e RBV e de pacientes do genótipo 3 com SOF, interferon e RBV por apenas 12 semanas mostrou eficácia subótima (89,5 e 83,3%), respectivamente. **Conclusão:** O tratamento da hepatite C com antivirais de ação direta é tão eficaz e

seguro em pacientes transplantados hepáticos quanto em pacientes não transplantados hepáticos, e a prescrição de RBV é desaconselhável devido ao aumento de eventos adversos graves sem melhora da resposta virológica sustentada.

Descritores: Hepatite C; Transplante de Fígado; Tratamento Biológico; Antivirais de Ação Direta.

INTRODUCTION

Hepatitis C, caused by the blood-borne hepatitis C virus (HCV), manifests as a chronic pathogenic condition with potential progression to liver fibrosis, cirrhosis hepatocellular carcinoma (HCC), and the need for liver transplantation.[1,2] A novel treatment regimen with direct-acting antivirals (DAA) has been able to achieve a sustained response or complete viral elimination in more than 95% of users, regardless of liver disease severity and viral genotype, resulting in high rates of clinical cure and reducing the need for retransplantation.[1,2] Previous HCV treatment consisted of a course of weekly subcutaneous pegylated interferon (PEG-IFN) supplemented by daily oral ribavirin (RBV) for 24 to 48 weeks, depending on genotype. This intervention was effective in approximately 55% of patients, with a significant incidence of serious side effects, such as hematologic toxicity, bacterial infections, and graft rejection, leading to premature treatment discontinuation in approximately 30% of cases.[3]

First-generation protease inhibitors, such as telaprevir and boceprevir, were the first drugs tested for the treatment of recurrent HCV infection after liver transplantation.[4]

The combination of these inhibitors with PEG-IFN and RBV significantly improved the sustained virologic response (SVR), with SVR rates ranging from 50 to 65% in genotype 1 HCV-infected recipients. However, this regimen is associated with concerns about compromised safety profiles and increased drug-drug interactions. Within the Brazilian regulatory framework, these drugs are currently not approved for use in liver transplant recipients.[5]

Prior to the advent of DAA, liver transplantation in hepatitis C patients was associated with higher mortality and graft loss than other liver transplant indications.[6,7]

A study conducted by the Polaris Observatory HCV Collaborators estimated that there would be approximately 56.8 million HCV infections worldwide in early 2020, which represents a deviation from the expected trajectory towards global elimination of viral hepatitis by 2030.[6,9] Only 12.9 million individuals within this population have been officially diagnosed.[9] If the current rate of DAA treatment remains below 1 million individuals per year, it is anticipated that the number of deaths stemming from liver disease will expected to increase. HCV-related end-stage liver disease and HCC are the main indications for liver transplantation in Western countries.[10,11]

Second-generation DAA, available in Brazil through a public access program since October 2015, represent a significant advance in addressing the challenges posed by individuals resistant to conventional treatments, mainly due to their increased antiviral efficacy and favorable tolerability profile, especially in the context of IFN-free combinations.[12]

Within the current literature, there is a paucity of data regarding the impact of DAA on improving survival outcomes in liver transplant recipients, particularly when compared to a control group, with a focus on the treatment course and pretreatment clinical and laboratory data. As a preeminent liver transplant center, particularly renowned in Latin America, our institution has accumulated decades of patient data following this surgical procedure. Therefore, the aim of this study was to comparatively evaluate the epidemiology, effectiveness and safety of DAA treatment in the hepatitis C liver transplantation group (LTG) and non-LTG (NLTG).

METHODS

Study design

This study was a real-life, retrospective, observational research of individuals with chronic hepatitis C infection who were treated with DAA from October 2015 to December 2023.

Study population

During the study period, 1,523 patients with hepatitis C were treated with DAA. Patients were excluded if they tested HIV-positive or received a renal transplant. Those without an assessment of SVR, defined as polymerase chain reaction (PCR)-RNA testing at least 12 weeks after cessation of treatment, were excluded from the treatment analysis but were included in the epidemiologic analysis.

Data collection

The extracted data were recorded online. Assessment sheets for the patients treated were recorded during the consultations. In cases where prior data were required or the form could not be completed during the consultation, the patient's chart was reviewed to ensure thorough data collection and confirmation. Adverse events of treatment were mostly collected from the patient's chart and from notifications from the pharmacy department for each medication dispensing return.

Data assessment

Treatment data consisted of demographic data (age, sex, weight, height, and education level), clinical data (chronic diseases, medications used, and epidemiology of HCV exposure), and pre-treatment liver disease staging data (presence of cirrhosis, liver biopsy, elastography, aspartate transaminase (AST) to platelet ratio index, and fibrosis-4 index). If cirrhosis was present, the Child-Pugh-Turcotte and Model for End-Stage Liver Disease (MELD) scores were used before and after treatment. Pre-treatment laboratory data, such as AST, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin, prothrombin time test (PTT)/international normalized ratio (INR), total bilirubin, serum creatinine, platelet count, HBsAg, and anti-HIV 1+2, were also obtained. For all patients, HCV genotyping (PCR-RNA for HCV pretreatment and at least 12 weeks after the end of treatment, HCV genotype), treatment data (prescription date, drugs and dosage, use of RBV and dose per kilogram of body weight, duration of treatment in weeks, use of treatment prior to current therapy and medications used, adverse events during treatment), and study outcomes (cure if SVR was present, death, treatment discontinuation, loss to follow-up) were extracted for all patients. Treatment failure was defined as a composite outcome of PCR-RNA HCV positivity at any time after treatment, discontinuation of treatment for any reason, and death during treatment.

Serious adverse events (SAE) were defined as anemia with a decrease of 3 g/dL or greater, life-threatening events, and the need for hemodialysis during treatment. Deaths were analyzed separately from SAE.

Statistical analysis

The initial phase of analysis focused on demographic data, with continuous variables presented as means and standard deviations, while categorical variables were expressed as proportions. To handle missing data, we used an available-case analysis (ACA) approach, based on the available information for each category without imputation. For continuous variables, we used unpaired *t*-tests after checking the assumptions of normal data distribution. In cases where the data did not meet normality assumptions, the Mann-Whitney test was used as an alternative. Univariable analysis included the use of chi-square and Fisher's tests for categorical variables as appropriate, with calculation of odds ratios and 95% confidence intervals for SVR assessment. Statistical tests were two-sided, and a two-tailed $p < 0.05$ indicated statistical significance. Electronic forms facilitated data collection to create a comprehensive database, which was subsequently imported into the statistical analysis software Jamovi and R.

Ethical considerations

This work was approved by the Hospital Universitário Walter Cantídio, Universidade Federal do Ceará ethics committee following the guidelines for clinical research with human beings of Helsinki and Istanbul.[10, 11]

RESULTS

In our cohort of 1,523 treated hepatitis C patients, 990 individuals were assessed for SVR, of whom 165 patients had previously undergone LTG and 825 patients were designated as NLTG recipients. Comparative analysis revealed significant differences in the epidemiologic profiles between the LTG and NLTG groups. Comparing the LTG and NLTG, we found that the transplanted patients had a higher proportion of males, older individuals, and a higher hepatitis C viral load compared to the NLTG group. On the other hand, NLTG patients had a significantly higher proportion of subjects with cirrhosis compared to LTG. The LTG and NLTG groups were similar in terms of genotype distribution and BMI (Table 1). Detailed descriptions of the epidemiologic characteristics of patients stratified into LTG and NLTG are presented in Table 1.

The average time between LTG and the start of treatment for hepatitis C was 34 months. The group of transplant patients is made up of those who underwent liver transplantation and received treatment with DAA, with treatment carried out both before and after liver transplantation. In contrast, the NLTG group exclusively includes those treated with DAA for hepatitis C without any history of liver transplantation, excluding patients who received treatment before undergoing liver transplantation.

Table 1. Epidemiological and virological characteristics of patients with hepatitis C treated with direct-acting antiviral drugs.

	LTG (n = 165)	NLTG (n = 825)	*p*-value
Age at treatment (years), median	61 (56-67)	57 (49-64)	< 0.001
Sex, n (%)			< 0.001
Male	118 (71.5)	468 (56.7)	
Female	47 (28.5)	358 (43.3)	
Body mass index, median	25.3 (23.7-27.0)	26.2 (23.4-29.9)	0.378
Naïve, n (%)	84 (50.9)	720 (87.3)	< 0.001
Cirrhotic patients, n (%)	12 (7.3)	418 (50.6)	< 0.001
Child-Pugh-Turcotte score			
A	5 (17.2)	325 (69.1)	< 0.001
B	4 (13.8)	50 (10.6)	0.596
C	0 (0.0)	5 (0.8)	1
Meld, median	18.0 (14.0-20.0)	9.0 (7.0-12.0)	1
Genotype, n			
1a	32	22	
1b	83	346	
1	122	389	
2	4	21	
3	52	195	
Pre-treatment viral load, median	1038044 (355874.8-3324491)	631818 (196607-1849501)	< 0.001

Source: Elaborated by the authors. *p*-value indicating the probability that the observed results are due to chance, thus determining the statistical significance of the study.

Regarding treatment history, the NLTG had a significantly higher proportion of treatment-naïve patients compared to the LTG, with 87.3% (n = 720) and 50.9% (n = 84), respectively ($p < 0.001$). None of the patients in this study had been previously treated with DAA.

The overall SVR rate among patients was 96%, which was comparable between LTG and NLTG patients ($p = 0.94$). Detailed information on the treatments administered and their corresponding SVR rates is shown in Table 2.

Table 2. Type of treatment hepatitis C and SVR.

Treatment	n	SVR n (%)	Failure n (%)	*p*-value
SOF+DAC+RBV	336	323 (96.1)	13 (3.9)	
SOF+DAC	257	244 (94.9)	13 (5.1)	
SOF+SIM	133	132 (92.2)	1 (7.8)	
SOF+SIM+RBV	27	26 (96.3)	1 (3.7)	
SOF+LED	67	64 (95.5)	3 (4.5)	
SOF+LED+RBV	1	1 (100.0)	0 (0.0)	
3D	59	59 (100.0)	0 (0.0)	
3D+RBV	12	8 (66.7)	3 (33.3)	
SOF+VEL	46	45 (97.8)	1 (2.2)	
SOF+VEL+RBV	4	4 (100.0)	0 (0.0)	
INF+SOF+RBV	6	5 (83.3)	1 (16.7)	
SOF+RBV	19	17 (89.5)	2 (10.5)	
GLECA+PIB	5	4 (80.0)	1 (20.0)	
Genotype				
1	697	678 (97,2)	19 (2,8)	0.0007
2	24	21 (88.0)	3 (12.0)	
3	240	222 (92,5)	18 (7,5)	
With RBV	417	394 (94.5)	23 (5.5)	0.11
Without RBV	557	539 (96.8)	18 (3.2)	
Treatment duration (weeks)				
12	718	687 (95.7)	31 (4.3)	0.99
24	82	79 (96.3)	3 (3.7)	
METAVIR				
F0, F1, F2	247	243 (98.4)	4 (1.6)	0.01
F3, F4	375	352 (93.9)	23 (6.1)	

Source: Elaborated by the authors. *p*-value indicates the probability that the observed results are due to chance, thus determining the statistical significance of the study. 3D = ombitasvir+veruprevir+ritonavir+dasabuvir; GLECA = glecaprevir; LED = ledispavir; PIB, pibrentasvir; VEL, velpastavir.

Table 3. Treatment hepatitis C and SVR in LTG e non-LTG.

	LTG	SVR n (%)	NLTG	SVR n (%)	*p*-valor
Genotype					
1	108	104 (96.3)	589	574 (97.5)	0.72
2	3	2 (66.6)	21	19 (90.5)	0.97
3	44	42 (95.5)	195	180 (92.3)	0.68
With RBV	62	60 (96.7)	320	302 (94.3)	0.64
Without RBV	56	55 (98.2)	500	485 (97.0)	0.92
Treatment duration (weeks)					
12	148	141 (95.2)	570	546 (95.7)	0.96
24	7	7 (100.0)	75	72 (96.0)	0.9
METAVIR					
F0, F1, F2, F3	101	97 (96.0)	339	335 (98.8)	0.15
F4	10	9 (90.0)	418	391 (93.5)	0.84

Source: Elaborated by the authors. *p*-value indicates the probability that the observed results are due to chance, thus determining the statistical significance of the study.

RBV was added to the treatment regimen in 417 out of 974 patients (43%), more frequently in LTG recipients (63.4%, 97/153) compared to NLTG patients (38.7%, 328/847). The median dose of RBV per kg of body weight used was 11.65 mg/kg/day (Δ9.33-14.9) in LTG recipients and 10.40 mg/kg/day (Δ7.9-11.9) in NLTG patients.

In the analysis of SAE, a higher incidence was observed in LTG compared to NLTG. The incidence of deaths during the treatment period was minimal and comparable between the two groups, as shown in Table 4. There were three deaths in the LTG group and six in the NLTG group (Table 4). The causes of death among the patients in the LTG group included bacterial sepsis (n = 1), recurrence of HCC (n = 1), and fungal infection (n = 1). In the NLTG group the causes of death were upper gastrointestinal bleeding (n = 2), sepsis (n = 1), and unknown causes (n = 4).

Table 4. SVR and SAE.

Treatment	n	SAE (%)	*p*-value	Death (%)	*p*-value
LTG	165	19 (11.5)	< 0.001	3 (1.8)	0.5
NLTG	825	28 (3.4)		7 (0.8)	
Total	990	47 (4.7)		10 (1.0)	

Source: Elaborated by the authors. *p*-value indicates the probability that the observed results are due to chance, thus determining the statistical significance of the study.

In the LTG group, anemia characterized by a decrease of more than 3 g of hemoglobin was the most common serious adverse event, occurring in 14 patients, all on the RBV regimen. Two patients with non-dialysis-related chronic renal failure progressed to the point of requiring dialysis during the course of treatment. In addition, one patient experienced an episode of appendicitis while on treatment.

Importantly, no cases of significant rejection were observed in liver transplant recipients during the course of hepatitis C treatment with DAA. Three patients experienced mild rejection characterized by transient elevation of liver enzymes and resolution after increased immunosuppression.

DISCUSSION

Treatment of HCV with SVR is a major goal, and results have long been hampered by the poor efficacy and high toxicity of PEG/RBV treatment, even in combination with first-generation protease inhibitors.[4] Prior to 2015, we treated hepatitis C with IFN and RBV for 48 weeks. Only 70% were able to complete the treatment due to adverse events, with only 55% SVR according to the intention-to-treat analysis.[3]

Although the LTG and NLTG groups are heterogeneous in terms of age, viral load, degree of fibrosis and liver function, this did not affect the overall response to treatment with DAA medications. Prior to the advent of DAA medications, chronic hepatitis due to hepatitis C was almost ubiquitous in liver transplant recipients. Within 5 years of transplantation, approximately one-third of patients would progress to cirrhosis, often leading to graft failure.[12,13] The European Association for the Study of the Liver (EASL) recommends prompt treatment for patients with decompensated cirrhosis (Child-Pugh B or C) who are

not yet listed for liver transplantation and do not have additional health conditions that could compromise their prognosis. Patients with decompensated cirrhosis (Child-Pugh B or C) and without HCC awaiting liver transplantation, with a MELD score below 18-20 should be treated prior to transplantation. None of the cirrhotic patients treated in this study had a MELD greater than 20 points.[14]

This finding was confirmed by the Brazilian multicenter study, which changed the policy of the Brazilian Ministry of Health. Currently, the treatment of hepatitis C does not require genotyping prior to treatment, and the use of SOF and daclatasvir (DAC) for 12 weeks is recommended for non-cirrhotic and compensated cirrhotic patients. For patients with decompensated cirrhosis, Child-Pugh B and C treatment with SOF and RBV is given for 48 weeks.[15, 16]

This is due to the small number of genotype 3 patients in our cohort who underwent the 24-week treatment regimen (n = 2), which limited our ability to draw conclusive associations. In this study, the genotype with the lowest SVR was genotype 2. This may be explained by the fact that the recommended treatment for these patients in Brazil was 12 weeks of SOF and RBV.[17]

This study did not influence the choice of treatment for hepatitis C. The Ministry of Health initially made only SOF, DAC, and simeprevir (SIM) available, justifying the large number of patients treated with these drugs. All regimens evaluated in large numbers of patients showed SVR rates above 90%, suggesting that availability and cost may be the criteria for treatment choice.[16,18]

With adequate use of DAA, 95% of the included patients were considered cured, and there was no difference between the patients who underwent liver transplantation and those who did not, suggesting that DAA therapy is effective for different stages of liver disease. A relatively smaller number of patients who underwent liver transplantation were treatment-naïve when they first arrived at the treatment center; however, most of these patients had never been treated with a DAA, highlighting the marked importance of these novel drug therapies in disease progression. An outline of potential treatment options for naïve patients examines the most potent DAA for this group, again demonstrating that prior treatment may lead to different outcomes, which was not addressed in this study.[19]

Although DAA are much safer drugs, the results of this study document that SAE are not as rare and are often associated with RBV use. SAE were more frequent in the LTG group compared to the NLTG group and were associated with RBV use. These results are consistent with other authors.[14] The addition of RBV to the treatment of hepatitis C with DAA was associated with adverse events that did not improve the SVR rate and was discouraged by the results of this study. Another uncontrolled Brazilian study evaluating the treatment of hepatitis C in liver transplant recipients documented SVR (97.6%) in 84 enrolled patients. Few SAE cases were reported. RBV was used in only 8.2% of patients.[20]

In Child-Pugh B and C cirrhotic patients with MELD ≥ 20, although hepatitis C treatment with DAA can be performed, the chance of cure is significantly lower than after liver transplantation. Therefore, the timing of treatment must be individualized, depending on the estimated time to liver transplantation. In cases where the waiting time on the transplant list exceeds 6 months, patients falling into the above category should be treated before transplantation, depending on local routines.[14] DAA after LTG treatment can eradicate infection and normalize liver function tests in the majority of treated patients. Improvement in long-term graft and patient outcomes can be expected. DAA treatment of patients with liver failure awaiting LTG eliminates infection and is associated with an improvement in liver function in the majority of treated patients. The majority still require transplantation, although some may improve sufficiently and rapidly enough to be removed from the LTG waiting list.[21] Rejection was not a major complication in the treatment of hepatitis C in liver transplant patients in this study, confirming the findings of other studies.[22]

Although the COVID-19 pandemic may have affected the plan to eliminate hepatitis C in Brazil, the availability of free drugs for every hepatitis C patient and the results of this study confirm that the effectiveness of hepatitis C treatment within the range predicted by the Brazilian government, both in LTG and in NLTG.[23]

CONCLUSION

Treatment of hepatitis C with DAA is as effective and safe in liver transplant patients as in non-liver transplant patients, and the prescription of RBV is not recommended because of the increase in SAE without improvement in SVR.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Hyppolito EB, Ramos Júnior AN; **Conception and design:** Hyppolito EB, Ramos Júnior AN; **Data acquisition:** Pereira KB, Linhares LMC, Araújo Filho AH, Viana CFG, Rocha TDS, Lima CA; **Data analysis and interpretation:** Hyppolito EB, Ramos Júnior AN, Ferreira AF, Pires Neto RJ, Garcia JHP; **Article writing:** Hyppolito EB, Teixeira LP, Marques LMS, Alencar VB; **Critical revision:** Hyppolito EB, Ramos Júnior AN, Pires Neto RJ, Garcia JHP; **Final approval:** Hyppolito EB.

DATA AVAILABILITY STATEMENT

The data is available at https://redcap.huwc.ufc.br/.

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REFERENCES

1. Pawlotsky JM, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, et al. EASL recommendations on treatment of hepatitis C: final update of the series. J Hepatol, 2020; 73(5): 1170-1218. https://doi.org/10.1016/j.jhep.2020.08.018
2. Gane EJ, Portmann BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, et al. Longterm outcome of hepatitis C infection after liver transplantation. N Engl J Med, 1996; 334: 815-821. https://doi.org/10.1056/nejm199603283341302
3. Garcia JHP, Araujo Filho AH, Braga LLBC, Viana CFG, Rocha TDS, Pereira KB. Pegylated interferon and ribavirin for treatment of recurrent hepatitis C after liver transplantation: a single-liver transplant center experience in Brazil. Arq Gastroenterol, 2015; 52: 216-21. https://doi.org/10.1590/S0004-28032015000300012
4. Burton JR, O'Leary JG, Verna EC, Saxena V, Dodge JL, Stravitz RT, et al. A US multicenter study of hepatitis C treatment of liver transplant recipients with protease-inhibitor triple therapy. J Hepatol, 2014; 61: 508-14. https://doi.org/10.1016/j.jhep.2014.04.037
5. Lobato CMO, Balassiano N, Hyppolito EB, Sanchez-Lermen RLP, Signorelli IV, Nicacio MYT, et al. Effectiveness of first-wave protease inhibitors in hepatitis C virus genotype 1 infection: a multicenter study in Brazil. Rev Soc Bras Med Trop, 2018; 51:14-20. https://doi.org/10.1590/0037-8682-0279-2017
6. Wiesner RH, Sorrell MF, Villamil FG, Balan V, Berenguer MC, Brown, RS. Report of the First International Liver Transplantation Society Expert Panel Consensus Conference on Liver Transplantation and Hepatitis C. Liver Transpl, 2003; 9: S1-9. https://doi.org/10.1053/jlts.2003.50268
7. Berenguer MC. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. J Hepatol, 2008; 49: 274-87. https://doi.org/10.1016/j.jhep.2008.05.002
8. D'Ambrosio R, Degasperi E, Colombo MG, Aghemo A. Direct-acting antivirals: the endgame for hepatitis C? Curr Opin Virol, 2017; 24: 31-7. https://doi.org/10.1016/j.coviro.2017.03.017
9. Blach S, Terrault NA, Tacke F, Gamkrelidze I, Craxi A, Tanaka J, et al. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. Lancet Gastroenterol Hepatol 2022; 7(5): 396-415. https://doi.org/10.1016/S2468-1253(21)00472-6
10. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA, 2013; 310(20): 2191-4. https://doi.org/10.1001/jama.2013.281053
11. Abboud OI, Abbud-Filho M, Abdramanov K, Abdulla S, Abraham GP, Abueva AV, et al. The declaration of Istanbul on organ trafficking and transplant tourism. Clin J Am Soc Nephrol, 2008; 3:1227-31. https://doi.org/10.2215/CJN.03320708
12. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology, 2002; 122: 889-6. https://doi.org/10.1053/gast.2002.32418
13. Gane EJ. The natural history of recurrent hepatitis C and what influences this. Liver Transpl, 2008; 14Suppl 2: S36-S44. https://doi.org/10.1002/lt.21646

14. European Association for the Study of the Liver. EASL Practice Guidelines. EASL recommendations on treatment of hepatitis C: final update of the series. J Hepatol, 2020; 73(5):1170-1218. https://doi.org/10.1016/j.jhep.2020.08.018

15. Lobato C, Codes L, Silva G, Souza A, Coelho H, Pedroso M, et al. Direct antiviral therapy for treatment of hepatitis C: a real-world study from Brazil. Ann Hepatol, 2019;18(6): 849-54. https://doi.org/10.1016/j.aohep.2019.08.001

16. Brasil. Ministério da Saúde. Brasília (DF): MS; 2015.

17. Huang JF, Huang CF, Yeh ML, Dai CY, Yu ML, Chuang WL, et al. Updates in the management and treatment of HCV genotype 3, what are the remaining challenges? Expert Rev Anti Infect Ther, 2018; 16: 907-12. https://doi.org/10.1080/14787210.2018.1544492

18. Brasil. Ministério da Saúde. Protocolo clínico e guia terapêutico da hepatite C e coinfecções. Brasília (DF): MS; 2020.

19. Ayoub WS, Tran TT. Regimens for the hepatitis C treatment-naive patient. Clin Liver Dis, 2015; 19(4): 619-27. https://doi.org/10.1016/j.cld.2015.06.003

20. Silva EU, Batista AD, Lopes EP de A, Filgueira NA, de Carvalho BT, Santos JC, et al. A real-life study on the impact of direct-acting antivirals in the treatment of chronic hepatitis C in liver transplant recipients at two university centers in Northeastern Brazil. Rev Inst Med trop S Paulo, 2021; 63: e6. https://doi.org/10.1590/S1678-9946202163006

21. Mutimer D. Pre- and post-transplant treatment of viral hepatitis C. Dig Dis, 2017; 35(4): 347-50. https://doi.org/10.1159/000456586

22. Booth IA, Clark JE, LaMattina JC, Barth RN, Haririan A, Ravichandran BR. The impact of treatment delay on hepatitis C liver transplant outcomes. J Pharm Pract, 2023; 36(2): 264-70. https://doi.org/10.1177/08971900211034261

23. Brasil. Ministério da Saúde. Plano de eliminação da hepatite C no Brasil. Brasília (DF): MS; 2018.