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Efficacy and Safety of Ledispavir/Sofosbuvir with or without Ribavirin in patients with Decompensated Liver Cirrhosis and Hepatitis C Infection: a Cohort Study

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ABSTRACT

Background & Aims: Ledipasvir/Sofosbuvir (LDV/SOF) with or without Ribavirin (RBV) has shown good results in terms of efficacy and safety in clinical trials in advanced liver cirrhosis, but real-life data are still needed in order to confirm this profile. We investigated the efficacy and safety of LDV/SOF in a large Romanian population with liver cirrhosis and genotype 1b hepatitis C virus (HCV).

Methods: We analyzed a multicentric retrospective cohort enrolling 349 patients with decompensated liver cirrhosis due to HCV who received LDV/SOF±RBV 12/24 weeks (301/48). Patients were included between 2017-2018, all with genotype 1b. Main inclusion criteria were liver cirrhosis and detectable HCV RNA. The cases were followed-up monthly during therapy and 12 weeks after the end of therapy.

Results: The cohort included 60% females with a median age of 61, 16% interferon (IFN) pre-treated, 53% with comorbidities, 40/53/7 % with Child Pugh A/B/C, 4% with virus B co-infection and 8% with previously treated hepatocellular carcinoma. Mean initial MELD score was 11.92 (6.82÷ 24.5). Six patients were lost during follow-up. Sustained virologic response (SVR) in intention-to-treat was reported in 85.1%. Predictive factors of SVR in decompensated cirrhosis were female gender (p=0.01), advanced age (p<0.001), lower bilirubin levels (p=0.002) and lower CTP score (p=0.02). In patients with CTP score B or C low bilirubin levels (p=0.003), low INR (p<0.001), increased platelet count (p=0.04), low CTP score (p<0.001), lack of encephalopathy (p=0.02), serum albumin >3.5g/dl (p=0.002) predicted improvement of liver function. Serious adverse events were reported in 16/349 (4.6%), most of them due to severe liver decompensation (9/16).

Conclusions: LDV/SOF±RBV proved to be highly efficient in our difficult to treat population with 85.1% SVR.

Key words: ledipasvir/sofosbuvir – ribavirin – liver cirrhosis – hepatitis C virus – direct acting antiviral agents.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTP score: Child-Turcotte-Pugh score; DAA: direct-antiviral agent; EASL: European Association for the Study of the Liver; EOT: end of treatment; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IFN: interferon; INR: international normalized ratio; ITT: intention-to-treat; LDV/SOF: ledipasvir-sofosbuvir; MELD: Model for End-stage Liver Disease; PCR: polymerase chain reaction; RBV: ribavirin; SVR: sustained virologic response.

INTRODUCTION

Hepatitis C virus (HCV) is an epidemic problem worldwide, affecting approximately 71 million people [1, 2]. In Romania, the estimated prevalence of chronic HCV according to data published in 2010 was approximately 4% [3], but it is decreasing now due to reimbursed direct direct-antiviral agents (DAAs), received by approximately 35,000 patients with more than a 96% sustained virologic response (SVR) rate [4-6]. In Romania, genotype 1b is almost exclusively present among the infected patients [7].

Ledipasvir/Sofosbuvir (LDV/SOF) was approved as the treatment for genotype 1 chronic HCV infection in October 2014. Efficacy and safety of LDV/SOF with or without Ribavirin (RBV) in compensated liver cirrhosis and genotype 1 HCV infection have been demonstrated in clinical trials, with a SVR rate of 96% [8]. Real-world data that included around 5,070 patients, reported a SVR rate of 93-98%, with very good tolerance [9-15]. LDV/SOF was tested in decompensated liver cirrhosis in two major clinical trials: SOLAR-1 and SOLAR-2,

which reported a SVR of 86% for a 12 week course of LDV/SOF and RBV [16, 17]. Real-life data reported a lower SVR of 78-83%, but also a good tolerance [18-21]. Model for end-stage liver disease (MELD) scores improved in treated patients (mean change 0.85) [18]. Patients with initial serum albumin <35g/L, aged >65 or with low baseline serum sodium concentrations (<135mmol/L), with ascites or encephalopathy, alanine aminotransferase (ALT) <60 U/L, and body mass index >25 kg/m^2 were least likely to benefit from therapy [18, 22].

The aim of the present study was to investigate the efficacy and safety of LDV/SOF in a real-world large Romanian population with liver cirrhosis caused by genotype 1b HCV.

METHODS

Out of the 772 patients with advanced HCV liver cirrhosis who received reimbursed DAAs therapy with LDV/SOF with or without RBV for 12-24 weeks during 2017-2018 in Romania, we analyzed a multicentric retrospective cohort enrolling 349 patients who started the therapy between September 2017 and July 2018 in the Gastroenterology Department and Internal Medicine Department of the Fundeni Clinic Institute, Bucharest, the Gastroenterology and Hepatology Institute Iasi, the Internal Medicine Department of the Emergency University Hospital Bucharest and the Gastroenterology Department of Elias Emergency Hospital, Bucharest, all with genotype 1b infection. The inclusion criteria were decompensated liver cirrhosis, detectable HCV-RNA viral load in serum, no significant ethanol consumption in the last 3 months. All the potential drug-drug interactions were checked, and concomitant therapy was administered only if potential interactions were excluded.

The diagnosis of cirrhosis was based on a liver biopsy detecting fibrosis corresponding to Metavir F4 score. In the absence of the liver biopsy, the presence of cirrhosis was proven by a median liver stiffness measurement ≥12.5 kPa at transient elastography (Fibroscan), advanced fibrosis (F4) confirmed by Fibromax testing or signs of portal hypertension (esophageal or gastric varices, portal gastropathy). The definition of decompensated cirrhosis was the presence of prior or current variceal hemorrhage, ascites, hepatic encephalopathy or hepatic hydrothorax.

According to the therapeutic guidelines for the reimbursement of DAAs therapy, patients co-infected with hepatitis B virus (HBV) received concomitant anti-HBV therapy with Entecavir during their anti-HCV therapy. Those with hepatocellular carcinoma (HCC) were treated if they had an absence of HCC relapse 3 months after their last session of therapy (surgery, radiofrequency ablation or transarterial chemoembolization).

Only serious adverse events leading to discontinuation of therapy were reported.

The study was approved by the National Ethics Committee of Medicines and Medical Devices (No 27SNI/October 10, 2016). All patients signed a written informed consent before entering the study.

Main outcome measures: efficacy of the DAAs therapy was assessed by the percentage of patients achieving SVR (HCV RNA undetectable) 12 weeks post-treatment (SVR12). To evaluate the liver function, the MELD score and the Child Turcotte-Pugh (CTP) score were calculated at the start of DAAs therapy, at the end of treatment (EOT) and at the SVR12.

The recorded patient data for analysis were: age, gender, prior antiviral therapy (and the patients' status: non-responder or relapser), presence of ascites, presence of encephalopathy and the degree of encephalopathy, history of variceal bleeding, presence of esophageal varices, presence of significant comorbidities, use of concomitant medications. Laboratory data were recorded 3 months before starting the antiviral therapy, at EOT and 12 weeks after the EOT. Parameters recorded included: platelet count, international normalized ratio (INR), total bilirubin, aspartate aminotransferase (AST), ALT, glucose level, albumin, HBs antigen, alpha-fetoprotein, creatinine and estimated clearance of creatinine. All patients who completed the antiviral therapy had their HCV-RNA viral load determined at the end of therapy and at 12 weeks after the end of therapy. HCV-RNA levels were assessed by quantitative polymerase chain reaction (PCR) assays: COBAS TaqMan HCV v2.0 (Roche Molecular Diagnostics, Pleasanton, CA, USA).

The patients were enrolled for treatment with LDV/SOF with or without RBV according to the therapeutic guidelines of the EASL and the manufacturer's recommendations [7].

A total of 301 patients received one tablet of LDV/SOF (90/400 mg per tablet) with or without RBV (starting dose of 600 mg, which can be titrated up to a maximum of 1,000/1,200 mg) for 12 weeks. Forty-eight cases considered ineligible for or intolerant to RBV were treated with LDV/SOF (90/400 mg) daily for a total of 24 weeks. These patients were with moderate-severe anemia, hemoglobinopathies (i.e. thalassemia major), decompensated heart failure or with poor tolerance to RBV on previous antiviral treatment.

All analysis was conducted in intention-to-treat (ITT). Results were summarized as median and range for non-normally distributed scales or ordinal variables or as numbers and percentages for categorical variables. We looked for differences concerning the independent variables by the outcome in bivariate analysis (Mann-Whitney U test or Fisher's exact test, depending on variables). A logistic regression model was computed, and all independent variables associated with $p<0.10$ with the dependent variable in bivariate analysis were introduced in a stepwise manner. The model with the independent variables retained by both the forward and the backward stepwise method was kept. A two-sided p value of < 0.05 was noted as statistically significant. Data analyses were performed with statistical software (Stata 11 from StataCorp LP, College Station, TX, USA, and SPSS version 20.0 from IBM Corporation, Armonk, NY, USA).

RESULTS

There were 349 patients with decompensated cirrhosis included in the cohort. Six patients were lost during follow-up and in 16 (4.6%) the treatment was interrupted due to adverse events: nine developed worsening hepatic function (2.6%), four experienced cardiovascular adverse events, one developed severe allergy and two had severe bacterial infections (Fig. 1). Baseline characteristics of patients with decompensated cirrhosis treated with LDV/SOF with or without RBV are shown in Table I.

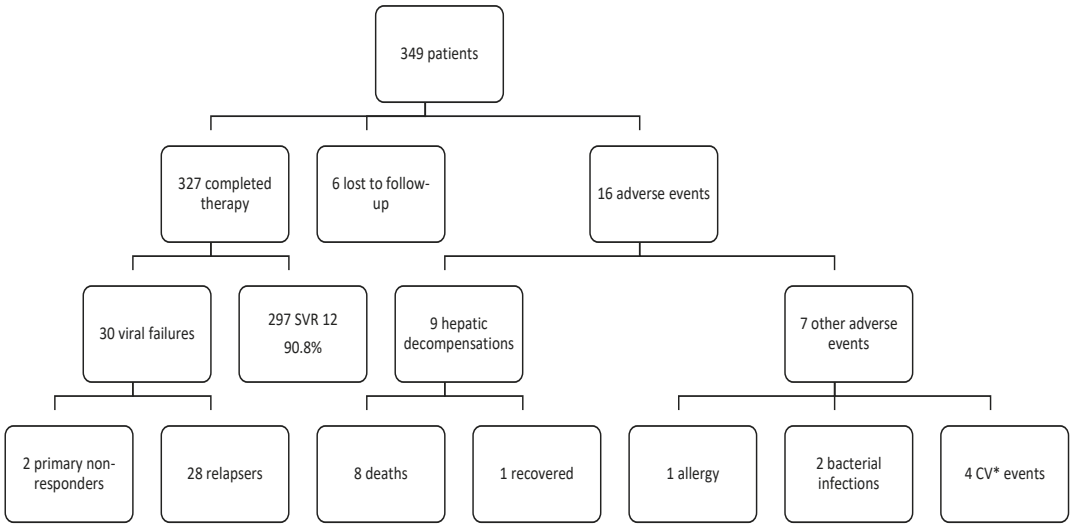

Fig. 1. The study flowchart. CV: cardiovascular

Table I. Baseline characteristics of patients with decompensated cirrhosis treated with LDV/SOF with or without RBV

Decompensated liver cirrhosis	349
Age* (years)	61 (35-83)
Gender male (%)	41.3
Co-morbidities (%)	53
IFN Pre-treated (%)	15.8
HBs-Antigen positive (%)	4
Treated HCC	8
AST* (IU/ml)	69 (20-396)
ALT* (IU/ml)	58 (15-497)
HCV-RNA* (IU/l)	247,000 (55-7,276,049)
Total bilirubin* (mg/dl)	1.8 (0.3-11)
MELD* score	11.92 (6.82-24.5)
CPT score (A/B/C) (%)	40/53/7

*median (minim-maxim); AST: aspartate aminotransferase; ALT: alanine aminotransferase; CTP: Child-Turcotte-Pugh; HCC: hepatocellular carcinoma; IFN: interferon; LDV/SOF: ledispavir/sofosbuvir; MELD: Model for End-stage Liver Disease; RBV: ribavirin; SVR: sustained virologic response

Briefly, this group consisted of 58.7% females; patients had a mean age of 61 years (35-83) and 16% had failed prior interferon-based therapies 53% of patients had comorbidities, most frequently being cardiovascular disease: 24.6% hypertension, 8% ischemic heart disease, 7% chronic heart failure, 3% atrial fibrillation, 2.6% had a history of stroke and 2% various valvular disorders. The prevalence of type 2 diabetes in our cohort was 23.5%. Other comorbidities were portal vein thrombosis: 3%, different types of anemia: 3%, different thyroid disorders: 3%, chronic obstructive pulmonary disease: 2.3%, colonic cancer operated 2%, peptic ulcer disease 1.7%, symptomatic cryoglobulinemia 1.4%.

Sustained virologic response rate by ITT analysis was reported in 85.1% (297/349), and per protocol was 90.8% (297/327). Sustained virologic response rate by ITT was 87.8% in patients with CTP A score at therapy initiation, 84% in patients with CTP B score and decreased further to 78.3% in those with CTP C (p=0.02).

In univariate analysis the predictive factors for SVR12 were in our cohort: female gender (p=0.01), advanced age (p<0.001), lower bilirubin levels (p=0.002) and lower CTP score (p=0.02) (Table II) (univariate analysis). The parameters that predicted SVR in a multivariable analysis were an age of more than 60 years (OR: 3.93; 95%CI: 2.03-7.6) and total bilirubin level below 2 mg/dl (OR: 2.98; 95%CI: 1.13- 3.84).

Table II. Predictive factors of SVR rate to in patients with decompensated liver cirrhosis (univariate analysis) by intention to treat

Parameter	Responders	Non-responders	p-value
Age* (years)	61 (35-83)	56 (37-72)	<0.001
Male gender (%)	38.4	57.7	0.014
Co-morbidities (%)	52.5	55.8	0.764
CTP* score	7 (5-11)	8 (5-12)	0.02
HCV-RNA* (IU/l)	276000 (55-7276049)	167000 (11400-1970000)	0.311
Total bilirubin* mg/dl	1.5 (0.3-9)	2.2 (0.4-11)	0.002
MELD* score	10.48 (6.14-19.71)	12.13 (6.26-24.5)	0.148
Ascites at baseline (%)	42.8	42.3	1.000
History of Variceal bleeding (%)	12.8	17.3	0.381

For abbreviations see Table I

Three hundred and one cases received LDV/SOF/RBV for 12 weeks and 48 were treated with LDV/SOF for 24 weeks. Their baseline characteristics and response to therapy are described in Table III. The SVR rate did not significantly differ between the 2 arms of treatment: 84.7% for LDV/SOF/RBV and 87.5% for LDV/SOF (p=0.83). The proportion of RBV-induced anemia was 18.9%. A percentage of 53.8 of the individuals treated with LDV/SOF/RBV improved their liver condition at SVR, compared with 58.3% of patients that received LDV/SOF (p=0.104). Regarding the rate of adverse events occurrence, this was the same in the both groups: 4%.

Table III. Baseline characteristics and response to therapy in patients with compensated cirrhosis and HCV infection treated with SOF/LDV/RBV versus SOF/LDV

	SOF/LDV/RBV 12 weeks (n=301)	SOF/LDV 24 weeks (n=48)	p-value
Male gender (%)	42.5	33.3	0.270
Age* (years)	61 (35÷83)	61 (37÷80)	0.34
SVR12 (%)	84.7	87.5	0.827
Co-morbidities (%)	49.5	75	0.001
MELD	10.63 (6.14-24.5)	11.13 (6.80-16.58)	0.022
CTP score	7 (5÷12)	6 (5÷11)	0.49

For abbreviations see Table I

MELD score at EOT decreased to 10.91 (6.06-23.12) and dropped further to 9.78 (6 -19.84) at 3 months' interval (Fig. 2). At 12 weeks after the EOT, 38% of cases maintained their liver function (also the CTP score) while 56% had improved liver function and 6% showed worsening liver function tests. From the 210 patients with CTP score B or C at therapy initiation, 97 improved to CTP score A (46.2%). Seven percent of the included patients died during the follow-up period of 12 weeks after the EOT.

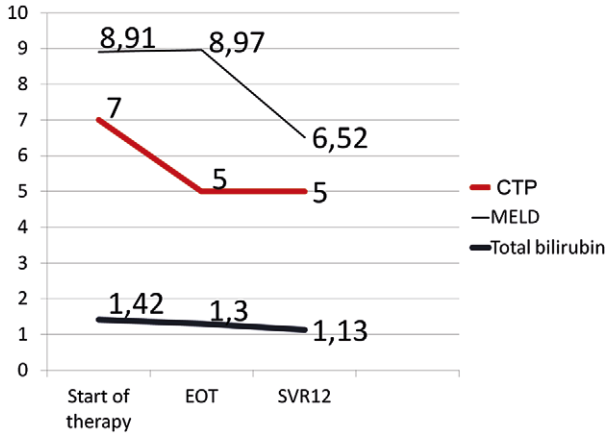

Fig. 2. Evolution of total bilirubin, MELD score and CTP (median) during DAAs therapy and at 12 weeks after the EOT.

At univariate analysis, we searched for predictors associated with improvements in decompensated cirrhosis after LDV/SOF with or without RBV therapy: lower levels of total bilirubin (p=0.03), lower INR (p<0.001), increased platelet count (p=0.04), low CTP score (p<0.001), lack of encephalopathy in patient's history (p=0.02), serum albumin >3.5g/dl (p-0.002) (Table IV). This was confirmed by the multivariable analysis (logistic regression): higher CTP score has an OR of 0.585 for improvement (95%CI: 0.441-0.777; p<0.001), lack of encephalopathy has 4.354 OR for improvement of liver function (95%CI: 1.524-12.442; p=0.006), serum albumin >3.5g/dl has 3.317 OR for improvement (95%CI: 1.317-8.357; p=0.01).

Serious adverse events were reported in 16/349 (4.6%), most of them due to severe liver decompensation (9/16). The occurrence of adverse events was more frequent in patients with a more severe liver disease: increased CTP score (p<0.001), higher MELD scores (p=0.008). The subjects who developed severe adverse events had a median MELD score of 12.3 (8.83-21.7) and a median CTP score of 9 (7-12), compared to a median MELD score of 10.56 (6.14-24.5) and a CTP score of 7 (5÷11) in patients who did not experience severe adverse events. At multivariable analysis, only the CTP score was confirmed as a predictor for adverse events occurrence, with an OR of 1.678 (95%CI: 1.205-2.336). Regarding the 4 cardiovascular events, there were 2 myocardial infarctions, 1 case of worsened heart failure and 1 ischemic stroke, resulting in 2 deaths (one patient with severe myocardial infarction and another one with stroke), probably not related to antiviral therapy or to drug-drug interactions.

Table IV. Predictive factors of improvement of Child score B/C to Child score A in patients with decompensated cirrhosis and HCV infection treated with LDV/SOF±RBV

	Patients with CTP score B/C at baseline and CTP score A at SVR12 N=97	Patients with CTP score B/C at baseline and CTP score B/C at SVR12 N=113	p-value
Male gender (%)	42.3	38.9	0.673
Age* (years)	61 (41-83)	59 (37-81)	0.281
Co-morbidities (%)	52.6	47.8	0.580
Platelets* (x109/L)	92 (29-491)	74 (10-255)	0.045
INR*	1.29 (0.91-1.85)	1.45 (0.94-2.89)	<0.001
Total bilirubin*	2.13 (0.50-9)	2.55 (0.40-11)	0.03
MELD*	11.38 (6.77-19.71)	12.03 (6.84-24.5)	0.117
No ascites at baseline (%)	60.8	50.4	0.164
History of variceal bleeding (%)	10.3	15.9	0.309
CTP* score	7 (7-10)	8 (7-12)	<0.001
No history of hepatic enphalopathy (%)	93.8	83.2	0.019
Serum albumin <3.5 g/dl (%)	75.3	91.2	0.002
ALT <60 IU/L (%)	48.5	55.8	0.333

For abbreviations see Table I

DISCUSSION

The Food and Drug Administration approval in 2014 for LDV/SOF in the treatment of chronic HCV infection has brought to the whole world an extremely efficient and well tolerated variant of DAAs treatment. Phase 3 registration studies estimated an SVR12 rate of 95% in naive genotype 1 patients and 94% in experimented cases [23, 24]. These registration studies included a relatively low number of individuals with compensated cirrhosis.

Our study reports a SVR12 per protocol of 90.8% in decompensated cirrhosis, which is very similar to the data resulting from earlier clinical trials: 86-87% in SOLAR-1 and SOLAR-2 [16, 17, 28]. Other real-life data report a SVR12 of 85-91% in patients with decompensated cirrhosis [14, 18, 28, 29].

We found two predictive factors for SVR in our cases with decompensated cirrhosis: advanced age (OR:0.949; 95%CI: 0.919-0.980) and lower bilirubin levels (OR:1.310; 95%CI: 1.126-1.532), similar to the findings of Lim JK et al [14] and Terrault et al. [27]. They reported two parameters associated with low SVR in their cohorts: albumin <3.5 g/dl and total bilirubin >1.2 mg/dl [14, 27].

No other clinical trial report or real-life study to date has found that male sex could be a predictive factor for non-response as we found in univariate analysis, but Lim JK et al [14] reported that a trend towards lower SVR was observed among males (OR: 0.49, 95%CI: 0.20–1.18).

Data regarding safety in our cohort of patients treated with LDV/SOF with or without RBV were very good, with only 16 serious adverse events recorded in 349 patients (4.6%). These data are similar with those reported by other authors [9-11, 13, 14, 25, 26].

Regarding liver condition improvement in decompensated cirrhosis treated with DAAs, we identified a low CTP score, lack of encephalopathy, serum albumin >3.5 g/dl as predictors of improved liver function. Other authors found that body mass index ≤25 kg/m^2, the absence of hepatic encephalopathy and of ascites, albumin >3.5 g/dl, and ALT ≥60 U/L were good predictors for achieving an improvement of CTP score to A [22]. A relatively preserved liver function predicted an improvement in the liver condition of the patients included in our study, due to the fact that a relatively small number of cases with MELD between 15 and 20 points were treated with LDV/SOF (25 out of 349, that is 7.2%). Only 3 individuals had MELD greater than 20 when included in treatment, and their evolution was very serious, with death recorded within the first 2 months of DAAs treatment due to hepatic decompensation and sepsis.

An important finding in our cohort is that there was no significant difference in SVR12 between cases treated with LDV/SOF/RBV 12 weeks or 24 weeks of LDV/SOF. It is important to mention that the baseline characteristics of the cases with 12 weeks therapy duration versus 24 weeks are similar, with one exception: proportion of comorbidities is significantly increased in those that received 24 weeks of LDV/SOF: 75% versus 50%. Other data from the literature confirm our findings [14], but there are authors that reported that SVR12 rates might be lower in patients with cirrhosis treated for 12 weeks (94 vs 99%) [13].

Our study has several strengths: it represents a relatively large and homogenous cohort of patients with decompensated liver cirrhosis, HCV infection, all genotype 1b. This cohort included patients that are not represented in clinical trials: with HBV co-infection, with prior history of treated HCC.

The most important limitation of our study, inherent to all real-world observations, is that adverse events may be under-reported, because only those adverse reactions that led to discontinuation of DAAs were recorded in our study. Secondly, we have no data regarding viral resistance. Thirdly, we do not have data on patient compliance, as this has not been systematically verified.

CONCLUSIONS

Our real-life study reported a SVR12 rate of 85.1% in ITT analysis and of 90.8% per protocol analysis, in decompensated cirrhosis, comparable with the data resulting from clinical trials and other real-life studies. SVR12 rates did not differ significantly between patients treated for 12 or 24 weeks, and between those treated with or without RBV. The main predictors of SVR were advanced age and lower bilirubin levels. An improvement of their liver function was observed in 66% of patients after therapy, LDV/SOF being very well tolerated in our difficult-to treat cases, with serious adverse events reported in only 16/349 (4.6%) of the cases, most of them represented by worsening of the liver function (9/16).

Conflicts of interest: L.S.G., L.I., A.T., M.D. received honoraria and educational grants from Gilead. The other authors declare no conflicts of interest concerning this article.

Authors' contributions: L.S.G and M.M. designed the study and critically revised the paper. C.M.P. drafted the manuscript. L.I., A.T., C.S. data acquisition and critical revision of the manuscript. D.I. and C.B statistical analysis. A.E.C., C.S.P., L.T., S.I., C.T., C.M.: data acquisition. M.D., T.V. critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval statement: The study was approved by the National Ethics Committee of Medicines and Medical Devices (No 27SNI/ OCTOBER 10, 2016).

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