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High Sustained Virological Response Rates in HCV-HIV Coinfected Patients Treated with Second Generation Direct Antiviral Agents (DAAs) in Southern Brazil

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Abstract

Introduction: Co-infection with the Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) infection is a frequent phenomenon, especially among individuals who have been infected by the parenteral route. In 2015, a new second-generation of Direct Antiviral Agents (DAAs), such as Sofosbuvir (SOF) and Daclatasvir (DCV), were incorporated into the therapeutic armamentarium for HCV-infection by the Ministry of Health in Brazil, achieving high sustained virological response rates (SVR) to 90% including those coinfected patients.

Objectives: Evaluate SVR rates in HCV-HIV co-infected patients using SOF and DCV ± Ribavirin (RBV) and describe the main demographic, epidemiological and HCV characteristics (genotype, hepatic fibrosis and viral load), as well as Serious and Related Adverse Effects (SAE) during therapy. Materials and methods: A retrospective analysis of HCV-HIV co-infected patient treated with SOF and DCV at the Liver Disease Outpatient Clinic at Gaffrée and Guinle University Hospital was performed between 2016- 2017.

Result: From the 86 patients studied, 81.40% were men, 57% were white, mean age was 53 years, mean BMI 23.88. The most prevalent route of infection was sexual (41.9%). The mean viral load of HCV RNA was 2.216.222 IU/ml. Majority (73.26%) of them were genotype 1, 25% were cirrhotic, all Child-Pugh A. Fifty-three patients were treatment-naive. Regarding HIV, 84 out 86 were using Antiretroviral Therapy (ART), being the more prevalent scheme with protease inhibitors. The dose of DCV varied according to the ART. Out of 84, 60 patients had a response evaluation at week 12 post-treatment, with 100% SVR. Anemia (7%), headache (7%), nausea (4%) and dizziness (4%) were the most described (> 4%) AEs

Conclusion: The RVS12 rate is extremely high in this special group (100%). No predictive factors had an impact on SVR, such as age, sex, gender, viral load, fibrosis grade, previous treatment, HCV genotype. The tolerance to DAAs was very good in our sample. In our series there was a predominance of male gender and sexual route as the main source of contamination in the patients involved in the study.

Keywords: Hepatitis C; Direct Acting Antiviral Drugs; Sofosbuvir; HIV; Daclatasvir; Sustained Virological Response; Route of Infection or Sexual Transmition

Introduction

It is estimated that currently about 71 million people are living with the Hepatitis C Virus (HCV) in the world [1]. From the total of 149,537 confirmed cases of hepatitis C in Brazil, between 2007 and 2016, 9.8% were coinfected with HIV [2].

Several studies have shown that HCV-HIV coinfection is associated with advanced complications of liver disease and that the progression to cirrhosis would occur in a proportion three times higher in these patients than in monoinfected ones [3-5].

The hepatitis C virus infection treatment in the subset of HIV co- infected patients presented a challenge, since the regimens based on pegylated interferons and Ribavirin (RBV) demonstrated lower Sustained Virological Response (SVR) rates compared to mono-infected HCV patients [6]. In addition, those co-infected with HIV have high rates of ineligibility for treatment of HCV due to concomitant medical and psychiatric conditions; non-adherence, drug intolerance, interactions with antiretrovirals, as well as use and abuse of substances, conditions that may be considered as barriers to treatment, and this resulted in fewer patients eligible for treatment [7].

Previous treatment of chronic hepatitis C and HIV co-infected patients with the administration of interferon-alpha monotherapy was associated with several adverse events and achieved low SVR rates of 17% [8] and the best variables that correlated with response were the highest titers of CD4 and HCV genotype other than 1.

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Subsequently, studies evaluated the efficacy of the combination of peginterferon-alpha and ribavirin in the treatment of coinfected patients achieving SVR rates of 27% to 44% [9-12]. When the first generation of NS3/NS4 protease inhibitors such as Telaprevir and Boceprevir were added to peginterferon and ribavirin for genotype 1 for 48 weeks this led to a significant improvement in SVR rates reaching 74% and 63%, respectively. However, these drugs had less practicality in their use and more frequency of adverse reactions [13].

The second generation of direct antiviral agents (DAA), such as Sofosbuvir (SOF) and Daclatasvir (DCV), were approved in Brazil in 2015, and dramatically increased cure rates in coinfected population, with shorter period of treatment and lower adverse effects [14] exactly in the same way as for monoinfected patients [15].

The objective of this real-life study was to evaluate the efficacy and safety of the administration of SOF and DCV for the treatment of HCV-HIV coinfected patients, as well as to describe the demographics, epidemiological and HCV characteristics in these patients.

Methods and Patients

This is a retrospective study based on the evaluation of medical records of HCV-HIV coinfected patients, followed at the liver disease outpatient clinic of the Gaffrée and Guinle University Hospital in Rio de Janeiro between 2017 and 2019.

All patients were treated with DAAS according to Clinical Protocol and Therapeutic Guidelines for Hepatitis C and Coinfections (2015) of the Brazilian Ministry of Health and all patients signed consent form. Protocol was approved by the Gaffrée e Guinle University Hospital Ethics Commitee.

Patients

The sample included HCV-HIV coinfected patients; aged ≥ 18 years; HCV-RNA detectable by a sensitive Real Time PCR for more than six months; infected by HCV genotypes 1, 2, 3 or 4. Women must be on effective contraception; Treatment-naïve or previously treated patients (with conventional interferon and Ribavirin, PEG-IFN and Ribavirin, and / or PEG-IFN, Ribavirin and Telaprevir / Boceprevir) were included with any grade of hepatic fibrosis; and treated with SOF and DCV ± Ribavirin for 12 or 24 weeks. Viral load of HCV-RNA were performed at baseline, at the 4th and 12th week of therapy, at the end and 12 weeks after the end of treatment. Exclusion criteria were pregnant women; patients with active opportunistic infections, CD_4 values lower than 200 cells / mm^3; and patients taking amiodarone.

Treatment

Patients were treated according to Guidelines of the Brazilian Ministry of Health (2015), and were therefore submitted to the following therapeutic regimen: SOF 400mg / day + DCV 60mg / day for 12 weeks. Patients taking efavirenz received 90mg / day of DCV and those taking atazanavir received 30mg / day as shown in table 1. Patients with advanced liver fibrosis also received RBV at a dose of 1000mg / day orally according to body weight up to 75Kg and 1250mg / day for patients over 75 kg. Patients previously treated with triple therapy (Peg-IFN, RBV and Telaprevir or Boceprevir) received treatment for 24 weeks.

Result

In this study 86 patients were included, being 70 (81.40%) male; 49 (57%) white, with a mean age of 53 years (± 8,80). Mean BMI was 23.88. Among the patients evaluated, 36 (41.9%) were considered as infected by sexual route as a probable source of infection, 22 (25.6%) had already undergone blood transfusion, seven (8.1%) had a history of Intravenous Drug Abuse (IVDA) and / or inhalable, four (4.7%) had a tattoo, one patient (1.2%) had a history of sharp puncture injury and 24 (27.9%) were unaware of the probable source of contamination, as evidenced in the figure 1.

The mean viral load of HCV-RNA was 2.216.222 IU / ml. About the genotype, 27 patients (31.40%) were genotype 1 without subtyping, genotype 1^a - 25 (29.07%); genotype 1^b-10 (11.63%); genotype 1^a and 1^b-1 (1.16%); genotype 2-1 (1.16%); genotype 3 - 15 (17.44%) and genotype 4 - 7 (8.14%), as demonstrated in figure 2.

Fifty-three (61.63%) patients were treatment-naive, 30 (34.88%) were experienced with Interferon (conventional or pegylated) + RBV, three (3.48%) patients were previously treated with triple therapy (Peg- IFN, RBV and Telaprevir or Boceprevir).

According to fibrosis stage, 43 (50%) presented F0-F1, 4 (4.65%) F2, 13 (15.12%) F3 and 25 (29.07%) F4 and 1 (1, 16%) patient had no data in the medical record. 25 with cirrhosis were classified as Child-Pugh A.

From the total of the 86 patients evaluated, 68 (79.07%) had undetectable HIV viral load prior to the start of treatment with the DAAS and there was no case of clinical progression from HIV infection to AIDS disease. The majority (54.65%) were using protease inhibitors (PIs).

All patients received SOF at a dose of 400mg / day and 44 (51.16%) received DCV 60mg / day, 18 (20.93%) received DCV 30mg / day and 24 (27.91%) DCV 90mg / day. RBV was used in 30 (34.88%)

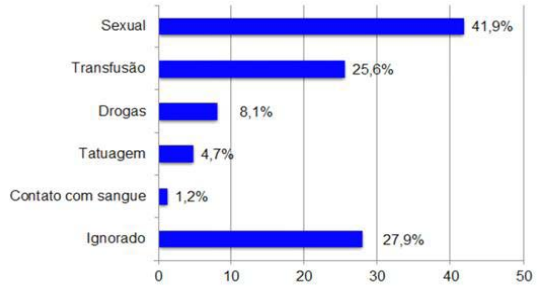

Figure 1: Transmission route.

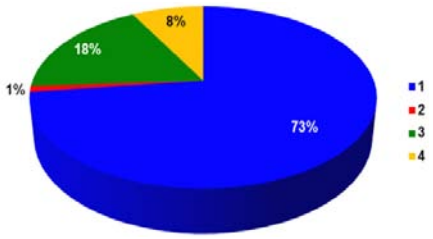

Figure 2: Prevalence of genotypes.

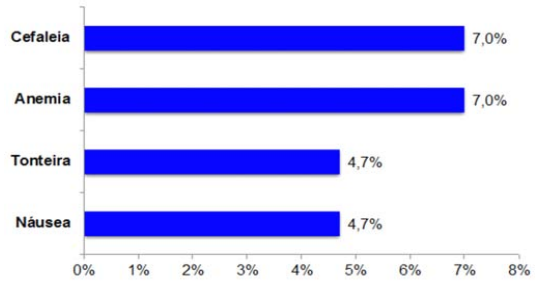

Figure 3: Adverse effects.

patients. Eighty-two (95.35%) received treatment for 12 weeks, the remainder 4 for 24 weeks. Of these, three were previously treated with triple therapy and one was a genotype 3.

Efficiency

Out of the 86 patients analyzed in this study, 60 (69.77%) had already performed HCV viral load of at week 12 of follow-up and all (100%) reached SRV12. The remaining patients were still in follow-up at the outpatient clinic and awaiting for the final clinical and virological evaluations.

When evaluating SVR rates by genotype, treatment-naive *vs* previously experienced patients; cirrhotic *vs*. non-cirrhotic patients there were no significant difference as all patients achieved SVR12, ie, HCV-RNA undetectable twelve weeks after treatment. The most frequent adverse events were anemia (7%), headache (7%), nausea (4.7%) and dizziness (4.7%), as shown in the figure 3. No patient had to discontinue treatment with DAAs due to severe adverse events.

Discussion

In our sample of HCV-HIV coinfected patients, genotype 1 (73.26%) was predominant, in agreement with the data published in the ALLY-2 clinical trial that also used SOF and DCV and in the ASTRAL-5 study, with SOF and velpatasvir [15-19]. Almost all of the coinfected patients (81.40%) in our sample belonged to the male gender, similar to what occurred in the majority of national and international studies involving coinfected patients [15]. It is relevant that the sexual transmission of HCV in men who make sex with HIV-infected men (MSM) has been increasing in recent years and may be reinforced by mucosal injury through anal intercourse [16]. This contributes to explain why the sexual pathway was identified as the most prevalent source of infection in 41.9% of the coinfected patients evaluated; A total of 22 (25.6%) patients had a previous history of blood transfusion, which refers to cases of infection prior to 1992, when screening tests for anti-HCV antibody were introduced in Brazilian blood banks, being 11.63% hemophiliacs. These data are in agreement with those obtained from the epidemiological bulletin of viral hepatitis of the Brazilian Ministry of Health of 2017, where the percentage of infections by sexual route was higher than by transfusion: 24.2% and 21.7%, respectively [17]. Half of the HCV-HIV coinfected patients involved in our study had mild fibrosis F0-F1 (Metavir), probably due to the fact that in the Brazilian guidelines of 2015, hepatitis C treatment is indicated and allowed for all those co-infected with HIV, independent of the degree of hepatic fibrosis. Cirrhosis was documented in 29.07% of the 86 patients in our series.

Table 1: Therapeutic regimens.

ESQUEMA	N	%
SOF 400mg + DCV 30mg	18	27,93
SOF 400mg + DCV 60mg	44	51,16
SOF 400mg + DCV 90mg	24	27,91
TOTAL	86	100

However, there were no differences in SVR among patients with or without advanced liver disease, similar to what has been demonstrated in studies such as ION-4 [18], where cirrhosis no longer proves to be a negative predictive factor. Similarly as ALLY- 2 study, where 98% of patients were on anti-retroviral therapy, the vast majority of the patients included in this study, 84 (97.67%) were using ART. Sixty-eight (79.07%) had undetectable HIV viral load in the period prior to initiation of treatment with DAAS, a similar profile described by Rockstroh et al. in the TURQUOISE-I study [20]. Antiretroviral regimen with protease inhibitors, was the most found (54.65%) in our series with high SVR rates in all of the antiretroviral regimens in use.

The efficacy of DAAS has been demonstrated in several studies that have shown high rates of SVR12 in HCV-HIV coinfected patients. In our real-life study, of the 86 patients, 60 already had SVR results at week 12 after treatment and we found an overall SVR rate of 100%. The remaining patients are still receiving treatment and follow-up at the outpatient clinic. No predictive factors had an impact on SVR, such as age, sex, gender, HCV viral load, degree of fibrosis, previous HCV treatment, similar to that observed in other studies [19-20].

In our study, the most common adverse events were anemia (7%), headache (7%), nausea (4.7%) and dizziness (4.7%). None of the patients discontinued the treatment due to serious adverse events, similar to other clinical trial with ledipasvir and SOF in HIV-HCV coinfected patients, which reported as the most common adverse events: headache (25%), fatigue (21%) and diarrhea (11%) [19-20]. In a phase III study with SOF and Velpatasvir which included 106 HCV-HIV coinfected patients, the most common adverse events were fatigue (25%), headache (13%), upper respiratory tract infection (8%) and arthralgia (8%). These data show that the most common side effects are of low severity, confirming the safety of DAAs and decreasing the concern of drug interactions with the ART as in the era of interferon [15].

The most common source of contamination in our series was the sexual (41,9%), a fact that may be due to male predominance in the studied population and is related to the growing evidence of sexual transmission of HCV in men who have sex with HIV-infected men. This pathway of HCV transmission may be enhanced by mucosal injury through traumatic anal intercourse and / or concomitant presence of other sexually transmitted diseases such as HIV [17].

In conclusion, DAAs have been shown to be drugs with a good safety profile and to promote high rates of SVR_{12}, despite the genotype, previous therapy and presence of cirrhosis in HCV-HIV coinfected patients.

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