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Research Article

# Treatment of Chronic Hepatitis C: An Experience Report from a Referral Center in Northeastern Brazil

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## 1. Abstract

**1.1. Background**: Therapy for the Hepatitis C Virus (HCV) has undergone a revolution with the introduction of Direct-Acting Antivirals (DAA). DAAs achieve Sustained Virological Response (SVR) in 90-95% of treated patients, compared to 50-70% of those receiving dual pegylated interfere on and ribavir in therapy. Although they are already available, there are few studies on DAAs efficacy in the Brazilian population.

**1.2**. **Objective**: To evaluate the efficacy of DAAs in individuals with hepatitis C at the Liver Study Center (LSC) in Hospital Universitario Onofre Lopes (HUOL).

**1.3. Methods**: Medical records of chronic HCV patients treated with DAAs from LSC were analyzed. Only those patients with a follow-up of at least 12 weeks after the end of treatment were included.

**1.4**. **Results**: A total of 50 patients underwent treatment with DAAs at LSC. Of these, genotype 1 was present in 39 patients (81.2%, 1a 8.3%, 1b 68.7%), genotype 2, in 2 patients (4.2%) and genotype 3, in 6 patients (14.5%, 3a 2%). Thirty-two were cirrhotic (64%), and 20 were treatment-experienced (40%). The therapeutic regimens used were mainly sofosbuvir (SOF) + simeprevir (SMV) in 23 patients (46%) and SOF + daclatasvir (DCV), in 22 (44%). SVR-12 was achieved in 92% of patients. Four patients had virological failure: three of them were cirrhotic and treatment experienced. The other one had advanced liver fibrosis (F3) with no previous treatment for HCV infection. No adverse events were reported during DAA treatment.

**1.5. Conclusion**: The experience of the LSC with DAAs showed a high rate of SVR and excellent tolerability.

**2. Keywords**: Hepatitis C; Hepatic cirrhosis; Liver fibrosis; Liver disease; Sustained virologic response; Sustained viral suppression; Antiviral drugs.

## 3. Introduction

Hepatitis C Virus (HCV) infection is one of the leading causes of chronic liver disease worldwide [1]. Hepatocyte lesion induced by HCV may lead to cirrhosis and hepatocellular

carcinoma [2]. Due to the silent progression of the disease and complications that require specialized care, hepatitis C has a significant impact on public health [3]. In the absence of treatment, there is chronification in 60%-85% of the cases and, on average, 20% progress to cirrhosis over time [4]. It is estimated that 170 million people are infected, which is equivalent to 2.8% of the world population [5-7]. In Brazil, 1.6 million people are carriers of the virus, and a higher frequency of genotypes 1 and 3 is present, with small variations in the prevalence ratio of these genotypes. Hepatitis C virus exhibits high genetic diversity, characterized by regional changes in genotype prevalence and is responsible for most deaths from viral hepatitis in our country, representing the third leading cause of liver transplants [8-10].Until 2015, the treatment regimen for HCV in Brazil was based on the combination of interferon or interferon-pegylated with ribavirin for 48 to 72 weeks. Unfortunately, the cure rate was only 40%-80%, and there were many adverse effects associated [11, 12]. These unsatisfactory outcomes led to the development of new drugs for the treatment of hepatitis C, the so-called direct-action antivirals, representing a new era in the history of this disease [13-15]. DAAs have brought encouraging expectations about the potential of the cure for Hepatitis C. Unlike the interferon regimens, this new treatment has shown cure rates above 95% with few adverse effects, shorter duration of therapy, and more straightforward dosing [16-18]. Monitoring for side effects is also of little to no practical use as new DAA regimens are generally well tolerated, with less than 1% of patients discontinuing treatment for side effects or reporting severe adverse events. DAAs have been initially sold at a very high price, limiting access. Opportunities to access low-price generic medicines are increasing [19, 20]. Since 2018, the Unified Health System (UHS/SUS-Brazil) made available DAAs treatment for all people with HCV infection in Brazil. Currently, the DAAs that are part of the therapeutic arsenal offered by the SUS are sofosbuvir, simeprevir, and daclastavir. The goal of chronic hepatitis C treatment is to achieve the status of sustained virological response (SVR) in post-therapy follow-up [21]. SVR is determined to be undetectable HCV-RNA within 12 or 24 weeks after completion of treatment. SVR is a marker of virological and clinical cure [19]. Many factors may complicate HCV medical treatment, including the genotype of the virus, co-infections with other viruses, and the stage of liver disease [21, 22]. Since Brazil has a considerable extension, geographical differences in the populations studied can also affect treatment response due to varied viral characteristics of patients. At present, only two studies are evaluating DAAs efficacy in Brazil, and they are restricted to the south region of the country [23, 24]. Based on the presented scenario, this paper aims to evaluate the efficacy of DAAs in individuals with hepatitis C in Northeast Brazil, at the Liver Study Center (LSC) of Hospital Universitario Onofre Lopes (HUOL/UFRN).

## 4. Methods

This research is a single-center retrospective observational study using records of patients diagnosed with chronic hepatitis C who were treated with direct-acting antiviral agents between December 2015 and February 2019. The study was carried out following the ethical principles of the Declaration of Helsinki. The Research Ethics Committee approved it of the Federal do Rio Grande do Norte University (UFRN), under registration number 78858417.4.0000.5292. As a primary endpoint for our analysis, we defined the achievement of a sustained virological response as 12 weeks after the end of antiviral treatment (SVR12). Patients that were lost to follow up or had treatment prematurely interrupted for any reason was excluded from this analysis. The unspecified therapeutic regimen was also considered an exclusion criterion. All other patients were included regardless of genotype, prior treatment, or liver fibrosis stage. Our patients were from the Liver Study Center (LSC), the liver patient unit from Hospital Onofre Lopes, in Natal, Rio Grande does Norte, Brazil. Data were collected from patient's records included demographic information (age, gender) and clinical characteristics (disease stage, HCV genotype, co infection with HBV or HIV, prior transplantation, previous therapy, side effects to DAA, and sustained virologic response). The following DAA regimens were used for 12-24 weeks: sofosbuvir (SOF) + simeprevir (SMV) +/- ribavirin (RBV); SOF + daclastavir (DCV) +/- RBV. A minority of patients were treated with alternative regimens: two with SOF + RBV, one with telaprevir + RBV + pegylated (PEG) interferon, and one with boceprevir + RBV + PEG interferon. Treatment decision was based on the Clinical protocol and therapeutic guidelines for hepatitis C and co infections (PCDT), considering the availability of the drugs in Brazil provided by the Unified Health System (UHS/SUS-BRAZIL), the HCV virus genotype and subtype, the presence of cirrhosis and other co morbidities and previous therapy for HCV.

### 4.1. Diagnosis of liver cirrhosis

The stage of liver fibrosis was determined mainly through elastography. Liver biopsy, APRI, and FIB4 scores were used in some cases. Patients with clinical signs and/or echographic findings of liver cirrhosis were considered eligible for treatment without the need for another staging test for liver fibrosis [25].

### 4.2. Statistical analysis

Results were processed using standard statistical analysis. Proportions were used for descriptive statistics. Data of 2 groups of patients were compared using Fisher's two-tailed test. The $p$-value<0.05 was considered significant. All statistical analyses were performed using SPSS

statistics version 24 (IBM® SPSS, Chicago, IL, USA).

## 5. Results

A total of 52 patients were treated for HCV infection in the LSC between December 2015 and February 2019. However, two patients were excluded due to the absence of therapeutic regimen information. There were two patients whose HCV genotype information was not present at the database.

### 5.1. Epidemiological characteristics

The clinical and demographic data of our patients are depicted in (Table 1). At baseline, there was a predominance of males (58%) over females (42%), and the mean age was 62.5 years. Twenty (40%) patients had already been treated with interferon-based therapy in the past, and 32 (64%) were diagnosed with liver cirrhosis before starting treatment with DAAs. One patient presented with hepatitis B virus co infection and diagnosis of unresectable hepatocellular carcinoma.

**Table 1:** Patients characteristics n = 50 (%).

| | |
|---|---|
| Male | 29 (58%) |
| Female | -42% |
| Age (years) | 62.5 (40-80) |
| **HCV genotype** | |
| Genotype 1 | 2 (4.2%) |
| Genotype 1 a | 4 (8.3%) |
| Genotype 1 b | 33 (68.7%) |
| Genotype 2 | 2 (4.2%) |
| Genotype 3 | 6 (12.5%) |
| Genotype 3 a | 1 (2%) |
| **Coinfection** | |
| HBV | 1 (2%) |
| HIV | 0 |
| Liver cirrhosis | 32 (64%) |
| Treatment naïve | 30 (60%) |
| Treatment experienced | 20 (40%) |
| **Treatment regimen** | |
| Sofosbuvir + simeprevir | 23 (46%) |
| Sofosbuvir + daclastavir | 22 (44%) |
| Sofosbuvir + RBV | 2 (4%) |
| Sofosbuvir + simeprevir + RBV | 1 (2%) |
| PEG IFN + RBV + telaprevir | 1 (2%) |
| Boceprevir + PEG IFN + RBV | 1 (2%) |
| **Treatment duration** | |
| 12 weeks | 38 (76%) |
| 24 weeks | 10 (20%) |
| 24 weeks incomplete | 1 (2%) |
| 1 year | 1 (2%) |
| HCV = Hepatitis C virus; HBV = hepatitis B virus; IFN = interferon; RBV = ribavirin, PEG = pegylated | |

### 5.2. Virological characteristics

In this analysis, genotype 1 was predominant (81.2%, 1a 8.3%, 1b 68.7%). Genotypes 2 and 3 represented the remaining 18.7% of the cases. We identified that more than half of our patients had a viral load above 0, 8 Mio. IU/mL.

### 5.3. Degree of liver damage

In this retrospective study, 32 (64%) individuals had cirrhosis. Of these, 18 (56.2%) had an F4 degree of fibrosis, and 14 (43.7%) had clinical signs or echographic findings of cirrhosis and not submitted for quantification of liver fibrosis. Eight patients had advanced fibrosis (F3). Data evaluating the Child-Pugh score was absent in most of our patients.

### 5.4. Efficacy of antiviral therapy

Almost all of our patients (96%) were treated with an interferon-free regimen. The therapeutic regimens used were: sofosbuvir (SOF) + simeprevir (SMV) +/- ribavirin (RBV) in 24 (48%) patients and SOF + daclastavir (DCV) in 22 (44%) for 12 to 24 weeks. One patient was treated with boceprevir + pegylated interferon (IFN) + RBV while the other patient was treated with telaprevir + pegylated IFN + RBV. RVS-12 was achieved in 92% of the subjects. Genotype 1 achieved SVR in 92, 3% of the cases (1b 90.9%, 1a 100%). Genotype 2 and genotype 3 SVR was 100% and 85.7%, respectively. Treatment naïve showed SVR is 96.6%, while treatment-experienced individuals presented with 85% SVR. We analyzed the efficacy of DAAs in this population and compared it to the patients without cirrhosis. As stated above, 32 (64%) of our patients were cirrhotic before starting a treatment regimen with DAAs. The overall SVR in cirrhotics was 90.9%, whereas in non-cirrhotics SVR-12 was 94.4%. (Table 2) summarizes the efficacy of DAA therapy according to genotype, disease stage, and treatment experience. Genotype 1 patients treated with SOF + SMP +/- RBV achieved SVR in 91, 7% of the cases, while those who were treated with SOF + DCV +/- RBV attained SVR is 90.9%. SVR, according to genotype and treatment regimen, is registered in (Table 3). Fisher's two-tailed test comparing SOF + DCV +- RBV and SOF + SMP +- RBV regimens in all groups of patients (cirrhotic, treatment naive, treatment-experienced, co infected and each genotype - 1a, 1b, 3a) showed *p*-value statistically non-significant. Four patients had virological failure: three of them were cirrhotic and treatment experienced. One of the cirrhotic patients had hepatitis B virus co infection and unresectable hepatocellular carcinoma. The other one had advanced liver fibrosis (F3) with no previous treatment of HCV infection. (Table 4) shows the details of each of those patients. No adverse events were reported during treatment with DAA.

**Table 2:** SVR-12 of DAA according to HCV genotype, disease stage and treatment experience.

| **SVR 12 n (%)** | **Overall n = 50** | **G1** | **G2** |
|---|---|---|---|
| **Overall** | 46 (92%) | 36 (92.3%) | 6 (85.7%) |

| | | | |
|---|---|---|---|
| **Patients with cirrhosis** | 29 (90.6%) | 24 (92.3%) | 3 (75%) |
| **Patients without cirrhosis** | 17 (94.4%) | 14 (93.3%) | 3 (100%) |
| **Patients treatment experienced** | 17 (85%) | 16 (88.9%) | 1 (50%) |
| **Patients treatment näive** | 29 (96.6%) | 20 (95.2%) | 5 (100%) |
| G1 = Genotype 1; G2 = Genotype 3; SVR-12 = Sustained virologic response after 12 weeks; DAA = Direct acting antivirals; HCV = hepatitis C virus. | | | |

**Table 3:** SVR-12 of DAA according to HCV genotype and treatment regimen.

| HCV genotype | DAA regimen | SVR 12 (%) |
|---|---|---|
| **Genotype 1 (n = 39)** | Sofosbuvir + simeprevir 12 weeks (n =24) | 22 (91.7%) |
| | Sofosbuvir + daclastavir 12 weeks (n = 5) | 5 (100%) |
| | Sofosbuvir + daclastavir 24 weeks (n =10) | 9 (90%) |
| **Genotype 3 (n = 7)** | Sofosbuvir + daclastavir 12 weeks (n = 7) | 6 (85.7%) |
| SVR-12 = Sustained virologic response after12 weeks, DAA = Direct acting antivirals, HCV= Hepatitis C virus. | | |

**Table 4:** Detailed characteristics of the patients who did not achieve SVR.

| | Gender | Age | Genotype | Liver cirrhosis | Coinfection | Näive | Treatment regimen |
|---|---|---|---|---|---|---|---|
| **1** | Male | 73 | 1b | Yes | No | No | SOF + SMV |
| **2** | Female | 66 | 3a | Yes | No | No | SOF + DCV |
| **3** | Male | 70 | 1b | Yes | No | No | SOF + SMV |
| **4** | Male | 55 | 1b | No | No | Yes | SOF + SMV |
| SVR = Sustained virologic response;SOF = Sofosbuvir; SMV = Simeprevir; DCV = daclastavir. | | | | | | | |

## 6. Discussion

In this retrospective study, we evaluated the efficacy and safety of DAA therapy in patients with HCV from an academic center in Northeast Brazil. Similarly, to data reported in other series, there was a predominance of males over females. Epidemiological studies show that genotype 1 is the most common presentation of VHC, being responsible for over half of the cases [6]. Although genotype distribution varies depending on the region, the majority of our patients (81.2%) belonged to genotype 1. The remaining ones were genotype 2 and 3. There were also patients with genotype 4 who were not included in this analysis due to a lack of SVR-12 results. Therapeutics with SOF + DCV or SOF + SMV for either 12 or 24 weeks demonstrated to be highly effective and safe in patient's treatment naïve and experienced, with excellent tolerability and no serious adverse effects reported. Overall, SVR-12 was achieved in 92% of our patients. SVR-12 was higher in patients without cirrhosis (94.4%), genotype 1 (92.3%) and 2 (100%) and treatment naive (96.6%). The results of our "real-life experience" were similar to other studies evaluating DAAs efficacy, including those made in the southern portion of Brazil [23-24, 26]. Although treatment with SOF + SMV +/- RBV showed better response over SOF + DCV +/- RBV, there was no statistically significant advantage of one regimen over the other to all groups of patients specified at (Table 3). Both schemes had similar results. One randomized clinical trial also showed no statistical significance between SOF + SMV and SOF + DCV [27]. The groups of patient's treatment-experienced and genotype 3 with cirrhosis obtained response below 90% SVR-12. This observation is following other reports corroborating the fact that the population with cirrhosis or genotype 3 is the most difficult to treat with DAAs regimens currently available [26]. However, this data has to be interpreted with caution since the number of our sample was limited. The presence of advanced fibrosis or cirrhosis is known factors that affect the choice of therapy regimen and worsens post-treatment prognosis, as well as post-treatment; follow up the schedule [25-27]. The limitation of real-life studies resides in the fact that it is non-randomized, allowing for selection bias. The population in this study consisted mostly of patients who received free therapy from Unified Health System (UHS/SUS-Brazil).

## 7. Conclusion

In conclusion, the treatment of HCV in Northeast Brazil confirmed DAAs high SVR rate and safety. The era of DAAs has revolutionized HCV therapy, with the vast majority of patients having access to treatment expected to be cured of HCV infection. Recently approved DAA combinations herald a new paradigm of shortened duration pan-genotypic regimens. Several factors pre-therapy still determine optimal regimens, but this may not be required in the future as we move towards pan-genotypic regimens. As treatments get more manageable in terms of adverse effects, and shorter, on treatment monitoring will also diminish for the vast majority of patients. Therefore, the introduction of DAAs for the treatment of hepatitis C can radically change the epidemiological picture of this disease worldwide. From the use of these new classes of medicines, it is possible to eliminate the infection in countries that are dedicated to responsible action to control the epidemic, guaranteeing better results in public health and sustainability of universal access to treatment.

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