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Original article

Effectiveness and tolerability of direct-acting antivirals for chronic hepatitis C patients in a Southern state of Brazil

Vinicius Lins Ferreira[a], Helena Hiemisch Lobo Borba[a], Astrid Wiens[a], Maria Lucia Alves Pedroso[b], Vanessa Ferreira de Camargo Radunz[b], Cláudia Alexandra Pontes Ivantes[c], Aline Satie Oba Kuniyoshi[d], Roberto Pontarolo[a,*]

[a] Universidade Federal do Paraná, Programa de Pós-Graduação em Ciências Farmacêuticas, Curitiba, PR, Brazil
[b] Universidade Federal do Paraná, Hospital de Clínicas, Serviço de Gastroenterologia, Curitiba, PR, Brazil
[c] Gastroenterology Service, Centro de Orientação e Aconselhamento da Secretaria Municipal de Saúde, Curitiba, PR, Brazil
[d] Prefeitura de Maringá, Atendimento Especializado, Maringá, PR, Brazil

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ABSTRACT

Background: This study aimed to evaluate the clinical effectiveness in terms of sustained virological response (SVR) and tolerability of available second generation direct-acting antivirals (DAAs) in Brazilian patients.

Methods: This was a retrospective observational study conducted in six centers in Southern Brazil. The sample comprised adult patients who were chronically infected with hepatitis C virus (HCV), regardless of virus genotype, fibrosis stage, or prior treatment. Statistical analysis was performed to compare the effectiveness among the treatments, and also to uncover the factors influencing the achievement of SVR.

Results: A total of 296 patients were included in the study, with the majority receiving sofosbuvir with daclatasvir (59%) or sofosbuvir with simeprevir (26%). Overall SVR rates were approximately 91.6%. For genotype 1, sofosbuvir with daclatasvir had an SVR rate of approximately 95%, while the SVR rate of sofosbuvir with simeprevir was 92%; this difference was statistically significant only for subtype 1b. The only treatment used for genotype 3 patients was sofosbuvir with daclatasvir, and lower rates of SVR were observed for this group, compared to genotype 1 (84% versus 95%, $p < 0.05$). Apart from this difference between genotypes, and a difference between patients who achieved rapid virologic response compared with those who did not, there were no other statistically significant factors associated with SVR.

Conclusions: The results point to the effectiveness of second-generation DAAs in HCV Brazilian patients, especially those with genotype 1. Furthermore, that patients with genotype 3 need more attention and adjustments in available treatment options.

* *Corresponding author.*
E-mail address: pontarolo@ufpr.br (R. Pontarolo).

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Introduction

Chronic hepatitis C is a serious health-related problem that affects more than 71 million people, causing almost 400,000 deaths worldwide every year.[1] In Brazil, it is estimated that 1.5–1.7 million patients are infected with the hepatitis C virus (HCV), which represents about 2% of the population. However, a higher proportion of cases is from the South of Brazil (about 24.2% of the total number of cases in the country), where Curitiba city, the capital of Paraná state, is one of cities with the highest number of cases per 100,000 inhabitants (36.3).[2–4] For many years, interferon-based therapies were the primary treatment choice for chronic hepatitis C, followed by the first generation of direct-acting antivirals (DAAs), boceprevir and telapravir, which were used in combination with pegylated interferon and ribavirin (RBV). However, these treatments were problematic due to limited efficacy, severe side effects, and contraindications.[5,6]

In the last few years, second generation DAAs have been developed to provide more effective, tolerable, and safe treatments for hepatitis C. These can be used in combination with other second generation DAAs, and without interferon.[7–11] Since 2015 three DAA options have been available in the Brazilian public health system: sofosbuvir, daclatasvir, and simeprevir. The Brazilian government makes these drugs available at no cost, according to national guidelines for treating chronic hepatitis C, which prioritize patients with advanced stage of the disease. Recently, another combination of drugs was approved for use in Brazil, i.e., ombitasvir with paritaprevir/ritonavir and dasabuvir.[4]

These combinations of drugs have shown high rates of sustained virological response (SVR; a primary efficacy outcome measured at least 12 weeks after the end of treatment) and a favorable tolerability profile in randomized clinical trials (RCTs) and previous systematic reviews.[12–14] It is expected that these outcomes would also be reproduced in clinical practice.

Observational and regional studies are needed for evidence to support decisions in clinical practice. It is well established that this type of study is an important step in investigating clinical outcomes for chronic diseases, especially because, in some situations, results from RCTs are not fully representative of the general population.[15,16] Hepatitis C is a disease which is associated with many factors that can complicate medical treatment. This includes HCV genotype, co-infections with other viruses (such as the human immunodeficiency virus, HIV), and patient conditions (e.g., cirrhosis, liver transplantation, renal failure). Geographical differences in the populations studied can also affect treatment response due to varied viral characteristics of patients; this may occur in Brazil, which is a country with considerable extension and regional diversities.

In this context, the study aimed to evaluate the clinical effectiveness, in terms of SVR, and tolerability of second generation DAAs in chronic hepatitis C patients through an observational cohort study conducted in a Southern state of Brazil. We also aimed to compare the results obtained from patients receiving sofosbuvir with daclatasvir versus sofosbuvir with simeprevir.

Materials and methods

Study design, eligibility criteria, and treatment outcomes

In this retrospective observational study, we analyzed data from chronic hepatitis C patients who were treated in six centers in the South of Brazil, located in five different cities of the State of Paraná: Curitiba, Londrina, Cascavel, Ponta Grossa, and Maringá. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki and was approved by the local Ethics Committee on Human Research.

Data were collected from databases from each center, which contain all the individual patient records. The sample comprised adult patients (≥18 years) diagnosed with chronic HCV infection who concluded or discontinued any second generation DAA treatment before April 2017. Patients were included regardless of genotype, prior treatment, or liver fibrosis stage. The choice, administration, and management of each patient's treatment was the responsibility of the centers, according to the national guidelines.[4]

The primary effectiveness outcome was SVR 12 weeks or more after the end of treatment (SVR12), which is defined as undetectable HCV by polymerase chain reaction (PCR). Secondary effectiveness outcomes included rapid virological response (RVR; defined as undetectable HCV RNA after four weeks of therapy) and end of treatment response (EOTr; defined as undetectable HCV RNA at treatment completion), both measured using PCR tests. Patients that completed therapy but did not have any SVR results (i.e., missing data or lost to follow up) were excluded from the analysis.

Clinical information collected at baseline included age, sex, weight, presence/absence of cirrhosis, prior treatment information, HCV genotype, viral load, liver biopsy information, intended treatment, comorbidities (hepatitis B, HIV), other clinical information (prior transplantation or hepatocarcinoma), and treatment discontinuation due to adverse events (tolerability outcome).

Statistical analysis

Baseline categorical variables are described as absolute and relative frequencies, while continuous variables are reported as medians and standard deviations. Analysis was carried out using the chi-square test and logistic regression to identify variables significantly associated with SVR (e.g., baseline parameters: treatment option, duration, sex, age, cirrhosis, prior treatment, and others). Bivariate logistic regression results are presented as odds ratios (OR) and their 95% confidence intervals (CI). A p-value less than 0.05 was considered statistically significant in all cases. Analysis was performed using SPSS Statistics version 24 (IBM SPSS, Chicago, IL, USA) and StatSoft Statistica version 10.

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