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Major Article

Effectiveness of first-wave protease inhibitors in hepatitis C virus genotype 1 infection: a multicenter study in Brazil

Cirley Maria de Oliveira Lobato*[1], *Natalia Balassiano*[2], *Elodie Bomfim Hyppolito*[3],[4], *Rafaela Liz Pellegrim Sanchez-Lermen*[5], *Izabelle Venturini Signorelli*[6], *Miguel Yasuo Tomita Nicacio*[1], *Alberto Pereira Firmino Filho*[1], *Thais Guaraná de Andrade*[2], *José Milton de Castro Lima*[3], *Talita Amorim de Arruda*[5], *Fernanda Schwanz Coutinho*[6], *Everton Felipe do Vale Araujo*[1], *Ticiana Mota Esmeraldo*[4], *Erlon Cortez*[5], *Rafaela Lorenzon Aragão Capeli*[6], *Melquior Brunno Mateus de Matos*[1], *Francisco Sérgio Rangel Pessoa*[7], *Hélder Cássio de Oliveira*[5], *Érico Antônio Gomes de Arruda*[4], *Patrícia Lofêgo Gonçalves*[6], *Antônio Haroldo Araújo Filho*[3], *Eliane Bordalo Cathalá Esberard*[2], *Francisco José Dutra Souto*[5]

[1]. Hospital das Clinicas, Universidade Federal do Acre, Rio Branco, AC, Brasil.
[2]. Hospital Universitário Antonio Pedro, Universidade Federal Fluminense, Niterói, RJ, Brasil.
[3]. Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, Fortaleza, CE, Brasil.
[4]. Hospital São José, Fortaleza, CE, Brasil.
[5]. Hospital Universitário Júlio Muller, Universidade Federal de Mato Grosso, Cuiabá, MT, Brasil.
[6]. Hospital Universitário Cassiano Antonio de Moraes, Universidade Federal do Espírito Santo, Vitória, ES, Brasil.
[7]. Hospital Geral de Fortaleza, Fortaleza, CE, Brasil.

Abstract

Introduction: In 2013, combination therapy using peginterferon, ribavirin, and boceprevir or telaprevir was introduced to treat hepatitis C virus genotype 1 infection in Brazil. The effectiveness of this therapy in four Brazilian regions was evaluated. **Methods:** Clinical and virological data were obtained from patients of public health institutions in five cities, including sustained virological response (SVR) and side effects. Patients with advanced fibrosis (F3/4), moderate fibrosis (F2) for > 3 years, or extra-hepatic manifestations were treated according to Ministry of Health protocol. Treatment effectiveness was verified by using bivariate and multivariate analysis; p-values of < 0.05 were considered significant. **Results:** Of 275 patients (64.7% men; average age, 57 years old), most (61.8%) were treatment-experienced; 53.9% had subgenotype 1a infection, 85.1% had advanced fibrosis, and 85.5% were treated with telaprevir. SVR was observed in 54.2%. Rapid virological response (RVR) was observed in 54.6% of patients (data available for 251 patients). Overall, 87.5% reported side effects and 42.5% did not complete treatment. Skin rash, severe infection, and death occurred in 17.8%, 2.5%, and death in 1.4% of cases, respectively. SVR was associated with treatment completion, RVR, and anemia. **Conclusions:** The effectiveness of hepatitis C virus triple therapy was lower than that reported in phase III clinical trials, possibly owing to the prioritized treatment of patients with advanced liver fibrosis. The high frequency of side effects and treatment interruptions observed supported the decision of the Brazilian authorities to suspend its use when safer and more effective drugs became available in 2015.

Keywords: Hepatitis C virus. Sustained virological response. Telaprevir. Boceprevir. Post-marketing surveillance.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a worldwide public health concern owing to its potential for progression to cirrhosis and hepatocellular carcinoma[1]. In addition, it is considered to be the main cause of liver transplants in Western countries[2]. Unlike hepatitis B virus and human immunodeficiency virus (HIV) infections, HCV can be eradicated by treatment[3]. However, the traditional treatment using pegylated interferon-alpha (peginterferon) and ribavirin, which was adopted for many years worldwide, achieved sustained virological response (SVR) rates of less than 50% in genotype 1[4]. In addition, the frequent side effects associated with this treatment regimen have made adherence to treatment problematic, especially in patients with decompensated hepatic cirrhosis.

The development of direct-acting antivirals against HCV and their commercialization in 2011 revolutionized the treatment of this disease. The two drugs initially launched,

Corresponding author: Dr. Francisco José Dutra Souto.
e-mail: fsouto@terra.com.br
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the first-generation HCV protease inhibitors, boceprevir and telaprevir, were active only against HCV genotype 1, which is the most common strain and was, hitherto, the most resistant to treatment. The combination of boceprevir or telaprevir with peginterferon and ribavirin increased SVR rates from less than 50% to approximately 70%[5-7].

However, two important factors limited the use of these new drugs on a large scale: the high cost of these agents and the increased incidence of side effects, particularly dermatological and hematological events. Furthermore, both drugs must be administered several times daily and their absorption in the digestive tract depends on the amounts of concomitantly ingested fatty foods. These characteristics make treatment adherence more difficult.

Brazil is in the vanguard of providing its population with treatments for chronic viral diseases; this began in the 1990s with an audacious program to control and treat HIV infection. In 2013, in addition to the provision of peginterferon and ribavirin to HCV patients, Brazil incorporated boceprevir and telaprevir into the therapies that were available in its public health system[8].

The clinical protocol for the use of these medications in Brazil was directed to patients infected with HCV genotype 1, who were in advanced stages of liver fibrosis (F3 or F4 according to the METAVIR histological score)[9]. As a consequence of the severe side effects reported in other countries, medications were released only to centers experienced in the treatment of HCV infection.

More recently, new molecules directed at other HCV targets were successful developed, which allowed the use of therapeutic regimens without interferon-alpha, which increased safety, while ensuring comfortable dosage and treatment adherence[10,11]. Boceprevir and telaprevir were withdrawn from the protocol, and replaced by more effective and safer options. However, an assessment of the results of this strategy may be useful to provide important information for future decisions about the incorporation of new technologies by health systems.

This study describes the experience of seven centers in five state capital cities, located in four different regions of Brazil, which used the first-generation direct-acting antivirals in accordance with the protocol adopted by the Brazilian health authorities.

METHODS

We collected data from patients at five university institutions, located in four out of the five regions of the country: *Hospital das Clínicas*, in Rio Branco, State of Acre (North); the Walter Cantídio Hospital, in Fortaleza, State of Ceará (Northeast region); Antonio Pedro Hospital, in Niterói, Rio de Janeiro State, and the Cassiano Antonio de Moraes Hospital, in Vitória, State of Espírito Santo (Southeast region); and Julius Muller Hospital, in Cuiabá, State of Mato Grosso (Midwest region). Data from two other public hospitals in Fortaleza were added to data from State of Ceará because the services were conducted by the same professional team from Walter Cantídio Hospital.

All patients received treatment by the national public health system and commenced treatment in the second half of 2013 or in 2014. Visiting professionals in each institution retrospectively completed a standardized form, which included demographic, epidemiological, and clinical information. In addition, treatment outcomes and complications were recorded. These data were subsequently grouped into a single spreadsheet.

In the clinical protocol adopted in Brazil, this treatment was directed at patients who were in the advanced stages of liver fibrosis (F3 or F4), but it was contraindicated for patients with decompensated cirrhosis (Child-Pugh B or C liver functional class). Patients with moderate fibrosis (METAVIR, F2), confirmed by liver biopsy performed more than three years ago, could also be included, in addition to patients with severe extra-hepatic manifestations, regardless of their degree of liver fibrosis. Treatment was available to both naïve patients and those who failed to achieve SVR with previous therapeutic regimens (i.e., treatment-experienced patients). The protocol favored telaprevir over boceprevir because of the easier dosage of the former. In order to better understand the potential side effects, medications were released only to centers that were associated with hospitals in the event of serious complications.

This triple therapy was initiated between late 2013 and 2014. Because the protocol indicated that patients with advanced fibrosis should be treated for 48 weeks, an assessment of the results of the adopted strategy was not possible until 2015.

The frequencies and indicators of the central tendencies were used to describe the characteristics of the sample. The EpiData Analysis 2.2 (EpiData Association, Denmark, 2008) statistical pack was used for data analysis. The odds ratio (OR) of the categorical variables and the respective 95% confidence intervals were calculated. The significance level was set at 5%. For the adjustment of the variables of interest by multivariate analysis, logistic regression models were constructed to evaluate the independence of variables associated with SVR in the bivariate analysis computed by using the Stata 6.0 software (Statacorp, College Station, USA, 1999).

As the treatments followed the guidelines defined by the Government health policy, and no breach of confidentiality occurred, the treatment protocol used was not submitted to a research ethics committee. In order to be included in the clinical protocol and therapeutic guidelines for HCV and co-infections, each patient gave informed consent, in which he/she acknowledged the risks associated with treatment, as established by the Brazilian Ministry of Health (2013)[8].

RESULTS

The data from 275 patients treated with peginterferon, ribavirin, and boceprevir or telaprevir were analyzed. The majority of patients were men (64.7%), and the median age was 57 years old (quartiles: 51 and 62 years old); the range was 29 to 76 years old. More than 75% of the patients were at least 50 years old. The majority [119 (43.3%)] of patients were treated in the hospital in Acre. Each of the Rio de Janeiro and Ceará centers accounted for approximately 20% of the patients. The HCV subgenotype 1a was slightly more (45.5%) common than the subgenotype 1b (38.9%). Advanced fibrosis (F3 or F4) occurred in 234 (85.1%) patients. Moderate fibrosis (F2)

was observed in 39 (14.3%) patients. Two patients received treatment for extra-hepatic manifestations. Telaprevir was more frequently used than boceprevir (85.5%). Most (61.8%) patients had already received prior treatment with interferon-alpha (standard or pegylated) and ribavirin (**Table 1**).

One hundred and fifty-four (56%) patients completed the 48-week treatment; 117 (42.5%) did not complete the treatment course. Data from four (1.5%) patients were missing. SVR was confirmed in 54.2% of patients after 12 or 24 weeks (**Table 2**). Data on the rapid virological response (RVR), defined as undetectable hepatitis C virus-ribonucleic acid (HCV RNA) at the end of the fourth week of treatment, were available for 251 patients; it was observed in 137 (54.6%) patients.

Side effects occurred in 87.5% of the patients (**Table 2**), with severe side effects reported in 124 (45.1%) patients. Thirty-two (11.6%) patients were intolerant to the medications. Anemia was detected in 178 (64.7%) patients. Eighty (29.1%) patients developed leukopenia, whereas thrombocytopenia was observed in 65 (23.6%) patients. Erythropoietin was used in 154 (56%) patients, with transfusion required in 24 of these patients. Filgrastim was administered to 44 (16%) patients. Skin rash was observed in 49 (17.8%); of these patients, 47 were treated with a regimen that included telaprevir. Seven cases of skin rash were severe. Serious infections occurred in seven (2.5%) patients. In addition, four (1.4%) patients died during treatment or soon after its discontinuation. Septicemia accounted for one death and the three other deaths resulted from decompensation and the complications of cirrhosis.

The analysis of the possible associations between SVR and the demographic, clinical, and viral kinetic variables is shown in **Table 3**. There were no differences between the responses associated with the use of boceprevir or telaprevir ($p = 0.952$). In addition, there was no difference between 1a and 1b subgenotypes ($p = 0.177$), regardless of whether the patient was naïve or had prior therapeutic failure ($p = 0.745$). SVR was more frequent among those who had RVR (72.3%, $p < 0.001$) and those that completed 48 weeks of treatment (83.1%, $p < 0.001$). SVR was also more common in patients treated in Acre and Espírito Santo ($p < 0.001$). The majority of patients in the centers located in these cities had stage 2 fibrosis (79.5%) and the minority had F4 (36.2%). However, SVR was less frequent in patients with stage 4 fibrosis ($p < 0.047$), anemia ($p < 0.01$), and severe side effects ($p < 0.001$). After adjustment by using multivariate analysis, the following factors were found to be associated with SVR: completion of 48 weeks of treatment (OR = 16.7, IC95% = 7.1 – 39.5, $p < 0.001$), RVR (OR = 3.6, IC95% = 1.7 – 7.6, $p < 0.01$), and development of anemia during treatment (OR = 2.2, IC95% = 1.0 – 4.6, $p < 0.05$) (**Table 4**).

DISCUSSION

Inaugural studies on the combination therapy of boceprevir or telaprevir with peginterferon and ribavirin showed improvements in the SVR[5-7,12]. Thus, at this time, the therapy was adopted in many countries as the best method to cure patients with HCV. Among treatment-naïve patients, 68% of the patients in the group that received boceprevir had SVR, whereas the

TABLE 1: Basal characteristics of patients with chronic hepatitis C treated with first-generation protease inhibitors in five Brazilian public centers.

Characteristics	Number (Percentage)
Sex	
male	178 (64.7)
female	97 (35.3)
Age (years)	
29–30	4 (1.5)
31–40	12 (4.4)
41–50	52 (18.9)
51–60	131 (47.6)
61–70	70 (25.5)
71–76	6 (2.2)
Treatment center	
Rio Branco, Acre, North	119 (43.3)
Niterói, Rio de Janeiro, Southeast	57 (20.7)
Fortaleza, Ceará, Northeast	55 (20.0)
Cuiabá, Mato Grosso, Midwest	28 (10.2)
Vitória, Espírito Santo, Southeast	16 (5.8)
Subgenotype	
1a	125 (45.5)
1b	107 (38.9)
1	43 (15.6)
Fibrosis stage (METAVIR)	
2	39 (14.2)
3	118 (42.9)
4	116 (42.2)
extra-hepatic manifestations	2 (0.7)
Naïve/experienced	
experienced	170 (61.8)
naïve	101 (36.8)
not informed	4 (1.4)
Protease inhibitor	
boceprevir	40 (14.5)
telaprevir	235 (85.5)

TABLE 2: Response and characteristics related to the treatment of patients with chronic hepatitis C with first-generation protease inhibitors in five Brazilian public centers.

Characteristics	Number (Percentage)
Sustained virological response	
no	126 (45.8)
yes	149 (54.2)
Patients who completed treatment	
no	117 (42.5)
yes	154 (56.0)
missing data	4 (1.5)
Rapid virological response*	
no	114 (45.4)
yes	137 (54.6)
Side effects	
anemia	178 (64.7)
leukopenia	80 (56.0)
thrombocytopenia	65 (23.6)
skin rash	49 (17.8)
severe infection	7 (2.5)
death	4 (1.4)

*Data are missing for 24 patients.

TABLE 3: Analysis of the association between sustained virological response and different factors in patients with chronic hepatitis C treated with first-generation protease inhibitors in five Brazilian centers.

Characteristics	SVR (%)	Failed (%)	OR	95% CI	*p*-value
Number total	149 (54.2)	126 (45.8)	-	-	-
Sex					
female	45 (46.4)	52 (53.6)	1.0	-	
male	104 (58.4)	74 (41.6)	1.6	0.9–2.6	0.074
Average age					
in years	55.1	56.5	1.6*	-	0.207
Treatment center**					
Mato Grosso	11 (39.3)	17 (60.7)	1.0	-	
Ceará	22 (40.0)	33 (60.0)	1.0	0.4–2.7	
Rio de Janeiro	25 (43.9)	32 (56.1)	1.2	0.5–3.1	
Acre	78 (65.5)	41 (34.5)	2.9	1.2–7.0	
Espírito Santo	13 (81.2)	3 (18.8)	6.6	1.5–33.7	< 0.001
Subgenotype					
1a	65 (52.0)	60 (48.0)	1.0	-	
1b	66 (61.7)	41 (38.3)	1.5	0.9–2.5	0.177
Fibrosis (Metavir)***					
2	26 (66.7)	13 (33.3)	1.0	-	
3	67 (56.8)	51 (43.2)	0.6	0.3–1.4	0.220
4	54 (46.6)	62 (53.4)	0.4	0.2–0.9	0.047
Naïve/experienced					
naïve	53 (52.5)	48 (47.5)	1.0	-	
experienced	94 (55.3)	76 (44.7)	1.1	0.6–1.9	0.745
Protease inhibitor					
boceprevir	21 (52.5)	19 (47.5)	1.0	-	
telaprevir	128 (54.5)	107 (45.5)	1.1	0.5–2.1	0.952
RVR					
no	47 (41.2)	67 (58.8)	1.0	-	
yes	99 (72.3)	38 (27.7)	3.7	2.2–6.3	< 0.001
Completed treatment					
no	19 (16.2)	98 (83.8)	1.0	-	
yes	128 (83.1)	26 (16.9)	24.9	13.2–48.7	< 0.001
Severe side effects					
no	118 (65.6)	62 (34.4)	1.0	-	
yes	30 (32.6)	62 (67.4)	0.3	0.1–0.4	< 0.001
Anemia					
no	35 (36.1)	62 (63.9)	1.0	-	
yes	114 (64.0)	64 (36.0)	3.1	1.9–5.3	< 0.001

SVR: sustained virological response; **OR**: odds ratio; **95% CI:** 95% confidence interval; **RVR**: rapid virological response. *Value of F statistic for analysis of variance.**OR as base in the worst result (Mato Grosso) and *p*-value of the chi-squared test. *** Two patients were not assessed for fibrosis and were treated because of extra-hepatic manifestations.

TABLE 4: Multivariate analysis of association between sustained virological response and different variables, adjusted for sex and age.

Characteristics	OR	95% CI	*p*-value
Sex			
female	1.0	-	
male	0.9	0.4–2.0	0.823
Age*	1.0	0.9–1.1	0.829
Treatment center			
Cuiabá + Fortaleza + Niterói	1.0	-	
Rio Branco	2.2	0.9–4.8	0.056
Vitória	9.4	0.8–103.2	0.067
Fibrosis (Metavir)			
F2	1.0	-	
F3	1.1	0.3–3.2	0.978
F4	1.2	0.6–2.6	0.544
RVR**			
no	1.0	-	
yes	3.6	1.7–7.6	0.001
Completed treatment			
no	1.0	-	
yes	16.7	7.1–39.5	0.000
Severe side effects			
no	1.0	-	
yes	1.5	0.5–3.8	0.426
Anemia			
no	1.0	-	
yes	2.2	1.0–4.6	0.041

OR: odds ratio; **95% CI:** 95% confidence interval; **RVR**: rapid virological response. **Age* analyzed as a continuous variable. ****Study included 244 patients. Pseudo-R2 = 0.36.

placebo group reached 40%[6]. Among previously treated patients, SVR was achieved in 66% of those administered the triple therapy, but only in 21% of the placebo group[5]. With regard to telaprevir, among treatment-naïve patients, SVR was between 69% and 75% in the groups administered regimens containing telaprevir, but reached 44% in the control group[12]. In the study with treatment-experienced patients, SVR was higher than 80% in the telaprevir group versus 24% in the control group[7].

Because of the high cost of these medications, many countries (including Brazil) adopted this treatment only for patients with advanced fibrosis. This policy was supported by evidence that the treatment of patients with more severe fibrosis was more cost-effective[10,13]. However, the majority of the patients included in the introductory studies had F2 or a more mild degree of fibrosis[5-7,12]. Only 21% and 47% of the patients included in the studies with telaprevir had F3 or F4, respectively[7,12]. In the boceprevir studies, patients with F3 or F4 accounted for 9% and 19% of the patients, respectively[5,6]. Nonetheless, patients with advanced fibrosis, particularly cirrhotic patients, are at a higher risk of complications from the combination of peginterferon, ribavirin, and protease inhibitors[14].

In France, the real-life cohort (CUPIC) analyzed a group treated with boceprevir or telaprevir, including patients with advanced fibrosis who had already received prior treatment with peginterferon and ribavirin[14,15]. The SVR in this group was lower than that reported in the approval studies. Among the 299 patients treated with telaprevir, 51.8% had a SVR, whereas this value was at least 69% in phase III trials[7,12]. For boceprevir, SVR was achieved in 42.9% of 212 patients, which was much lower than the 66% to 68% reported in the boceprevir approval studies[5,6].

Moreover, there were alarming, serious adverse effects: 6.4% of the patients had severe complications (hospitalization, severe infections, hepatic decompensation, and/or death), 50.7% needed erythropoietin, and 12.1% required transfusion. In particular, cirrhotic patients with platelet counts less than 100,000/mm^3, and albumin lower than 3.5g/dL had a 44% risk of death or serious complications[14]. These parameters were then used as indicators of absolute contraindications to treatment.

Reports from Brazil showed similar, less effective results for this triple therapy. Almeida et al. reported that 20.8% of 24 patients in southern Brazil were not able to complete the treatment regimen, with only 50% achieving SVR[16]. Borba et

al. showed a 79% RVR rate in 117 patients in the five centers in the State of Paraná, South Brazil; however, these authors did not describe the SVR rates[17]. Recently, Callefi et al. described a multicenter experience involving six Brazilian states[18]. Among the 715 patients, 59% had cirrhosis and 67% were treatment-experienced; SVR was reached in 56.6%.

Our study focused on the experience of hospitals in four different Brazilian regions that provided triple therapy against HCV. The majority of the 275 patients evaluated in this study had advanced fibrosis (85.5%) and 42% had cirrhosis. More than half of the patients had failed to reach SVR in a previous treatment. For the triple therapy, 54.2% of patients reached SVR, which was similar to that reported by other Brazilian authors[16,18]. Our findings suggested that the attainment of SVR was lower in patients with advanced fibrosis than that reported in the initial studies. The relatively high rates of side effects (45%) and treatment cessation (42.5%) indicate the difficulty using these drugs in patients with more advanced disease. For all cases, reaching the end of treatment was the main factor associated with the therapeutic response and was associated with a fifteen-fold chance of attaining SVR in the multivariate analysis. Interestingly, some patients (16.2%) achieved SVR without completing treatment.

Rapid virological response has been shown to be a good prognostic indicator of therapeutic success; 72.3% of the patients who reached RVR also achieved SVR. Patients that achieved RVR had an almost four-fold greater chance of achieving SVR compared with those who did not ($p < 0.01$). In addition, tolerance and adherence to treatment were very important. SVR was higher among those who finished treatment (83.1%), which depended not only on tolerance but also on the frequency of serious side effects. Severe side effects were frequent; seven patients developed serious infections, and four patients died.

The development of anemia showed a potential association with SVR. This phenomenon has already been described as an indicator of good therapeutic prognosis in regimens containing only interferon and ribavirin[19]. Patients who develop anemia in the initial weeks of treatment displayed higher serum concentrations of ribavirin and better SVR rates[20]. The present study did not include information on the doses of ribavirin or its serum levels, which hindered further analysis of the association between SVR and anemia.

In the multivariate analysis, there were no significant differences in the results among the centers. However, the SVR rates obtained in Ceará, Mato Grosso, and Rio de Janeiro were lower (<50%) than those obtained in Acre and Espírito Santo. This may have occurred because the latter two centers included a higher proportion of patients with F2 fibrosis (23.1%) than the other three centers (5.7%).

In the present, post-approval study, the SVR values were lower than those described in the inaugural studies. Our results were similar to the findings of the French cohort and other studies conducted by Brazilian researchers[14-16,18]. In addition, the rates of treatment cessation because of intolerance or side effects were very high and medications were not well tolerated by the majority of the subjects. In spite of the complications, nearly half of the patients included in this study achieved SVR, which justified the 2013 decision to introduce boceprevir and telaprevir into the Brazilian protocol. However, in light of the current knowledge, their rapid withdrawal in 2015 also appeared to be a good and timely decision, taken after a cost-benefit analysis conducted by the public health authorities of the country.

In conclusion, patients who achieved RVR and completed the treatment had a greater chance of achieving SVR. However, the SVR rates achieved by different centers across Brazil were much lower than the rates in the approval studies and included high rates of side effects and treatment withdrawal. The 2015 decision from the Ministry of Health to stop using boceprevir and telaprevir appears to have been appropriate[21]. The new incorporated drugs, daclatasvir, simeprevir, and sofosbuvir, offer greater efficacy and safety, as well as a more comfortable dosage regimen. In the new Brazilian protocol, the use of peginterferon is limited by its side effects and the use of ribavirin remains an option in specific situations.

Conflict of interest

The authors declare that there is no conflict of interest.

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