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Major Article

First-wave protease inhibitors for hepatitis C genotype 1 treatment: a real-life experience in Brazilian patients

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Abstract

Introduction: Licensed for chronic hepatitis C treatment in 2011, the protease inhibitors (PIs) telaprevir (TVR) and boceprevir (BOC), which have high sustained viral responses (SVR), ushered a new era characterized by the development of direct-action drugs against the hepatitis C virus (HCV). The aim of this study was to analyze the effectiveness and safety of BOC and TVR administered with pegylated interferon and ribavirin and to share the experience of a Brazilian reference center. **Methods:** A retrospective descriptive study was conducted in patients with HCV genotype 1 infection who started treatment between July 2013 and December 2015. Data were collected using a computerized system. **Results:** A total of 115 subjects were included, of which 58 (50.4 %) had liver cirrhosis and 103 (89.6 %) used TVR. The overall SVR rate was 61.7 % (62.1 % for TVR and 58.3 % for BOC). The presence of cirrhosis was associated with a lower SVR rate, whereas patients who relapsed after prior therapy had a greater chance of showing SVR than did non-responders. The incidence of adverse drug reactions (ADRs) was high. Almost all patients (~100 %) presented with hematologic events. Furthermore, treatment had to be discontinued in 15 subjects (13 %) due to severe ADRs. **Conclusions:** In conclusion, the SVR rates in our study were lower than those reported in pre-marketing studies but were comparable to real-life data. ADRs, particularly hematological ADRs, were more common compared to those in previous studies and resulted in a high rate of treatment discontinuity.

Keywords: Hepatitis C virus. Boceprevir. Telaprevir. Adverse drug reaction.

INTRODUCTION

The use of first-wave protease inhibitors (PIs) boceprevir (BOC) and telaprevir (TVR) was the first step in direct antiviral therapy against hepatitis C virus (HCV). Initial studies showed a promising increase in the sustained viral response (SVR) among patients infected with HCV genotype 1, despite high costs and increased adverse drug reactions (ADRs), which often resulted in early treatment discontinuation[1-5].

Licensed for the treatment of chronic hepatitis C in 2011 and registered in Brazil in the same year, TVR and BOC were incorporated into the Brazilian public health system in 2013. According to Brazilian Ministry of Health (MH) recommendations, patients with HCV genotype 1 infection with moderate or severe liver fibrosis and/or presenting extrahepatic manifestations (EHMs) were indicated for TVR or BOC based therapy[6]. Between 2013 and 2015 in Brazil, individuals with HCV genotype 1 infection were treated with pegylated interferon (Peg-INF) and ribavirin (RBV) in addition to one of the first-wave PIs. The experience gained by healthcare teams from reference centers authorized for the care of patients with hepatitis C led to the incorporation of new concepts of HCV treatment, including the discussion on direct-action-drug resistance induced by select mutant viral strains.

There are few published, real-life studies that have evaluated the use of first-generation PIs in Latin America, particularly in Brazil[7-9]. Thus, this study was aimed at analyzing the safety and effectiveness of the above-mentioned triple regimens, in addition to sharing the experience of a referral center established at a tertiary/quaternary university hospital in Southeastern Brazil.

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METHODS

Study setting, population, and measurements

This retrospective descriptive study was performed between July 2013 and December 2015. The study included adult patients treated with Peg-INF and RBV with TVR or BOC for HCV genotype 1 infection. The subjects were followed up at the Viral Hepatitis Outpatient Clinic at University Hospital of the Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP).

According to the health policies established by the MH[6], triple therapies were made available to individuals infected with HCV genotype 1 who presented with the following conditions related to the degree of hepatic fibrosis according to the METAVIR[10] classification: cirrhosis, F4; advanced fibrosis without cirrhosis, F3; or moderate fibrosis, F2 demonstrated by an examination performed more than three years ago. Liver cirrhosis was diagnosed based on the findings of liver biopsy, by a non-invasive method of assessing the degree of fibrosis (transient elastography), by the presence of clinical signs such as esophageal varices, ascites, splenomegaly, and/or morphological alterations of the liver. Compensated cirrhosis was defined in terms of Child-Pugh prognostic classification (Child-Pugh A)[11]. Treatment was also recommended for patients with HCV-related EHMs, regardless of the degree of hepatic fibrosis[6]. Patients who eventually did not meet the criteria for indication of treatment with TVR or BOC by the recommendations of the Ministry of Health and who purchased the medications themselves were also included. Although some of the patients did not present with symptoms or sign that were in line with the criteria for treatment defined by the MH, there was a medical indication for antiviral therapy[12].

By using the hospital information system, demographic data (gender and age) and the following data regarding clinical history prior to treatment were collected: viral genotype and subgenotype; history of pharmacological therapy for chronic hepatitis C; type of response to prior therapy; EHMs; degree of liver fibrosis; presence of esophageal varices based on upper digestive endoscopy; and diagnosis of obesity, diabetes mellitus (DM), and/or hepatic steatosis. With regard to laboratory tests, creatinine, total bilirubin, and aminotransferase levels; international normalized index (INR); and pretreatment viral load were recorded. The last available examination results were considered before starting treatment with BOC or TVR, provided that the examinations were performed within six months before the start of pharmacological therapy. For an analysis of the association of pretreatment viral load with SVR, hepatitis C virus ribonucleic acid **(**HCV RNA**)** values <600,000IU/mL were classified as *low viral load* and HCV RNA values >600,000IU/mL were classified as *high viral load*.

Regarding the type of response to previous treatment, patients for whom drugs were discontinued during treatment because of a lack of a response and individuals who had detectable HCV RNA levels at the end of the dual therapy were considered non-responders. Patients whose viral load remained undetectable throughout the treatment but who had detectable HCV RNA levels after the end of the therapy were defined as relapsers.

All patients started treatment with a once-weekly subcutaneous Peg-INF α-2a 180mcg dose with RBV capsules (1,000 or 1,250mg daily, for body weight less than or greater than 75kg, respectively). TVR was used at a dose of 750mg (2 tablets of 375mg) every 8h, and BOC at a dose of 800mg (4 tablets of 200mg) every 8h. The expected treatment time for both regimens was 48 weeks, and TVR was used only in the first 12 weeks. A lead-in phase with Peg-INF and RBV was indicated for all patients who used BOC[6,12]. The medical criterion indicated TVR or BOC.

During the use of the medications, clinical and laboratory information associated with ADRs were collected, including hematological events (complete blood count results). Anemia was defined according to the reference values adopted by HCFMRP-USP (below 13.5g/dL for men and below 12g/dL for women). To evaluate the response to treatment, HCV RNA levels at the 4th, 12th, and 24th weeks of treatment were recorded. Medical appointments, complete blood count, and determination of serum creatinine levels happened every 15 days. Finally, viral load results were obtained at the end of the treatment, and at the 12th week and 24th week after treatment, if the latter data were available. Pharmacological therapy outcomes were defined as SVR; relapse; virological breakthrough discontinuity; and discontinuation according to the stopping rule, due to an ADR, or due to death. Virological breakthrough refers to the detection of HCV RNA during treatment after being undetectable during the same, or an increase of more than 1 log of HCV RNA relative to the lowest viral load observed during therapy[12,13]. Discontinuity by the stopping rule occurred on observation of a viral load greater than 1000 IU/mL in the 4th or 12th week of TVR therapy or greater than 100IU/mL in the 12th week of BOC therapy, or HCV RNA detectable at 24 weeks after the start of any therapeutic regimens[6]. As a result, the SVR at 12 weeks after treatment (SVR12) was considered, since in some patients, the HCV RNA levels at 24 weeks after treatment had not been determined when the data collection was finalized.

All procedures followed in this study were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Ethical considerations

The study was approved by the Research Ethics Committee of the hospital (authorization No. 345.034/2013), and all patients gave written informed consent to participate.

Statistical analysis

For the variables age; INR; and aspartate aminotransferase, alanine aminotransferase, creatinine, and total bilirubin levels, the following summary measures were calculated: mean, standard deviation, and interval between the minimum and maximum values. The frequencies of the variables sex, type of PI used, EHMs, previous treatment, type of response to previous treatment, viral subgenotype, DM, obesity, hepatic steatosis, fibrosis grade, esophageal varices, and pretreatment viral load (low or high) were determined, in addition to the frequencies of each of the outcomes to treatment with the most commonly observed triple therapies and ADRs. A univariate analysis was performed using the chi-square test to verify the association

between SVR and the variables cirrhosis, viral subgenotype (1a x 1b), pretreatment viral load, previous treatment, type of response to previous treatment, DM, obesity, and PI used. For the cirrhosis patients alone, the association between SVR and the presence of esophageal varices was analyzed. Variables for which the association analysis resulted in *p*-value <0.25 (univariate analysis) were selected for binary logistic regression analysis, which was also performed using the chi-square test. A level of significance (α) of 5% was set and the Statistical Package for Social Sciences (SPSS) program (SPSS Inc., version 17.1.0) was used for the analyses. Most analyses were performed considering all patients included in the study as a single group due to the small sample of the BOC group and consequential differences in samples between the BOC and TVR groups. The analyses were divided into TVR and BOC groups for analysis of PI and SVR type association, for description of treatment outcomes, and description of the most common ADRs.

RESULTS

A total of 115 patients were included, of which 78 (67.8%) were men, 96 (83.5%) were white, 58 (50.4%) had liver cirrhosis, 74 (64.3%) had been treated previously, and 103 (89.6%) used TVR. The age range was 29 to 74 years. These and other characteristics related to the clinical condition of the patients are described in **Table 1**.

Among patients diagnosed with EHMs, four presented with late porphyria cutanea tarda and two with mixed cryoglobulinemia without renal involvement. About treatment outcomes, considering the total number of individuals treated with triple therapy, 71 (61.7%) achieved SVR12 and nine (7.8%) were relapsers. For 65 (91.5%) of the 71 patients with SVR12, the 24-week post-treatment viral load result was available and HCV RNA remained undetectable. With regard to only those patients who used TVR, the treatment was discontinued for seven (6.8%) patients because of virological breakthrough, while the stopping rule motivated the suspension of treatment for eight (7.8%) individuals. Early discontinuation of treatment for another seven (6.8%) patients can be explained by virological breakthrough and concomitant application of the stopping rule.

Regarding patients who used TVR, the treatment of 13 (12.6%) was suspended due to ADRs. Of these individuals, for nine, therapy was discontinued because of an isolated ADR (six presented with a skin rash, one with anemia, one with decompensated liver disease, and one with psychiatric manifestations). Four other patients showed at least two adverse events that led to the discontinuation of therapy: one presented with a skin rash, anemia, neutropenia, and altered renal function; another presented with the four events associated with thrombocytopenia and gastrointestinal disorders (nausea/vomiting); the third presented with anemia, neutropenia,

TABLE 1: Clinical characteristics of patients treated with telaprevir or boceprevir.

Variables	Values
Age (years)	
mean (SD), range	52.9 (9.6), 29-74
Sex, n (%)	
male	78 (67.8)
female	37 (32.2)
Race	
white	96 (83.5)
black	3 (2.6)
Asian	2 (1.7)
other	14 (12.2)
AST ratio[a]	
mean (SD), range	2.1 (1.4), 0.5-6.1
ALT ratio[a]	
mean (SD), range	2.5 (1.8), 0.6-9.6
Creatinine (mg/dL)	
mean (SD), range	0.9 (0.1), 0.6-1.3
Bilirubin total (mg/dL)	
mean (SD), range	0.9 (0.3), 0.3-2.1
INR	
mean (SD), range	1.1 (0.2), 0.9-2.4
Protease inhibitor, n (%)	
BOC	12 (10.4)
TVR	103 (89.6)

Continue...

TABLE 1: Continuation.

Diabetes mellitus, n (%)	
yes	25 (21.7)
no	90 (78.3)
Obesity, n (%)	
yes	32 (27.8)
no	47 (40.9)
unavailable	36 (31.3)
Liver steatosis, n (%)	
yes	37 (32.2)
no	78 (67.8)
History of previous treatment, n (%)	
yes	74 (64.3)
no	40 (34.8)
unavailable	1 (0.9)
Previous treatment response, n (%)[b]	
relapse	39 (52.7)
non-response	33 (44.6)
unavailable	1 (1.4)
not applicable	1 (1.4)
Viral genotype, n (%)	
1	9 (7.8)
1a	60 (52.2)
1b	39 (33.9)
1a/1b	7 (6.1)
METAVIR fibrosis score, n (%)	
F0	1 (0.9)
F1	11 (9.6)
F2	20 (17.4)
F3	15 (13)
F4	58 (50.4)
unavailable	10 (8.7)
Esophageal varices, n (%)[c]	
yes	28 (48.3)
no	30 (51.7)
EHMs, n (%)	
yes	6 (5.2)
no	109 (94.8)
Baseline HCV RNA, n (%)	
≤600,000UI/mL	30 (26.1)
>600,000UI/mL	84 (73)
unavailable	1 (0.9)

SD: standard deviation**; AST:** aspartate aminotransferase **ALT:** alanine aminotransferase; **INR:** international normalized ratio**; BOC:** boceprevir**; TVR:** telaprevir**; FHMs:** extrahepatic manifestations**; HCV RNA:** hepatitis C virus-ribonucleic acid. [a]Ratio between the test result and the upper limit value of the reference range. [b]For the calculation of frequencies, the total number of patients who were previously treated were considered (n = 74). [c]For the calculation of frequencies, only patients with cirrhosis (F4) (n = 58) were considered.

and altered renal function; and the fourth presented with thrombocytopenia and decompensated liver disease. Four patients who were treated for a shorter time than expected due to ADRs had SVR: two patients with a cutaneous rash were treated for eight and 10 weeks respectively, a patient with anemia whose treatment lasted 14 weeks, and a patient whose treatment suspension was motivated by six associated adverse events and treated for 11 weeks. Among these four individuals, only those who were treated for eight weeks had no cirrhosis. There was no death among the patients treated with TVR.

With regard to the patients for whom BOC was indicated, the pharmacological therapy for one (8.3%) patient was discontinued due to the stopping rule. Suspension of treatment of two other individuals can be explained by virological breakthrough and the stopping rule. Pharmacological therapy of two patients treated with BOC (16.7%) was suspended because of ADRs: one patient had anemia and the other had neutropenia. The patient who showed a significant decrease in neutrophil levels used triple therapy for only 12 weeks, showed cirrhosis of the liver, and achieved SVR. Similar to the TVR group, there was no death among patients in the BOC group. **Figure 1** summarizes the treatment outcomes for each drug.

The SVR rate among individuals with cirrhosis was 51.7%. Statistical analyses showed an association between liver cirrhosis

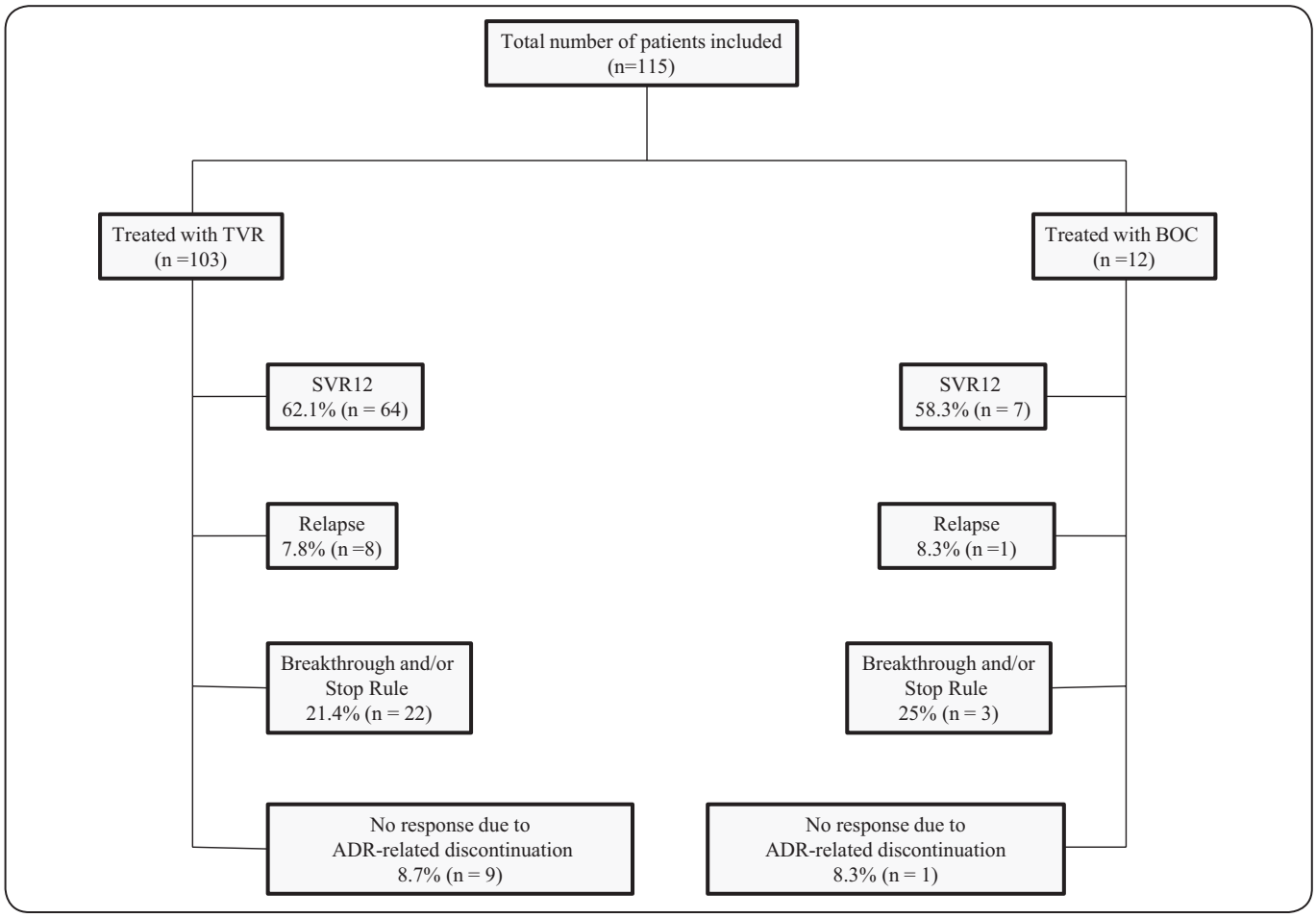

FIGURE 1: Flowchart of patients included in the study, treated with pegylated interferon, ribavirin, and boceprevir or telaprevir. **TVR:** telaprevir; **BOC:** boceprevir; **SVR:** sustained viral responses; **ADR:** adverse drug reactions.

and a lower chance of achieving SVR with triple therapy. With regard to previous treatment, 76.9% of the relapsers achieved SVR. There was evidence that these patients had a greater chance of achieving SVR relative to the non-responders. On the other hand, there was no evidence of an association between SVR and the following variables: previous treatment (treated vs. untreated), type of PI used, DM, obesity, viral subgenotype, pretreatment viral load, and presence of esophageal varices **(Table 2)**. The multivariate analysis showed that cirrhosis would be the most strongly associated variable with treatment response **(Table 3)**.

Regarding the univariate analysis and the clinical variables associated with SVR, the TVR and BOC groups were similar in relation to subgroup frequencies, particularly with regard to the variable previous treatment response. Among the patients who used TVR, who were previously treated, and for whom previous therapy data were available, 53.2% were relapsers and 46.8% were non-responders; among those who used BOC, 54.5% were relapsers and 45.5% were non-responders. Considering the variable cirrhosis, 54.3% of patients for whom data related to hepatic fibrosis were available and received TVR treatment were classified as F4, while 63.6% of individuals who used BOC were cirrhosis patients.

Hematologic events, asthenia, cutaneous reactions, anorectal manifestations, gastrointestinal complaints (nausea and/or vomiting), neuropsychiatric disorders, loss of appetite, dry cough, dyspnea, dysgeusia, and flu-like symptoms were the main adverse reactions observed for all patients included. The frequencies of cutaneous, anorectal, and nausea and/or vomiting events were higher in the TVR group, while that of dysgeusia was higher in the BOC group (**Table 4**).

DISCUSSION

As observed in the major phase 3 clinical trials involving TVR and BOC[1-5], the SVR in this study were higher than the response rates associated with the use of dual therapy with Peg-INF and RBV, and in general, did not exceed 50%[14,15]. On the other hand, they were lower than those found in the pre-marketing clinical trials of the above-mentioned PIs. Considering real-life data, the SVR rates were similar to those described in two European studies, one of which was a multicenter study involving 47 different centers in Italy[16,17] and higher than the SVR rates of real-life studies conducted in the USA[18,19]. The non-statistical association of the SVR with the PI used can be explained by the important difference between

TABLE 2: Results of univariate analysis for the association between clinical variables and sustained viral response.

Variables	OR	95% CI	p-value*
Liver cirrhosis[a]	0.410	0.180-0.931	0.03
Baseline HCV RNA level[b]	1.667	0.682-4.072	0.26
History of previous treatment[c]	1.095	0.498-2.408	0.84
Previous treatment response[d]	4.222	1.543-11.553	0.02
Viral genotype[e]	0.550	0.231-1.307	0.20
Obesity[f]	0.664	0.264-1.670	0.48
Diabetes mellitus[g]	0.598	0.244-1.463	0.35
Protease inhibitor[h]	1.172	0.348-3.950	0.51
Esophageal varices[i]	0.374	0.125-1.117	0.11

OR: odds ratio; 95% **CI**: confidence interval 95%; **HCV RNA:** hepatitis C virus-ribonucleic acid. **vs:** versus. *Values obtained through the chi-square test. [a]Cirrhosis vs absence of cirrhosis. [b]<600.000UI/mL (low viral load) vs ≥600.000UI/mL (high viral load). [c]Treated vs untreated. [d]Relapsers vs non-responders; [e]Genotype 1a vs genotype 1b. [f]Obesity vs absence of obesity. [g]Diabetes mellitus vs absence of diabetes mellitus. [h]Telaprevir vs boceprevir. [i]Diagnosis of esophageal varices vs absence of esophageal varices, considering cirrhosis patients.

TABLE 3: Results of multivariate analysis for the association between clinical variables and sustained viral response.

Variables	OR[1]	95% CI	*p-value**
Liver cirrhosis[a]	0.218	0.048-0.983	0.05
Previous treatment response[b]	2.062	0.494-8.611	0.32
Viral genotype[c]	1.297	0.301-5.586	0.73
Esophageal varices[d]	0.265	0.060-1.170	0.08

OR: odds ratio; 95% **CI**: confidence interval 95%; **vs:** versus. *values obtained through the chi-square test; [a]Cirrhosis vs absence of cirrhosis. [b]relapsers vs non-responders. [c]genotype 1a vs genotype 1b. [d]Diagnosis of esophageal varices vs absence of esophageal varices, considering cirrhosis patients.

samples that limits the robustness of the analysis and by the similarity of the groups in relation to the variables associated with the SVR.

The statistical difference between the SVR and PI used can be explained by the significant difference in sample sizes that limits the robustness of the analysis and the similarity between the groups in relation to variables associated with the response, such as the type of response to therapy.

Regarding the variables associated with SVR, evidence suggested that the diagnosis of cirrhosis is associated with a lower chance of SVR. This finding corroborates findings from several other studies, including phase 3 clinical trials and real-life studies[2,3,17-20], in addition to a meta-analysis published by Pecoraro et al[21]. The type of response to previous treatment was another variable statistically associated with SVR. Relapsers after dual therapy were more likely to achieve SVR than patients who have had another type of response since this also corroborates findings from other studies[3,4,17,20,22,23]. A binary logistic regression analysis indicated that absence of cirrhosis would be more strongly associated with SVR. Studies suggest that cirrhosis is also associated with response to the available therapies prior to TVR and BOC approval, which may explain the outcome of the multivariate analysis[13,14].

About the variables for which no evidence of association with SVR was found, Ascione et al[17] indicated, through multivariate analysis, that there is a positive association between not having diabetes and SVR. Although studies on the first-generation PIs are scarce, data from the literature involving dual therapy and analyses of the pathophysiological mechanism suggest a relationship between obesity and lack of SVR[24-26]. In the present study, the analysis of these two variables was limited by the high number of patients for whom no information related to body mass index was available and the large difference between the numbers of patients with and without diabetes.

With regard to the relationship between the pretreatment HCV RNA levels and SVR, the results of published studies are contradictory and these studies used different viral load values to define *high viral load* and *low viral load*[2,3,5,16,17,19,22,27]. In a meta-analysis, Cooper et al[28] found no statistically significant difference between the SVR of treatment-naive patients and treatment-experienced patients, a finding similar to that observed in this study.

Another result supported by studies published in the literature is the non-association between SVR and viral subgenotype[5,16,17,27]. Regarding the possible association between

TABLE 4: The most common adverse events associated with the use of telaprevir or boceprevir regimens.

Adverse Drug Reactions	Telaprevir (n=103)	Boceprevir (n= 12)
Anemia, n (%)	98 (95.1)	12 (100.0)
Anemia and use of erythropoietin, n (%)	72 (69.9)	9 (75.0)
Neutropenia, n (%)	91 (88.3)	12 (100.0)
Neutropenia and use of filgrastim, n (%)	29 (28.2)	5 (41.7)
Thrombocytopenia, n (%)	82 (79.6)	11 (91.7)
Skin reactions (Rash and/or pruritus), n (%)	89 (86.4)	7 (58.3)
Anorectal symptoms, n (%)	50 (48.5)	3 (25.0)
Nausea and/or vomiting, n (%)	50 (48.5)	3 (25.0)
Diarrhea, n (%)	24 (23.3)	1 (8.3)
Constipation, n (%)	9 (8.7)	2 (16.7)
Psychiatric disorders (depression, irritability and/or anxiety), n (%)	31 (30.1)	4 (33.3)
Flu-like symptoms (Fever, headache, chills, sweating, myalgia, malaise and/or arthralgia), n (%)	79 (76.7)	8 (66.7)
Asthenia, n (%)	84 (81.6)	11 (91.7)
Anorexia, n (%)	58 (56.3)	8 (66.7)
Epigastralgia, n (%)	14 (13.6)	2 (16.7)
Dysgeusia, n (%)	27 (26.2)	6 (50.0)
Dry cough, n (%)	33 (32)	3 (25.0)
Dyspnea, n (%)	36 (35)	5 (41.7)
Insomnia, n (%)	21 (20.4)	0 (0.0)
Somnolence, n (%)	14 (13.6)	2 (16.7)
Dizziness, n (%)	21 (20.4)	4 (33.3)
Peripheral edema, n (%)	15 (14.6)	5 (41.7)
Renal dysfunction, n (%)[a]	10 (9.7)	0 (0.0)
Blurred Vision/Visual acuity deficit, n (%)	7 (6.8)	0 (0.0)
Alopecia, n (%)	9 (8.7)	1 (8.3)
Oral ulcers, n (%)	11 (10.7)	1 (8.3)
Epistaxis, n (%)	12 (11.7)	0 (0.0)
Tachycardia, n (%)	5 (4.9)	0 (0.0)
Paresthesia, n (%)	4 (3.9)	1 (8.3)
Xerostomia, n (%)	4 (3.9)	1 (8.3)
Decompensated of liver disease, n (%)	3 (2.9)	0 (0.0)

[a]Renal dysfunction serum creatinine values above 1.5mg/dL were considered for individuals without alteration of this parameter prior to treatment.

the type of PI used and SVR, this study also corroborates data from other studies[16,20,28]. There was no evidence of an association between the diagnosis of esophageal varices and SVR. However, for this analysis, only patients with cirrhosis were considered, and the small sample size may have been a limiting factor.

Regarding safety, while phase 3 studies indicated that about 40% of patients who used TVR had anemia[1,4,5], 95.1% of the patients in this study who used the same drug had anemia. In general, all events related to the use of TVR, including other commonly observed events such as other hematological ADRs (neutropenia and thrombocytopenia), flu-like symptoms, asthenia, cutaneous events such as rash and pruritus, and anorectal discomfort were more frequent than in the previous studies[4,5,17,23]. A multicenter, real-life study carried out in Spain showed frequencies of anemia and other hematological events for TVR to be similar to those in the present study[21]. The main ADRs that caused discontinuation of pharmacological therapy were rash and anemia, similar to that in phase 3 and real-life studies[1,4,5,17].

About safety related to BOC use, as observed in most previous studies, cutaneous and anorectal reactions were less frequent than in the TVR group. On the other hand, the most

common ADRs were more frequently observed in the BOC group in comparison to the frequencies in previously published studies involving BOC[2,3,17,22]. The frequencies of hematological events in the previously mentioned Spanish multicenter study were similar to those in the present study[9]. Neutropenia and dysgeusia were frequent adverse events associated with BOC and more commonly related to the use of BOC relative to the use of TVR; this finding is supported by those of other studies[2,21,28,29]. The two BOC treatment interruptions due to ADRs were attributable to hematological reactions (anemia and neutropenia), which is explained by the high frequency of these events. It is important to emphasize that hemoglobin levels used for the diagnosis of anemia are not uniform across studies. However, the incidence of anemia in this study was higher, even if only the incidence of more severe anemia (which required the use of erythropoietin) was compared with the incidence of anemia in the other studies.

This study has limitations. It is a retrospective study based on data collection using a computerized system. Studies with this methodological design may be associated with an incomplete information retrieval due to underreporting of clinical data. Furthermore, there was no validated instrument or direct method used to measure adherence to pharmacological treatment. Considering that non-adherence is an important factor influencing the lack of SVR for antiviral drug therapies, it is a limiting factor for the interpretation of the results. Additionally, there is little information on this type of therapy in Latin American and Brazilian literature. Furthermore, although this study was carried out at a regional university reference center, which caters to 1,300,000 individuals, the sample size should be considered a potential limitation as it is relatively small and comprises patients treated at a single health center.

In conclusion, this study, which shares experience related to the indication of the first-wave PIs in triple therapy for Brazilian patients with HCV genotype 1 infection, showed lower SVR rates than those shown by pre-marketing studies, but comparable to those found in real-life studies performed in other populations. The frequency of ADRs, particularly hematological ADRs, was high and resulted in discontinuation of treatment in a considerable number of cases.

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Conflict of interest

The authors declare that there is no conflict of interest.

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