Revista de Ciências Farmacêuticas Básica e Aplicada
*Journal of Basic and Applied Pharmaceutical Sciences*

**Rev Ciênc Farm Básica Apl**, 2018;39:e629
ISSN 1808-4532

# Effectiveness and safety of protease inhibitors for the Hepatitis C treatment in a hospital of South Brazil: real life data

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## ABSTRACT

**The combination of Inhibitors of protease boceprevir (BOC) or telaprevir (TLV) concomitantly with peginterferon (PEG) and ribavirin (RBV) constitute the triple therapy (TT) for Hepatitis C treatment. To describe the experience of the TT treatment of chronic hepatitis C patients, besides discussing safety issues, in real life. Observational and retrospective study with 180 patients attended in a specialized center, between July 2014 and December 2015. Were evaluated variables as gender, age, access to drugs, pattern of alcohol consumption, pathway of contamination reported by the patient, previous treatment, degree of fibrosis, treatment regimen, treatment interruption and reason and Sustained Viral Response (SVR). Adverse Drug Reactions (ADRs) were collect through monthly self-report by the patient to the pharmacist. 65 patients used BOC and 115 TLV, and the mean age was 54.20 (BOC) and 53.92 (TLV) years. End of treatment rate was 52.3% (BOC) and 53.3% (TLV). ADRs occurred in 18.5% of the patients (BOC) and 13.9% (TLV), being more frequent the severe anemia. Erythropoietin (EPO) used in 45.4% (BOC) and 58.2% (TLV). SVR rate calculated by intention to treat was 38.5% (BOC) e 50.4% (TLV). This study has shown that the effectiveness of TT is not significantly higher than double therapy and is lower than the reported in clinical trials. High dropout rates due to ADRs have been demonstrated, as well as a lower SVR found in clinical trials.**

**Keywords: Hepatitis C. Drug-related Side Effects and Adverse Reactions. Treatment Outcome.**

## INTRODUCTION

It is estimate around 3% of the world's population infected with the hepatitis C virus (HCV), that it is mean 170 million people. To make matters worse, a significant number of people carry the virus unaware of the fact (Lavanchy, 2011; Cammà et al., 2012; Pavio & Lai, 2003). In Brazil is estimated between 1.4 and 1.7 million people with hepatitis C don´t know the diagnosis. There has been a worldwide effort increase to reduce the global impact of hepatitis C not only by implementing programmatic actions to promote awareness about viral hepatitis C but also by improving the monitoring, prevention, and treatment (Miotto et al., 2018).

The goal of hepatitis C treatment is eliminate the virus and the disease progression to cirrhosis, thereby reducing the possibility of terminal hepatic failure and hepatocellular carcinoma (Ghany et al., 2011; Teixeira et al., 2013). In the year 2013, triple therapy (TT) was standardized with protease inhibitors (PI) boceprevir (BOC) or telaprevir (TLV) both associated with peginterferon (PEG) and ribavirin (RBV) for patients with hepatitis C Chronic, carriers of genotype 1 (Brasil, 2013).

Shortly thereafter, in 2015, after researches and the development of new drugs, the Direct-Acting Antivirals (DAAs) in the Guideline replaced the PI for Hepatitis C in Brazil. The DAAs to be more effective, safer, and dosage convenience (Brasil, 2015a; Brasil, 2015b).

Although TT has been already replaced, the analysis of this results in real-life obtained during the treatment brings invaluable lessons that help to understand the difference from clinical trials to real life studies, and it is helps policy makers to anticipate challenges in healthcare to achieve satisfactory effectiveness rates in available therapies. Thus, the aim of this study is to describe the experience of the treatment of chronic hepatitis C boceprevir or telaprevir, both associated with peginterferon and ribavirina, besides discussing safety issues regarding this therapy.

## MATERIAL AND METHODS

*Study design*

This study is an observational cross sectional study with retrospective data from medical records.

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*Setting and participants*

All patients who began the treatment for hepatitis C between July 2014 and December 2015 were included. The had the patients HCV genotype 1, were older than 18 years, and were attended at the Center for the Injection and Monitoring of Injectable Medicines (CAMMI) of the Hospitalar Conceição Group of the Porto Alegre, Brazil. The evaluated drugs were TLV+PEG+RIB or BOC+PEG+RIB, according to the Brazilian Guideline (Brasil, 2013).

In this service, the clinic pharmacist had a consult with the patients on time for month. During this consult were check the ADR, exams, and treatment outcomes. All data were collected from pharmacotherapeutic follow-up records.

The study was submitted to the Ethics Committee of the Conceição Porto Alegre Hospital Group. It was approved on September 26, 2014 under the protocol number 14152.

*Variables*

The variables evaluated were gender, age, access to drugs (administrative process or Brazilian courts), city of residence, and pattern of alcohol consumption. Clinical variables included: pathway of contamination reported by the patient, previous treatment, previous transplant, number of prescribed and non-prescribed medicines in use during hepatitis C, degree of fibrosis according to METAVIR classification (Poodard et al., 2011), treatment regimen, treatment interruption and reason, end treatment rate, use of erythropoietin (EPO) or filgrastim to adverse drug reactions (ADR), and Sustained Viral Response (SVR).

The following ADRs were collect through monthly self-report by the patient to the pharmacist. ADRs included according Brazilian Guideline to Hepatitis C Treatment were alopecia, severe anemia (hemoglobin <8g/dl), anorexia, arthralgia, asthenia, chills, depression, dyspepsia, dyspnea, headache, chest pain, fatigue, fever, insomnia, irritability, myalgia, nausea, nervousness, severe thrombocytopenia (<40,000 per microliter), pruritus, sinusitis, somnolence, dizziness, vomiting, severe leukopenia (<1200 mm3), severe neutropenia (<750 mm3), forgetfulness, wounds, ascites, jaundice, hematuria, dementia, hemorrhage, xerostomia, thrush, cramps, sweating, heartburn, apnea, blurred vision, metallic taste in the mouth, skin rash, severe skin rash, anal pruritus, anal bleeding, and secondary infections (Brasil, 2013).

*Statistical Methods*

The analysis was perform using Statistical Package for Social Sciences (SPSS), version 18.0. In order to evaluate the association of BOC or TLV) with the categorical variables Pearson's chi-square test was apply and, when necessary, Fisher's exact test. Differences in means of the continuous variables in relation to the medication were evaluated using T student test. Normality was verified with the Kolmogorov-Smirnov test. The level of statistical significance considered was 5% ($P \leq 0.05$).

## RESULTS

A number of 180 patients who received TT were included. Table 1 shows the socio-demographic profile, lifestyle and hepatitis C treatment.

Patient clinical profile was present in Table 2. Both groups had a higher number of patients with F4 fibrosis grade (corresponding to cirrhosis) in the METAVIR classification, with moderate activity (A2).

**Table 1.** Characteristics of patients with hepatitis C virus genotype 1, and treat with boceprevir, peginterferon and ribavirin (BOC) or telaprevir peginterferon and ribavirin (TLV), between July 2014 and December 2015 in a specialized center to Hepatitis C treatment (n=180).

| Patients Characteristics | BOC (n=65) | TLV (n=115) | *P value* |
|---|---|---|---|
| *Sex* | | | |
| Female | 34 (52.3%) | 39 (33.9%) | 0.024* |
| Male | 31 (47.7%) | 76 (66.1%) | |
| *City of residence* | | | |
| Porto Alegre | 21 (32.3%) | 61 (53.0%) | 0.011* |
| Metropolitan region | 44 (67.7%) | 54 (47.0%) | |
| *Route of access to medicines* | | | |
| Unified Health System (according guideline) | 58 (90.6%) | 113(98.3%) | 0.025* |
| Judicial | 6 (9.4%) | 2 (1.7%) | |
| Mean age (in years) | 54.20 | 53.92 | 0.148 |
| *Pathway of contamination reported by the patient* | | | |
| Transfusion | 41 (63.1%) | 52 (45.2%) | 0.050 |
| Injectable drugs | 8 (12.3%) | 15 (13.0%) | |
| Others | 16 (24.6%) | 48 (41.7%) | |
| *Previous treatment* | | | |
| Sim | 50 (76.9%) | 69 (60.0%) | 0.032* |
| Não | 15 (23.1%) | 46 (40.0%) | |
| *Previous transplant* | | | |
| Yes | 0 (0.0%) | 1 (0.9%) | 1.000 |
| No | 65(100.0%) | 114 (99.1%) | |

**Table 1.** Continued...

| Patients Characteristics | BOC (n=65) | TLV (n=115) | *P value* |
|---|---|---|---|
| *Number of prescription medicines in use during hepatitis C treatment* | | | |
| None | 14 (21.5%) | 18 (15.8%) | 0.520 |
| 1 | 13 (20.0%) | 30 (26.3%) | |
| 2 | 6 (9.2%) | 10 (8.8%) | |
| 3 | 19 (29.2%) | 25 (21.9%) | |
| ≥4 | 13 (20.0%) | 31 (27.2%) | |
| *Number of non prescription medicines in use during hepatitis C treatment* | | | |
| None | 32 (49.2%) | 46 (40.0%) | 0.497 |
| 1 | 19 (29.2%) | 44 (38.3%) | |
| 2 | 11 (16.9%) | 23 (20.0%) | |
| 3 | 1 (1.5%) | 1 (0.9%) | |
| ≥4 | 2 (3.1%) | 1 (0.9%) | |
| *Alcohol use in the past* | | | |
| Yes | 51 (78.5%) | 96 (83.5%) | 0.525 |
| No | 14 (21.5%) | 19 (16.5%) | |
| *Frequency of alcohol use in the past* | | | |
| Daily | 14 (27.4%) | 23 (23.9%) | 0.789 |
| Socially | 37 (72.5%) | 73 (76.0%) | |
| *Alcohol use* | | | |
| Yes | 15 (23.1%) | 37 (32.2%) | 0.262 |
| No | 50 (76.9%) | 78 (67.8%) | |
| *Frequency of alcohol use* | | | |
| Daily | 3 (20.0%) | 8 (21.62%) | 1.000 |
| Socially | 12 (80.0%) | 29 (78.3%) | |

**Table 2.** Clinical profile of patients with hepatitis C virus genotype 1, and treat with boceprevir, peginterferon and ribavirin (BOC) or telaprevir peginterferon and ribavirin (TLV), between July 2014 and December 2015 in a specialized center to Hepatitis C treatment (n=180).

| Clinical Characteristics | BOC (n=65) | TLV (n=115) | P value |
|---|---|---|---|
| *Type of PEG* | | | |
| PegIfn α2b | 49 (75.4%) | 19 (16.5%) | 0.000* |
| PegIfn α2a | 16 (24.6%) | 96 (83.5%) | |
| *METAVIR classification (fibrosis grade)* | | | |
| F1 | 1 (1.5%) | 2 (1.7%) | 0.508 |
| F2 | 15 (23.1%) | 16 (13.9%) | |
| F3 | 19 (29.2%) | 49 (40.0%) | |
| F4 | 17 (26.2%) | 27 (23.5%) | |
| Cirrhosis without biopsy | 9 (13.8%) | 13 (11.3%) | |
| No biopsy | 4 (6.2%) | 11 (9.6%) | |
| *METAVIR classification (inflammatory activity)* | | | |
| A0 | 2 (3.1%) | 0 (0.0%) | 0.274 |
| A1 | 14 (21.5%) | 20 (17.4%) | |
| A2 | 26 (40.0%) | 55 (47.8%) | |
| A3 | 11 (16.9%) | 15 (13.0%) | |
| No biopsy | 12 (18.5%) | 25 (21.7%) | |
| *Use of complementary therapy* | | | |
| Erythropoietin | 26 (40.0%) | 52 (45.2%) | 0.871 |
| Filgrastim | 4 (6.2%) | 5 (4.3%) | |
| The two together | 10 (15.4%) | 15 (13.0%) | |
| None | 25 (38.5%) | 43 (37.4%) | |

In general, patients undergoing treatment for Hepatitis C use others drugs to control the severe adverse effects related to the hematopoietic system (anemia, neutropenia, and thrombocytopenia).

Erythropoietin use at least once time during treatment in 55.4% (BOC) and 58.2% (TLV). Filgrastim was use in 21.6% (BOC) and 17.3% (TLV) of patients during HCV treatment.

Treatment outcomes is present in Figure 1. For patients who received BOC, the end of treatment rate according to the guideline were 52.3%. Non-completion treatment reasons included therapeutic failure (24.6%), ADR (18.5%), voluntary abandonment (1.5%) and others (3.1%). For patients who received TLV, the end of treatment rate according to the guideline were 58.3%. Non-completion treatment reasons

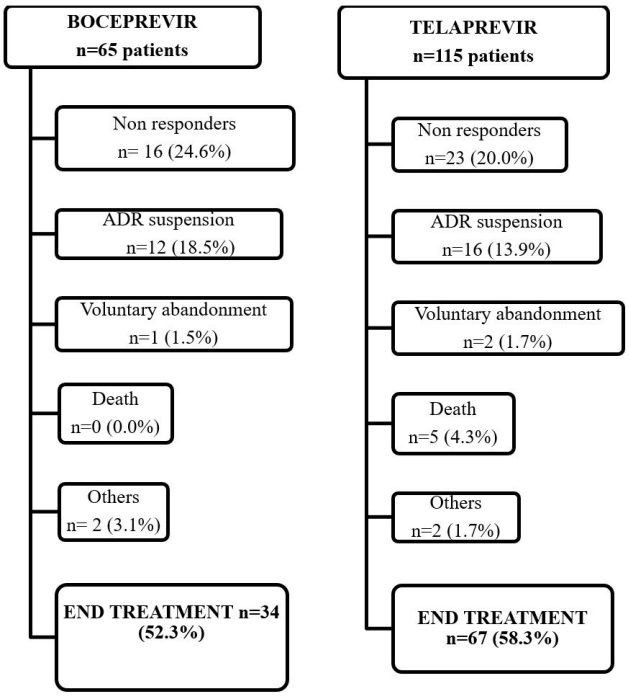


**Figure 1.** Outcomes of patients with hepatitis C virus genotype 1, and treat with boceprevir, peginterferon and ribavirin (BOC) or telaprevir, peginterferon and ribavirin (TLV), between July 2014 and December 2015 in a specialized center to Hepatitis C treatment (n=180).

**Table 3.** Frequency of the adverse drug reaction in patients with hepatitis C virus genotype 1, and treat with boceprevir, peginterferon and ribavirin (BOC) or telaprevir peginterferon and ribavirin (TLV), between July 2014 and December 2015 in a specialized center to Hepatitis C treatment (n=180).

| Adverse drug reaction | BOC (n=65) | TLV (n=115) | $X^2$ |
|---|---|---|---|
| Anemia* | 37 (56.9%) | 63 (54.8%) | 0.903 |
| Asthenia | 28 (43.1%) | 67 (58.3%) | 0.071 |
| Chills | 28 (43.1%) | 41 (35.7%) | 0.479 |
| Headache | 41 (63.1%) | 70 (60.9%) | 0.894 |
| Fever | 27 (41.5%) | - | 0.143 |
| Irritability | 33 (50.8%) | 53 (46.1%) | 0.673 |
| Myalgia | 43 (66.2%) | 59 (51.3%) | 0.076 |
| Nausea | 34 (52.3%) | 63 (54.8%) | 0.903 |
| Pruritus | 23 (35.4%) | 63 (54.8%) | 0.019 |
| Dizziness | 24 (36.9%) | 46 (40.0%) | 0.804 |
| Metallic taste | - | 43 (37.4%) | 0.345 |

*Hemoglobin < 8 g/dL.

included therapeutic failure (20.0%), ADR (13.9%), voluntary abandonment (1.7%), death (4.3%) and others (1.7%).

SVR rate calculated by intention to treat was 38.5% (BOC) e 50.4% (TLV) and per protocol was 73.5% (BOC) e 86.6% (TLV).

Anyone death was report during treatment with patients with BOC. Five deaths were report in the group of patients using TLV. One patient demonstrated loss of consciousness and fainting followed by cardiac arrest in the sixth week of treatment. Other patient, in the 32nd week of treatment, was diagnose with gastrointestinal bleeding. Two patients, the death was associated with septicemia, one had unspecified sepsis in 44 weeks of treatment. Another case of septicemia was associated with decompensated cirrhosis at the 12th week of treatment. The fifth patient had mental disorders prior to initiation of therapy and died in the second week of treatment. However, the family did not report the reason for the death.

The ADR proportions were similar in both groups (Table 3). A statistically significant difference was observe between BOC and TLV groups only for the presence of pruritus, more often seen among patients that used TLV.

## DISCUSSION

In this study, the incidence of hepatitis C in men was 47.7% (BOC) and 66.1% (TLV). In general, in the literature, a larger number of infected men is expected and consequently in HCV treatment (Colombo et al., 2014).

Participants of the BOC group had a mean age of 54.20 years and the TLV group 53.92 years. Comparing with literature, the average age could be considered similar. Since it is a silent disease, many patients discover it at a later in life after carrying the virus for many years. The age of the patient when acquiring the HCV infection is relevant, with a worse prognosis in subjects older than 40 years (Bacon et al., 2011; Garcia et al., 2012; Colombo et al., 2014; Almeida et al., 2015; Le et al., 2015).

The degree of liver disease severity is associated with lower SVR rate, our sample, 37.78% patients were cirrhotic. End treatment rate was 52.3% (BOC) and 58.3% (TLV). In Phase III clinical trials (SPRINT-2 and RESPOND-2) the reported completion rates for BOC are 68.5% and 66.4%, respectively, in TLV clinical trials (ILLUMINATE, REALIZE and ADVANCE) these rates were 66.5%; 70.1% and 73.8%, respectively (Jacobson et al., 2011; Sherman et al., 2011; Zeuzem et al., 2011).

Among the reasons that lead to high rates of non-completion of treatment, the therapeutic failure was the main reason found in the present study. About one quarter of the patients had their treatment discontinued due to a lack of virological response (24.6% BOC and 20.0% TLV). ADR suspension also represented an important rate (18.5% BOC and 13.9 TLV). Voluntary abandonment cases can also be related to ADR. These drugs also associated with severe adverse events, which often required additional treatment (Wehmeyer et al., 2014; Stahmeyer et al., 2016), with dropout rates due to adverse events ranging from 12 to 27% (Ascione et al., 2016; Gomes et al., 2018; Miotto et al., 2016).

The SVR rate calculated by intention to treat was 38.5% (BOC) e 50.4% (TLV), and is below the rates, around 60%, of international studies (Wehmeyer et al., 2014; Ascione et al., 2016). On the other hand, the results are close to data from national studies, with rates between 45 and 57% (Gomes et al., 2018; Miotto et al., 2016; Nunn et al., 2007).

Brazilian Guideline to Viral Hepatitis C and Coinfections provide for discontinuation of treatment early if there is no significant reduction in viral load (Brasil, 2013). This procedure aims to avoid exposing the patient to unnecessary

risks without proven therapeutic benefit, including quality of life. According to the guideline, polymerase chain reaction test (PCR) is performed to monitor virological response, and patients on BOC treatment should be discontinued when: HCV-RNA> 100 IU / mL at week 12 or detectable at week 24 For TLV the treatment should be suspended when HCV-RNA> 1,000 IU / mL at week 4 or 12 (Brasil, 2013).

ILLUMINATE e ADVANCE trial interruption treatment rates due to therapeutic failure were inferior to those found in ours: 6.7% and 10.7% to TLV (Jacobson et al., 2011; Sherman et al., 2011). In observational study, 25.2% interruption rate due to therapeutic failure to BOC or TEL (Werner et al., 2015).

Identifying the variables that help predict therapeutic success may help to optimize the usage of these drugs with greater efficacy and lower risks. It may be helpful to identify individuals with high probability of virologic failure, in order to allocate public resources optimally (Brasil, 2012a, b).

The healthcare in a specialized center provides the appropriate management to the patient, contributing to the success of therapy. The guideline treatment of hepatitis C in Brazil provides for the pharmacist's participation in patient follow-up (Brasil, 2013). At the development of this work, the pharmacist and the CAMMI team carry out qualified work that includes pharmaceutical-oriented drug dispensing and recording of service data, contributing to the success of therapy, as well as contributing to the optimization of public financial resources.

This study had some limitations, such as retrospective data collection and single center development. The small sample did not allow subgroup analyzes. On the other hand, it brings clinical practice data that are important in monitoring the therapies incorporated in the public health system in Brazil.

This study has shown that the effectiveness of TT is not significantly higher than double therapy and is lower than the reported in clinical trials. It became evident the importance of having access to the exams results and the monitoring to interruption due to therapeutic failure, to identify severe ADRs, in order to provide safe treatment to the patients. The hepatitis C treatment is complex and the monitoring of results in real life enables the qualification of care provided to patients, as well as generating evidence that may support the review of care guideline and incorporation of drugs into the Brazilian public health system (Gomes et al., 2018; Stepanova & Younussi, 2017).

The present real life study has proven the high dropout rates due to ADRs of the hepatitis C triple therapy, as well as a lower SVR found in clinical trials.

*Acknowledgments*

The study was supported by a grant from the Brazilian National Research Council (CNPq). Grant Nº 457464/2013-5.

*Conflict of interest*

All authors have none to declare.

**RESUMO**

*Efetividade e segurança dos inibidores de protease para o tratamento da hepatite C em um hospital no sul do Brasil: dados de vida real*

**A combinação de inibidores da protease boceprevir (BOC) ou telaprevir (TLV) concomitantemente com peginterferon (PEG) e ribavirina (RBV) constitui a terapia tripla (TT) para o tratamento da hepatite C. Descrever a experiência da TT em pacientes com hepatite C, além de discutir questões de segurança, na vida real. Estudo observacional, retrospectivo, com 180 pacientes atendidos em um centro especializado, entre julho de 2014 e dezembro de 2015. Foram avaliadas variáveis como sexo, idade, acesso a medicamentos, padrão de consumo de álcool, via de contaminação relatada pelo paciente, tratamento prévio, grau de fibrose, regime de tratamento, interrupção e razão do tratamento e Resposta Viral Sustentada (RVS). As reações adversas a medicamentos (RAM) foram coletadas por meio de auto-relato mensal do paciente ao farmacêutico. 65 pacientes usaram BOC e 115 TLV, e a idade média foi de 54,20 (BOC) e 53,92 (TLV) anos. A taxa de final de tratamento foi de 52,3% (BOC) e 53,3% (TLV). As RAM ocorreram em 18,5% dos pacientes (BOC) e 13,9% (TLV), sendo mais frequente a anemia grave. Eritropoietina (EPO) usada em 45,4% (BOC) e 58,2% (TLV). A taxa de RVS calculada pela intenção de tratar foi de 38,5% (BOC) e 50,4% (TLV). Este estudo mostrou que a eficácia do TT não é significativamente maior que a terapia dupla e é menor que a relatada em ensaios clínicos. Foram demonstradas altas taxas de abandono por RAMs, bem como uma menor RVS encontrada em ensaios clínicos.**

**Palavras-chave: Hepatite C Crônica. Efeitos Colaterais e Reações Adversas Relacionadas a Medicamentos. Resultado do Tratamento.**

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Received on November 16th 2018
Accepted on December 1st 2018