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Treatment of Hepatitis C with First Generation Protease Inhibitors

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Abstract

Recent changes in the treatment of hepatitis C have increased the demands for medical care and pharmacovigilance. The aim of this study was to evaluate the epidemiological profile, drug therapy, and response to treatment of chronic hepatitis C patients treated with interferon plus ribavirin in combination with Telaprevir (TVR) or Boceprevir (BOC), in an outpatient hospital in Northeast Brazil. A retrospective review of patient records archived at the Hepatology Unit of the University Hospital of the Federal University of Sergipe was conducted. A total of 48 treatments were analyzed, with TVR (35) being the most used antiviral drug. The overall Sustained Virologic Response (SVR) rate after a 48-week treatment course was 61.5% among patients who received TVR and 50% among patients who received BOC. However, the SVR rate was lower when intention-to-treat was considered, decreasing to 22.8% for TVR treatment, and 15.4% for BOC treatment. Cirrhosis was one of the main characteristics of patients with suspension of treatment due to adverse reactions associated with TVR use. During combination drug treatment, adverse reactions caused by the different drugs are cumulative, creating a scenario that is difficult to control. These findings indicate the need for multidisciplinary care, and for review of therapeutic indications or even evaluating the anticipation of treatment of chronic carriers of hepatitis C, in order to achieve better results. The availability of new direct antiviral drugs will negate the need for a therapy associated with significant adverse reactions and low therapeutic response.

Keywords: Hepatitis C; Pharmacotherapy; Drug Safety; Protease inhibitors; Telaprevir; Boceprevir

Introduction

The treatment of hepatitis C has advanced considerably in recent decades. The discovery of Protease Inhibitors (PIs), the first Direct Acting Antivirals (DAAs), was promising as these drugs were able to dramatically decrease the Viral Load (VL) [1,2]. In 2011, the first generation of DAAs, Telaprevir (TVR) and Boceprevir (BOC), was released for use against infection with Hepatitis C Virus (HCV) genotype 1, and triple therapy was subsequently considered the standard therapy [3,4]. In Brazil, the Ministry of Health began to provide these drugs in 2012 for patients with advanced fibrosis (F3 and F4) and/or for patients not responding to previous treatment [5].

The proposed treatment includes the elimination of the virus and a decrease in the progression of liver disease. The inclusion of PIs in association with Pegylated Interferon (PEG-IFN) and Ribavirin (RBV) increased the Sustained Virologic Response (SVR) rate, defined as the absence of detectable viral RNA in serum 3–6 months after the end of therapy; SVR is the best indicator of effective treatment [6,7]. The SVR to triple therapy can reach up to 83%, higher than the SVR to drug regimens with PEG-IFN and RBV [8]. In addition, triple therapy has been very effective in both treatment-naïve patients and in treatment-experienced patients, including the null response [9,10].

Treatment of hepatitis C is associated with increased medical demands due to increased costs and adverse reactions [8,11]. According to Kiser et al. [12], the correct use of TVR and BOC requires careful observation because there is clinical evidence of adverse reactions and more frequent drug interactions. Moreover, the long period of treatment and the negative experience associated with pharmacotherapy may contribute to an adverse clinical outcome [13-15].

Surveillance measures are essential for the collection and detection of data on adverse effects of drugs and for developing protocols for guidance on the use of medicines, risk minimization and prevention of adverse reactions [16]. Moreover, the use of PIs in Brazil is recent and there are not many studies evaluating the reactions of these drugs in our country. In the state of Sergipe, for example, to date there are no studies assessing the impact of implementation of these technologies?

The aim of this study was to evaluate the epidemiological profile, drug therapy, and response to treatment of patients with chronic hepatitis C treated with interferon plus ribavirin and TVR or BOC in an outpatient hospital in northeastern Brazil.

Material and Methods

A cross-sectional review was conducted of the medical records of all hepatitis C patients treated with BOC or TVR in combination with the alfa peginterferon 2a or 2b and ribavirin, between January 2013 and October 2015, as part of the Hepatology Service at the University Hospital of Sergipe in Northeast Brazil. The work was approved by the Research Ethics Committee of the Federal University of Sergipe. The study population included outpatients with chronic hepatitis C, regardless of sex or race, commencing treatment with triple therapy during the study period.

To characterize drug therapy, the following data were collected: Genotype, histologic evaluation (based on METAVIR classification), medical condition, and duration of treatment, antiviral drugs administered, and changes during drug therapy, adverse reactions,

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and medication used to treat adverse reactions. Antiviral therapy was assigned in accordance with the Clinical Protocols and Therapeutic Guidelines for viral hepatitis C and co-infections, issued by the Brazilian Ministry of Health. The medications administered were classified according to the Brazilian Common Denomination.

Patients with hepatitis B and HIV infection were excluded from the treatment response analysis. Patient response to antiviral treatment was categorized according to the Ministry of Health protocol [4,5]: RVR response; Extended Rapid Virologic Response (eRVR); virologic response at the End of Treatment (ETR); SVR; viral breakthrough. The evolution of the VL and manifestation of adverse reactions were monitored at weeks 4, 8, 12, 24 and 48 of treatment.

By intention-to-treat, all patients who started treatment were considered. Completion of treatment excluded patients who did not complete the proposed treatment. SVR and medication type were analyzed using the Chi-square test and Fisher's exact test (GraphPad Prism version 5®). The 95% confidence interval was calculated and a value of $p<0.05$ was considered significant. Following analysis, the results were expressed as text, graphics, and tables, using Microsoft Excel 2010.

Results

Records from 57 patients with clinical indication for triple-drug treatment with first generation PIs for treatment of chronic hepatitis C genotype 1, between January 2013 and October 2015, were selected from the archives of the Hepatology and Liver Diseases Sector. Six patients were excluded because they did not use the PIs: 2 used a single dose of PEG-IFN and ribavirin, 2 did not present VL decline >1 log after lead-in, 1 developed descompensated cirrhosis during the double-drug treatment, and one evaded treatment after the third week of treatment. For 3 further patients, no information was recorded regarding the reason for premature interruption of therapy.

According to the METAVIR classification, 15 patients presented with F4 fibrosis (31.9%), diagnosed by hepatic biopsy (8) and non-invasive methods, as elastography (7) (Table 1). One transplanted patient presented with F1 fibrosis.

The degree of fibrosis in patients receiving treatment for chronic hepatitis C, and treated with different PIs, is presented on Figures 1 and 2. A survey of the pharmacotherapeutic profile showed that 37.5% (18/48) of the patients were hepatitis C treatment-naive. The remaining 61.7% (30/48) did not respond to previous therapy with PEG-IFN+RBV, of which 46.6% (14/30) were relapsing, 6.6% (2/30) experienced virological breakthrough, 23.4% (7/30) were partial responders, and 23.4% (7/30) were null responders.

The TVR treatment was suspended in 48.6% of patients (17/35), 18% (3/17) did not complete the first 4 weeks of treatment, 2 patients (12%; 2/17) suspended treatment on week 10, and 2 (12%; 2/17) suspended treatment between week 12 and 24. Treatment suspension (53%; 9/17) was the main adverse reactions, and was more common in patients with advanced fibrosis (89%; 8/9). The reasons for treatment suspension included virological breakthrough (35.3%; 6/17), observed on week 4 (1/6), 12 (2/6) and 24 (3/6); and non-response (partial and null) (11.7%; 2/17).

For patient's treatment with BOC, treatment suspension occurred in 54% (7/13) of patients, due to the following: the presence of one or more reactions adverse (71.4%; 5/7), which was more common in cirrhotic patients (60%; 3/5); virological breakthrough in 1 case (14.3%) and failure to respond to treatment in 1 patient (14.3%). Virological breakthrough occurred between week 24 and 48, and the reactions that determined treatment suspension were observed between week 4 and 12 (Table 2).

Variables	Patients selected for antiviral treatment		
	All patients	BOC	TVR
Patient number (n/%)	48	13/48 (27.1)	35/48 (72.9)
Mean Age ± SD (years)	55.2 ± 16	-	-
Gender (n/%)			
Male	36/48 (75)	9/36 (25)	27/36 (75)
Female	12/48 (25)	3/12 (25)	9/12 (75)
HCV genotype (n/%)			
1A	20/48 (40,4)	10 (50)	10 (50)
1B	25/48 (51,1)	3 (12)	25 (88)
1 not specified	3/48 (8,5)	-	3 (100)
Treatment experienced (n/%)			
Yes	30/48 (62,5)	-	-
No	18/48 (37,5)	-	-
Fibrosis stage (n/%)			
F1	5/48 (10.4)	2/5 (40)	3/5 (60)
F2	13/48 (27.1)	5/13 (38.4)	8 (61.6)
F3	15/48 (31.25)	4/15 (26.6)	11 (73.4)
F4	15/48 (31.25)	2/15 (13.3)	13/15 (86.7)
Viral charge	-	1.000.000 log 6.0	630.957 log 5.8

Table 1: Baseline characteristics of the study.

The association between SVR and lead-in was shown to be statistically significant for treatment with TVR ($p=0.0238$) and non-significant for BOC ($p>0.05$). The SVR and RVR associations were not significant for both drugs. The SVR for patients with different degrees of fibrosis and treatment conditions are presented in Figures 1 and 2.

Approximately 60 different types of reactions adverse were described, with a higher average frequency in patients using the IFN+RBV+BOC combination than in patients receiving the IFN+RBV+TVR combination. It should be noted that, because all patients received IFN+RBV+IP, the adverse reactions observed in the present study were associated with the triple-drug combination. Symptoms of depression, including irritability, insomnia, and despondency, which may be characteristic of the use of IFN, were therefore considered to be associated with the use of PIs (Figure 3). For patients receiving TVR, the following complaints were reported: weight loss (42.8%; 15/35), body itching (62.8%; 22/35), skin rash (32%; 11/35), anal discomfort and/or itching (28%; 10/35), and lower limb pain (23%; 8/35). For patients receiving BOC, the following complaints were reported: weight loss (46.1%; 5/13), body itching (38%; 5/13), and skin rash (15.4%; 2/13). These symptoms were prevalent in 46.1% (6/13) of patients treated with BOC, and 14.3% (5/35) of patients treated with TVR (Figure 3).

Discussion

A close association was observed between the predictive factors for response to treatment and the factors referred to in the literature as barriers to successful treatment. The higher prevalence of chronic hepatitis C observed for men, which was even higher than the reported hepatitis C prevalence for men in Brazil [5]; indicate a greater exposure of men to risk factors and an increased concern with their health. In addition, the prognosis of treatment outcome is worse for men than for women [17], making treatment more difficult. According to Poynard et al. [18], Tanaka et al. [19], Narciso-Schiavon et al. [20], women have not only fewer changes in liver biochemical tests, but also lower rates of fibrosis progression, and a lower risk of developing hepatocellular

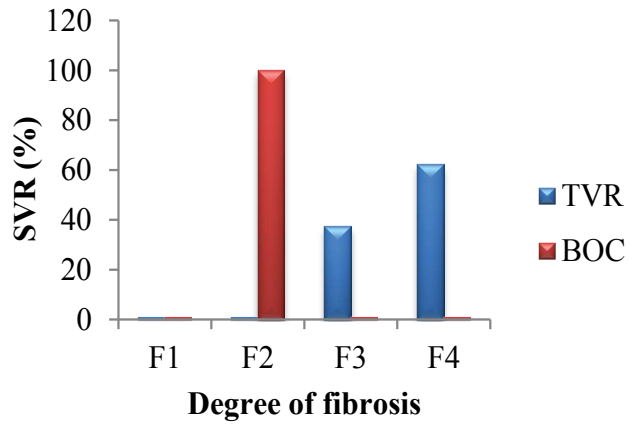

Figure 1: SVR for patients presenting different degree of fibrosis, and treated with TVR or BOC.

Variables	Patients selected for Antiviral Treatment		
	All patients	BOC	TVR
Effectiveness Variables			
Lead-in			
Patients number (n/%)	44/48 (91.6)	13/13 (100%)	31/35 (88.6)
Reduction of ≥1 log (n/%)	28/44 (64)	12/13 (90%)	16/27 (59.5)
Average log reduction (n/%)	-	2,9	1,9
RVR			
Rates (n/%)	32/48 (66.6)	5/13 (38.5)[1]	27/35 (77.1)[2]
SVR			
Related to Lead-in (n/%)	10/31 (32.25)	2/12 (16,6)	8/16 (50)
Related to RVR (n/%)	9/31 (29)	2/4 (50)	7/27 (25.9)
Global (n/%)	10/17 (58.8)	2/4 (50)	8/13 (61.5)
Intention-to-treat (n/%)	10/43 (23.25)	2/13 (15.4)	8/35 (22.8)
Other outcomes			
Breaktrough (n/%)	7/24 (29.2)	1/7 (14.3)	6/17 (35.3)
No answer (n/%)	3/24 (12.5)	1/7 (14.3)	2/17 (11.7)
Withdrawal due to adverse reactions (n/%)	14/24 (58.3)	5/7 (71.4)	9/17 (53)
Security variables			
Incidence of adverse reactions (n/ average per patient)	314/48 (6.5/ patient)	104/13 (8/ patient)	210/35 (6/ patient)
Anemia	28/48 (58.3)	8/13 (61.5)	20/35 (57.1)
Modification of dosage (n/%)	14/48 (29.2)	2/13 (15.4)	12/35 (34.3)
Use of erythropoietin (EPO) (n/%)	13/48 (27.1)	2/13 (15.4)	11/13 (84.6)
Use of packed red blood cells (n/%)	1/48 (2)	-	1/20 (5)
Leukopenia (n/%)	30/48 (62.5)	5/13 (38.5)	25/35 (72)
Neutropenia (n/%)	20/48 (41.6)	7/13 (54)	13/35 (13)
Use of Filgastrima (n/%)	15/33 (45.5)	5/15 (33,3)	10/15 (66,7)

Note: [1]Week 8 of BOC treatment; [2]Week 4 of TVR treatment

Table 2: Characteristics evaluated after the beginning of treatment.

carcinoma than men. It is believed that all of that is related to the protective effects of estrogen [21].

Regarding the election criteria adopted by the Brazilian guidelines, most patients presented advanced hepatic fibrosis (METAVIR F3 and F4), and hepatic fibrosis was detected in almost 71% of patients receiving TVR. These drugs were first available in 2013 to patient's monoinfected with genotype 1 and with advanced fibrosis (Metavir F3 and F4) or compensated hepatic cirrhosis (Child-Pugh ≤ 6) [6]. The degree of liver fibrosis, particularly the presence of cirrhosis, is directly related to response to treatment [22]. Patients with F3 and, particularly, F4 fibrosis, usually present lower SVR rates. However, the success of treatment in these patients is essential to avoid complications, such as hepatocellular carcinoma, liver transplant, decompensation, and death [23].

The observed higher overall SVR rate in relapsing patients corroborates the findings by Mchutchison et al. [24] and Krawitt et al. [25], who observed that relapsing patients represented the group that best responded to retreatment. Null-responders are usually the most difficult group to retreat, because their VL never becomes negative, either during treatment or at the end of treatment [26]. The average pre-treatment VL (>600,000 IU/ml) observed in the present study was higher than the levels observed by McHutchison et al. [24] as good predictors of SVR. This may have contributed to the low response rate observed.

Out of the 64% (28/44) of patients presenting with VL decline ≥1 log during the lead-in period, only 35.7% (10/28) achieved SVR; none of the patients with no VL decline ≥1 log during the lead-in period achieved SVR. This is in accordance with previous reports. Despite being a good predictor of response to PI treatment [27-29], the lead-in SVR rates presented by this study were low and showed a significant association only for the treatments with TVR ($p<0.05$), in that the lead-in scheme is not mandatory. Nevertheless, SVR rates from the lead-in were low. According to Poordad [28], the lead-in is based upon the premise that if the viral load decreases in this 4-week period, relapse rates and treatment resistance may be reduced, while the no reduction of the viral load during this period requires more frequent viral load monitoring due to the increased risk of developing resistance.

Furthermore, in the lead-in period is possible to test adherence to pharmacotherapy and tolerance to peg IFN plus ribavirin before initiating the use of boceprevir, and patients who do not tolerate dual therapy should not be treated with the IP [28].

For patients treated with TVR, only 1 patient who achieved SVR (3.2%; 1/31) presented no prior positive RVR. For patients treated with BOC, all patients who achieved SVR previously, had a RVR. However, only a small proportion of patients who had a RVR achieved SVR, specifically, 26% (7/27) of patients treated with TVR, and 15.4% (2/13) treated with BOC. Although the RVR/SVR associations were not

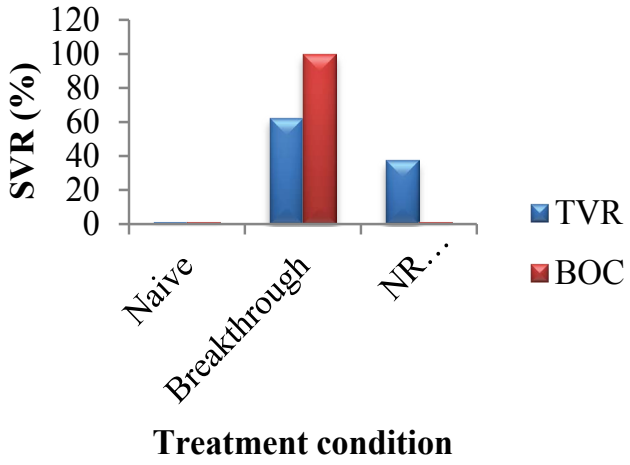

Figure 2: SVR in patients presenting different treatment condition, and treated with TVR or BOC.

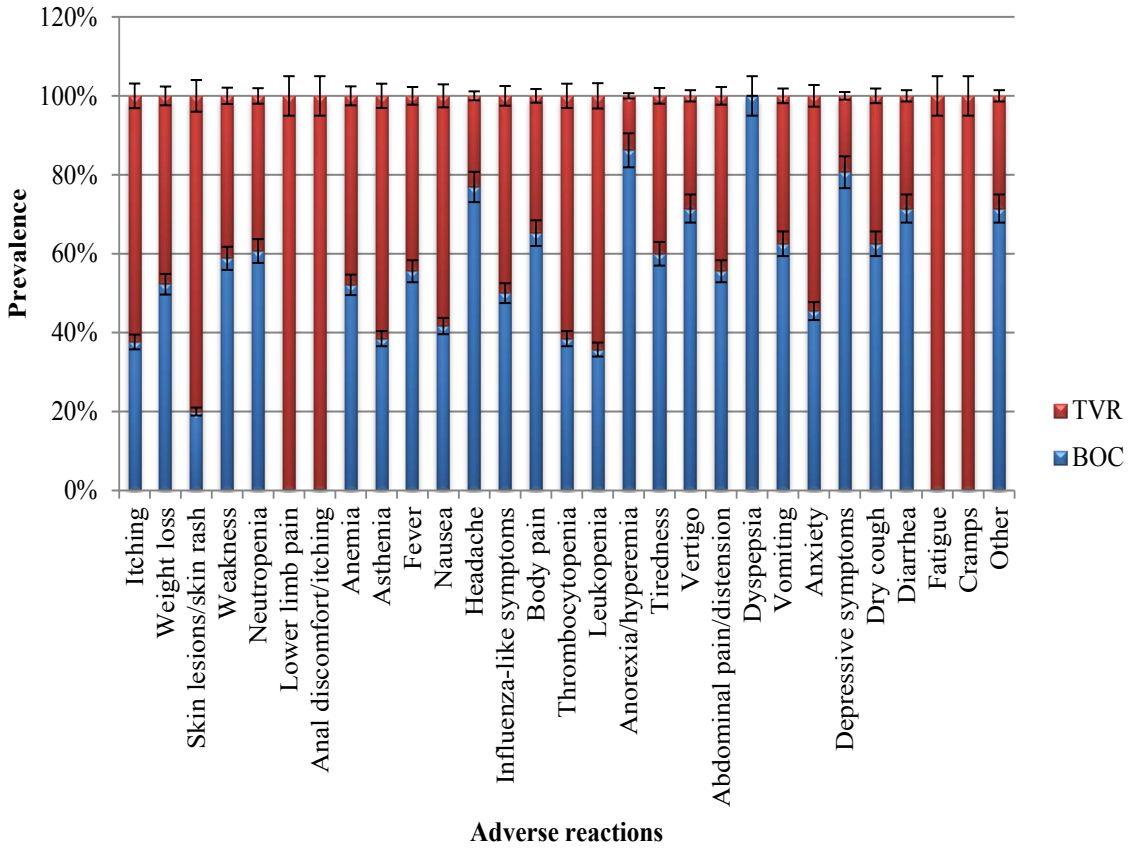

Figure 3: Frequency of the main adverse effects of triple therapy for hepatitis C.

significant in the present study, other studies highlight the predictive value of these variables [30,31].

As observed, patients that do not respond quickly to treatment (non-RVR) have decreased chances of achieving SVR. This indicates that the treatment for these patients should be reevaluated and, in selected cases, the period of treatment should be shortened to 24 weeks for TVR and 28 weeks for BOC, avoiding adverse reactions, for potentially curative treatments. The imposition of response-guided therapy (RGT) for the treatment with these drugs has already been highlighted in the literature, showing that it is possible to reduce the treatment time of certain patients within 24 weeks with peg IFN+RBV, without affecting SVR that is, in these cases the patient will not benefit from the 48-week treatment [28, 32]. In this way, RGT is essential to patient safety.

Adverse reactions were some of the causes for suspending treatment (24/48), and were slightly more frequent among cirrhotic patients [52.9% (9/17)] just as Vierling et al. [29]. The frequency of adverse reactions was considered serious in 41.4% (12/29) of patients with hepatic cirrhosis, and was even higher in the Model for End-stage Liver Disease (MELD) subgroup, when compared to patients without complications [33].

The main adverse reactions associated with treatment of the subjects were similar to those found in previous studies using PI [34]. However, the average frequency of side effects was higher than previously reported. Colombo et al. [35] described an average of two to four adverse reactions experienced by patients receiving TVR, leading to suspension of treatment in 16% of cases. The average reported rate of treatment suspension due to adverse reactions during triple-drug therapy is 12.5% [24,27,31,36-37], lower than in the present study. However, Hezode et al. [38] highlighted the high incidence of adverse reactions associated with cirrhosis, including death and serious complications. The high incidence of adverse reactions observed in the present study were probably related to the severity of the hepatic disease, as most patients (62.5%; 30/48) presented with a high degree of fibrosis (F3, F4).

Anemia was more often prevalent with BOC than with TVR treatments, which is in agreement with the Comparative Assessment of Effectiveness of Antiviral Therapies in Hepatitis C (CMPASS) [39]. Anemia was the main adverse reaction associated with the use of BOC. However, the frequency of anemia in the present study was considerably higher than in previous studies and this is likely to be due to the higher proportion of cirrhotic patients. Hezode et al. [38] reported a frequency of anemia of approximately 50% for triple therapy with BOC, and 40% with TVR, lower than observed in the present study. The impact of anemia on SVR does not seem to be important in treatment-naive patients treated with TVR. However, it may have a negative impact in patients treated with BOC [38]. In the present study, no patients presenting with anemia during treatment with BOC achieved SVR.

The indication for EPO in patients treated with BOC was higher than in previous studies, with a reported variation of up to 46% [27-28,40]. This supports the conclusions of Hezode et al. [38] that the use

of EPO does not seem to have a positive effect on SVR rates in studies with BOC. Blood transfusions were performed in 5% of patients, similar to previously reported rates (3-5%) [31-31,34,37]. It should be highlighted that in cirrhotic patients, in addition to the difficulty of managing anemia, the use of EPO (50.7%) and transfusions (12.1%) are more frequent [34]. Neutropenia occurrence was also higher than previously reported for both drug combinations. Although it is associated with the use of PEG-IFN [41], studies of treatments with BOC and TVR reported lower neutropenia values, approximately 25% for INF+RBV+BOC [40] and 37% for TVR [37].

The use of TVR caused anal discomfort and/or itching in 28% of patients, much higher than the 6% reported in the studies for drug approval [31,42]. In the present study, no association was observed between anal itching and BOC, in accordance with previous reports. The following adverse reactions were observed, with lower occurrence than previously reported: Dysgeusia [27-28,42], body itching in patients receiving TVR [31,42], skin lesions or rash [24,31,40], headaches [31,40], and depression and/or depressive symptoms [43]. It should be highlighted that the presence of neuropsychiatric symptoms is quite common during interferon treatment. Similar to in the present study, the psychiatric adverse reactions more often reported by patients are fatigue and sleep disturbance [43].

Because it is a combined drug treatment, the adverse reactions for each drug are cumulative and this is clinically challenging. Some of these reactions are quite significant, and may determine continuity of treatment, whereas others may affect the quality of life of patients. Fagundes et al. [44] reported that the transient decrease in quality of life in patients treated with TVR or BOC was higher than in patients treated with IFN+RBV double treatment. The authors highlighted that even subjective adverse reactions, such as fatigue, have a direct impact on patient quality of life, and decrease the chances of achieving SVR.

In addition to adverse reactions, the chances of achieving SVR may be lower in clinical practice and depend on several factors [45,46]. El-Zayadi [47], Loannou et al. [48] observed that a high percentage of patients with cirrhosis and comorbidities did not achieve SVR. Kim [49] suggested that medical conditions, such as diabetes, blood pressure, or thyroid diseases, should be optimized before commencing treatment. Namely, a careful selection of the individuals to be treated is crucial, particularly in patients presenting with advanced liver disease [50]. In a multidisciplinary context, studies have shown that the collaborative work of other professionals, such as the pharmacist, may prevent adverse reactions and improve the provision of adequate information associated with medications and pharmacotherapeutic management. Some of the pharmaceutical interventions still resulted in referral to other professionals (e.g., nutritionists, psychiatrists, dermatologists), which may have contributed to a higher SVR rate [51,52].

Differences in population characteristics may also account for the lower SVR rates observed among patients receiving BOC, compared to those of subjects involved in studies for drug registration. Sample selection is a weak point of randomized clinical assays, where samples are generally composed of white patients, presenting absent or minimal hepatic fibrosis, and include few null-responders to prior treatment. For example, in the REALIZE study [37], the percentage of white individuals was 93.5%. Fried et al. [17] indicated afro-descendant ethnicity as a predictor of bad prognosis. In ADVANCE [31], only 6% of patients were cirrhotic, comparable to the studies with BOC, where 11% of patients were METAVIR F3 or F4 [28] and 10% were cirrhotic [29]. These values were much higher in the present study (48%).

All these factors may have contributed to the different clinical outcomes observed in the large randomized studies used to define guidelines, and should be analyzed and considered in future drug therapy adjustments and individualization. The high incidence of adverse reactions and low SVR rate observed in the present study indicates that the processes of identification of the clinical indication for treatment and treatment monitoring should be reevaluated, particularly in eligible patients, and included in specific protocols.

Silva et al. [53] noted that, for non-urgent patients, it is prudent to wait for the inclusion of new treatment options into a single health system. Studies have shown that direct-acting antivirals have better cure rates, together with a reduction in the complexity of pharmacotherapy (e.g., reduction in the number of drugs, time of treatment, need for tests to monitor viral load, and incidence of adverse reactions) [54,55].

Although the results are expected, the data presented is relevant, and it does bring a great novelty to the evaluation of these treatments from the perspective of Brazil, thereby contributing to support and complement biomedical research and decisions in the field of hepatitis C drug policy.

Conclusion

The present results show that the treatment of chronic hepatitis C using triple therapy is not satisfactory, due to high rates of treatment suspension and several complications. These findings indicate the need for multidisciplinary care, and for review of therapeutic indications or even evaluating the anticipation of treatment of chronic carriers of hepatitis C, in order to achieve better results.

The availability of new direct antiviral drugs will negate the need for a therapy associated with significant adverse reactions and low therapeutic response.

Study limitations and future prospects

The study has some limitations, such as selection bias. This is not a prospective, randomized, controlled study, but a retrospective analysis of the results observed in the medical records of patients treated for hepatitis C. Single-centered research and the small sample size are also limiting. Therefore, loss of information wills likely results in extrapolation of data. However, this is a real life study that has allowed the evaluation of the use of medicines in various limiting conditions, such as biopsychosocial characteristics, encompassing all patients treated in the state, contributing to the medico-social and economic basis of regulatory activities and other decisions in the field of medication policy and treatment of hepatitis C.

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