[1]Universidade Federal de Santa Catarina, Centro de Ciências da Saúde, Departamento de Ciências Farmacêuticas, Florianópolis, Santa Catarina, Brazil

[2]Hospital Nossa Senhora da Conceição, Porto Alegre, Rio Grande do Sul, Brazil

[3]Universidade de São Paulo, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Departamento de Ciências Farmacêuticas, Ribeirão Preto, São Paulo, Brazil

[4]Universidade Federal de Pelotas, Faculdade de Medicina, Pelotas, Rio Grande do Sul, Brazil

[5]Universidade Federal da Bahia, Faculdade de Farmácia, Salvador, Bahia, Brazil

[6]Universidade Federal de São Carlos, Departamento de Medicina, São Carlos, São Paulo, Brazil

[7]Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Clínica Médica, Ribeirão Preto, São Paulo, Brazil

[8]Universidade Federal de Pelotas, Instituto de Biologia, Departamento de Fisiologia e Farmacologia, Programa de Pós-Graduação em Epidemiologia, Pelotas, Rio Grande do Sul, Brazil

[9]Universidade Federal de Ciências da Saúde de Porto Alegre, Departamento de Farmacociências, Porto Alegre, Rio Grande do Sul, Brazil

Correspondence to: Mareni Rocha Farias
Universidade Federal de Santa Catarina, Centro de Ciências da Saúde, Departamento de Ciências Farmacêuticas, Campus Universitário Trindade, CEP 88049-979, Florianópolis, SC, Brazil
Tel: +55 48 3721-3940.

E-mail: marenif@pq.cnpq.br

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Hepatitis C in Brazil: lessons learned with boceprevir and telaprevir

Lenyta Oliveira Gomes[1], Marina Rodrigues Teixeira[1], Júnior André da Rosa[1], Alberi Adolfo Feltrin[2], João Paulo V. Rodrigues[3], Mariane D'Avila Vecchi[4], Jane Meire M. Carneiro[5], Lúcia de Araújo C. B. Noblat[5], Silvana Gama F. Chachá[6,7], Ana de Lourdes C. Martinelli[7], Leonardo Regis L. Pereira[3], Marysabel Pinto T. Silveira[8], Carine Raquel Blatt[9], Mareni Rocha Farias[1]

ABSTRACT

In 2012, the first-generation protease inhibitors telaprevir (TVR) and boceprevir (BOC) were introduced in the Brazilian health system for treatment of chronic hepatitis C, after their approval by the National Committee for Health Technology Incorporation (CONITEC). However, these medicines were discontinued in 2015. The short period of use in therapy and their high cost require a discussion about the consequences for patients and for the health system of the early incorporation of new therapies. The article presents a qualitative analysis of the incorporation process of both medications in Brazil and the results of a multicenter study that included patients treated with BOC or TVR between January 2011 and December 2015 in five Brazilian cities. The study included 855 patients (BOC: n=247) and (TVR: n=608). The document analysis showed that CONITEC's decision to incorporate BOC and TVR was based on results of phase III clinical trials that compared sustained virologic response (SVR) rates of patients treated with BOC and TVR with rates of those that received placebo. However, these studies included a low percentage of cirrhotic patients. The SVR rates observed in this multicenter study were worse than clinical trials pointed out (BOC: 45.6%; TVR: 51.8%), but similar to those achieved with previously adopted therapies. The discontinuation rate due to adverse events was (BOC: 15.4%; TVR: 12.7%). Based on these unsatisfactory results, the study brings a discussion that goes beyond the therapy outcomes, exploring the incorporation of these high-cost medicines and the related decision-making process, contributing to future decisions in medicine policies and in the treatment of chronic hepatitis C.

KEYWORDS: Chronic hepatitis C treatment. Protease inhibitors. High cost medicines. Real life studies.

INTRODUCTION

Decisions in clinical and health policies require careful weighing of risks and benefits. It involves the health and quality of life of treated patients and mobilizes a large amount of public funds. Scientific evidence must guide this process along with the analysis of health gain returns in different social scenarios. This fact comes into sharp focus in the case of the introduction of new therapies to treat chronic hepatitis C (CHC) in Brazil.

Treatment of hepatitis C virus (HCV) infection rapidly evolved in the last two decades. The first-generation protease inhibitors (PIs) boceprevir (BOC) and

telaprevir (TVR) have emerged as a breakthrough in terms of effectiveness and safety. As of 2011, these drugs were approved by regulatory agencies, also in Brazil and marked a unique event, with two new drugs launched simultaneously for the same disease[1,2]. However, these treatments were much more expensive than previous therapies, leading the health systems, both public and private, to have limit access to patients in advanced stages of the disease[3,4].

In Brazil, the public health system (Unified Health System – SUS) is responsible for providing the HCV therapy. In 2012, the National Committee for Health Technology Incorporation (CONITEC) recommended the introduction in SUS of TVR and BOC for use with pegylated interferon (PEG-INF) and ribavirin (RBV), the "triple therapy", for patients with genotype 1 HCV in advanced clinical conditions[5,6].

The process-making decision to incorporate these pharmaceutical technologies in SUS started by public requirements to the CONITEC. A set of requirements were submitted by public applicants, including: number and validity of the technology registration in the National Health Surveillance Agency (ANVISA); scientific evidence showing that the technology is at least as effective and safe as those available in SUS for the intended use; an economic evaluation study comparing the requested technology with those available in the SUS. Then, the CONITEC's initial recommendations were submitted for public consultation for 20 days. Then, public contributions were evaluated and CONITEC deliberated its final recommendation to the BOC and TVR incorporation. However, the drugs were early discontinued in Brazil in mid-2015 due to its adverse events (AEs), costs and low effectiveness[7]. Furthermore, new direct acting drugs, such as the second-generation of PIs, simeprevir (SMV)/(NS3/4A protease inhibitor); daclatasvir (DCV)/(NS5A protease inhibitor) and the NS5B viral polymerase inhibitor sofosbuvir (SOF), were included in the Brazilian guideline[8]. International phase III and real-life trials have indicated that this new generation of DAAs would be more effective and safer than TVR and BOC[9-11].

Although TVR and BOC are no longer in use for treatment of hepatitis C in the SUS, they are still valid in ANVISA. Thus, data on the Brazilian experience with the triple therapy may be useful in future protocols using these drugs, as well as in the analysis of demands for incorporation of drugs for treatment of hepatitis C. We analyzed the decision-making process on drug incorporation, criteria for inclusion of patients in treatment guidelines, expenditure on medication purchase and results of the treatment of 855 patients with chronic hepatitis C compared to the findings of clinical trials.

MATERIALS AND METHODS

Analysis of the decision-making process of incorporation

The decision-making process of BOC and TVR incorporation was evaluated based on a qualitative document analysis. The three main documents generated during the decision-making process were analyzed: CONITEC's minutes of final meeting (official document provided by the Ministry of Health); public consultation contributions[12] and CONITEC's final deliberation[6].

Criteria for inclusion of patients in the clinical trials cited in the guidelines were compared with socio-demographic and clinical data of the real life treatment.

Expenditure on the purchase of TVR and BOC was provided through e-Sic (Electronic System of the Citizen Information Service), adjusted by the National Consumer Price Index / year (2012: 1.37; 2013: 1.27; 2014: 1.20; 2015: 1.16) and calculated in UDS (Dollar exchange rate 3.18).

Real life treatment

This retrospective study enrolled 855 patients with HCV-genotype 1 chronic infection from different regions of Brazil: South (cities of Florianopolis-SC, Porto Alegre-RS and Pelotas-RS), Southeast (city of Ribeirao Preto-SP) and Northeast (city of Salvador-BA). All patients were treated with PEG-INF-2a or 2b, RBV and either TVR or BOC provided by the Brazilian health system from January 2011 to December 2015.

Data were collected from the patients' records by means of a standardized form including demographics, medical history and information on treatment outcomes. Data on treatment outcomes encompassed SVR, Non-response, relapse (collected from patients' laboratory exams), discontinuation due to adverse events (AEs), treatment withdrawal and death. SVR was defined as the maintenance of negative HCV RNA 24 weeks after the end of the treatment and was calculated by intention-to-treat analysis. The AEs implicated in case of treatment discontinuation were grouped as per hematologic events (anemia, neutropenia, thrombocytopenia, bleeding and thrombosis), cutaneous reactions (rush, pruritus and dry skin) or other (renal dysfunction, liver decompensation, sepsis, peripheral neuropathy and psychiatric disorders).

All patients included in the study were treated in accordance with the Brazilian guidelines[5]. The Clinical Protocol and Therapeutic Guidelines (PCDT) for hepatitis C treatment indicates a combination of TVR (750 mg, 3 times a day) or BOC (800 mg, 3 times a day) associated

with PEG-IFN-2a (180 mcg) or 2b (1.5 mcg/kg) once a week plus RBV (weight-adjusted dose, daily). The use of TVR could be initiated on the first week of treatment or after 4 weeks using PR (lead-in phase) and was continued for 12 weeks, then it went on with only PR for 36 weeks. For the BOC regimen, lead-in phase was required and triple therapy was conducted for 44 weeks. During both therapeutic regimens, the Polymerase Chain Reaction (PCR) was performed to guide suspension or continuation of treatment. To TVR or BOC schemes, the therapy was discontinued whether viral load (VR) > 1,000 UI/mL on the 4th or 12th or 24th weeks. Discontinuation was performed if VR > 100 UI/mL on the 12th week or VR detectable on the 24th week of the therapy[5].

Ethics Statements

The study was approved by the Ethics Committee on Human Research of the authors' institutions (Protocol Nº 27185514.3.1001.0121).

Statistical Methods

A unified database comprising data collected in all research centers was created using the Excel software. The statistical analysis was performed using the software STATA version 14 - License 301406276417 - (Stata Corp, College Station, USA). Demographics and clinical characteristics were compared as per treatment (BOC or TVR) using the Chisquare tests or the Fisher exact test.

RESULTS

Results of document analysis

Analysis of the CONITEC's minutes of final meeting showed that the decision for the incorporation of BOC and TVR was based on the results of efficacy studies (phase III clinical trials) of both medicines, presented by a pharmaceutical industry consultant. According to the document description, the presented studies compared SVR rates of patients in advanced fibrosis levels (F3 and F4) with those of patients who received placebo. The consultant emphasized that the BOC's study did not evaluate the treatment response for cirrhotic patients, due to the low percentage of these patients in the study. The main adverse events associated with the use of BOC and TVR were also presented and consisted of anemia, altered taste, dry skin, rash and anorectal symptoms. Finally, at the end of the meeting, CONITEC members asked some questions to the consultant and decided, by a simple majority, to incorporate

BOC and TVR for treatment of CHC, and requested the public consultation.

Concerning the analysis of the public consultation results, educational institutions, associations related to patients and the pharmaceutical company gave contributions. No evidence was found regarding public manifestations contrary to the medicines incorporation. According to the public consultation document, most contributions requested details of the of BOC and TVR indication, for example, criteria for patients' inclusion (request for the inclusion of patients F2), which was not followed by CONITEC. The general analysis of the CONITEC's final deliberation (after public consultation) did not show any relevant findings.

Expenditure on BOC and TVR purchase

In the period 2013-2015, the Ministry of Health spent more than 220 million dollars on the acquisition of BOC and TVR. Considering the treatment duration and the posology recommended in the Clinical Protocol and Therapeutic Guidelines, the quantity purchased would allow the treatment of approximately 14,000 to 18,000 individuals (Table 1).

Results of BOC and TVR "real world" outcomes

The study included 855 patients of whom 247 (28%) used BOC and 608 (72%) TVR. Table 2 shows demographic and clinical characteristics as per treatment, all equally distributed between both treatments. Most patients were male 564 (66%) and white 451 (86.9%). The mean age was 54 years (SD = 8.8), ranging from 20 to 78 years. Concerning the clinical characteristics, most patients presented cirrhosis (BOC: 37.0%; TVR: 41.4%) and F3 score (BOC: 30.6%; TVR: 36.4%) and received prior HCV treatment (BOC: 61.2%; TVR: 54.4%).

The outcomes are described in Table 3 as per treatment regimen. Among the patients treated with BOC or TVR, 45.6% and 51.8% achieved SVR, respectively.

DISCUSSION

Shortly after FDA approval, the first generation of DAA, the protease inhibitors BOC and TVR, were introduced in the health system of many countries[1-3]. The approval of new drugs came with expectation of the addition of either BOC or TVR to PEG and RBV would higher significantly SVR rates. As comparative safety and effectiveness data in real-world populations with comorbidities or relative contraindications upon which to make formulary decisions did not exist, the new guidelines was supported just by

Table 1 - The amount invested in the purchase of TVR and BOC medicines in Brazil between 2013 and 2015 (in US million dollars)

Drugs	Amount	Average cost per unit U$	Custs U$	Estimated number of treatments*
Boceprevir 200mg (capsule)	4,955,664	4.46	21,242,289.49	1,341
Telaprevir 375mg (tablete)	6,485,292	31.56	203,151,973.67	12,868 to 17,157
TOTAL			**224,394,263.17**	**14,208 to18,498**

*TVR => considering the dosage of 2 tablets / 8 hour = 6 tablets / day x 12 weeks (84 days) = 504 tablets (beginning in the first week) or performed lead-in (starting from the fourth week) = 63 days = 378 tablets. BOC => considering the dosage of 4 capsules / 8 hours = 12 capsules / day X 44 weeks (308 days) = 3696 capsules. ** Values adjusted by the National Consumer Price Index/ year, ((2013: 1.27); (2014: 1.20); (2015: 1.16). Dollar exchange rate (3.18)

Table 2 - Baseline characteristics of the 855 patients enrolled in the study to evaluate the outcomes of the triple therapy with boceprevir or telaprevir in Brazil, January 2011 to December 2015

	boceprevir (n=247)		telaprevir (n=608)		P value[a]
	n	%	n	%	
Sociodemographic characteristics					
Age, mean 54; SD 8,8					
Sex					0.420
Male	168	68.0	396	65.1	
Female	79	32.0	212	34.9	
Skin color[b]					0.828
White	140	86.4	311	87.1	
No White	22.0	13.6	46	12.9	
Clinical characteristics					
Metavir score					
Liver Fibrosis[b]					0.005
F0/F1[c]	14	5.9	13	2.2	
F2	62	26.4	116	19.9	
F3	72	30.6	212	36.4	
Cirrhosis[d]	87	37.0	241	41.4	
Activity[b]					0.397
A0/A1	76	40.2	172	37.4	
A2	90	47.6	213	46.3	
A3	23	12.2	75	16.3	
Comorbidities					
HIV	6	2.4	18	3.0	0.670
Diabetes Mellitus	37	15.0	104	17.1	0.462
Hypertension	66	26.8	201	33.1	0.075
Obesity[b]	40	17.8	107	20.0	0.493
Dyslipidemia[b]	10	4.4	18	3.2	0.424
Steatosis[b]	14	8.6	66	14.1	0.070
Previous Treatment[b]	142	61.2	317	54.4	0.076
Treatment Duration					<0.0001
< 24 weeks	58	23.6	171	28.2	
25-36	56	22.8	63	10.4	
37-48	132	53.7	373	61.4	
Way to access the treatment[b]					<0.0001
Adminsitrative	152	61.5	521	85.7	
Lawsuit	88	36.7	82	13.6	

[a]Chi square test. [b]Missing (n): skin color (336); fibrosis, (38); activity,(206); obesity (93); steatosis (223); dyslipidemia (65), Way to access the treatment (12) and previous treatment (40). [c]In variable F0/F1, patients with METAVIR SCORE F0 and F1 were grouped. [d] For variable cirrhosis, patients with METAVIR SCORE F4 and clinical cirrhosis were grouped

Table 3 - boceprevir or telaprevir therapeutic regimen outcomes

	boceprevir (n=247)		telaprevir (n=608)		P value[a,b]
	n	%	n	%	
SVR[c]	99	45.6	273	51.8	0.125
No responder	48	19.4	122	20.0	0.104
Abandonment	11	4.5	23	3.8	0.649
Relapse[c]	37	17.0	61	11.6	0.050
Discontinuation due to AEs	38	15.4	77	12.7	0.291
Hematologic events[d]	18	7.3	38	6.3	0.689
Cutaneous reactions[e]	3	1.2	19	3.1	0.117
Others events[f]	17	6.9	23	3.8	0.077
Dead	3	1.2	8	1.3	0.905

SVR: sustained virological response. AEs: adverse events. [a]Chi square test. [b]Fisher's exact test. [c]Missing (n): SVR and relapse (111), partial responders (25). [d]Hematologic events considered: anemia, neutropenia, thrombocytopenia, bleeding and thrombosis. [e]Cutaneous reactions considered: rush, pruritus and dry skin. [f]Other events considered: renal dysfunction, liver imbalance, sepsis, peripheral neuropathy, psychiatric disorders. The total number of outcomes for telaprevir and boceprevir are higher due the same patient may present more than one outcome

efficacy and safety demonstrated by clinical trials. As presented on the results, the CONITEC's decision was based on comparative efficacy studies with placebo and a low percentage of cirrhotic patients.

The ADVANCE, ILLUMINATE and REALIZE studies performed with TVR demonstrated SVR rates of 75%, 72%, 80% (previous relapse), respectively. The SPRINT-2 and RESPOND-2 studies performed with BOC showed SVR rates of 66%[13-16]. We found the overall SVR rate for treatment with TVR (51.8%) or BOC (45.6%). These results are broadly consistent with others from real life studies around the world[17-23].

We found high discontinued prescription rates due to AEs, 15.4% of the patients treated with BOC and 12.7% with TRV. Hematologic events were the main cause of discontinuation of both drugs, followed by cutaneous reactions, which were more significant among patients treated with TVR (3.1%) than with BOC (1.2%). Corroborating our results, a Brazilian cohort study developed with 203 patients showed high rates (19.2%) of therapy discontinuation owing to AEs. These authors reported that 41% and 37.5% of the BOC or TVR discontinuations, respectively, also occurred due to hematologic events and cutaneous reactions[20]. It was previously described that patients with comorbidities and advanced cirrhosis are more vulnerable to AEs[18,21]. Hematologic reactions, as well as psychiatric disorders and changes in thyroid function are associated with the use of PEG-INF and RBV. Serious AEs were the main cause of early discontinuation of triple therapy in the Brazilian health system[7].

The discrepancy between the outcomes of clinical trials and real-life studies may be related to the profile of the population of patients enrolled, which was carefully selected. Patients treated in trials must meet stringent entry criteria, which may do not reflect the population treated in routine medical practice. The ADVANCE, ILLUMINATE, REALIZE SPRINT-2 and RESPOND-2 clinical trials included a low proportion of patients with cirrhosis (3%, 16%, 18%, 12% and 9%, respectively), or fibrosis without cirrhosis and no one with comorbidities in the evaluated groups, while our real life study enrolled a higher proportion of cirrhosis (BOC: 37.0%; TVR: 41.4%), fibrosis without cirrhosis (F3-BOC: 30.6%; TVR: 36.4%) and comorbidities as hypertension, obesity, DM, steatosis, dyslipidemia and HIV coinfection. It has been reported that cirrhosis is a negative predictive factor for successful therapy and patients with comorbidities and advanced liver disease are difficult to treat and more likely to treatment discontinuation due to AEs[14,17,18,24-27].

The Brazilian guidelines established that just F2 (for more than three years) or F3, F4 or cirrhotic patients were entitled for treatment with METAVIR offered by the public health system. On the other hand, trials suggested a higher efficacy in patients with mild or moderate fibrosis[6]. The improvement of SVR was expected with the triple therapy, however, the results was similar to those achieved with INF-PEG 2a/2b + RBV regimen-based. Brazilian studies that analyzed the dual therapy showed SVR rates between 40-50%[28,29]. Additionally, as shown in the results, the public investment to acquire the triple therapy was much higher when compared with the dual therapy acquisition.

As mentioned in the introduction, the CONITEC's decision to recommend the triple therapy was also based in cost-effectiveness studies supported by clinical trials[5].

However, considering the facts pointed out, a question comes across: cost-effectiveness studies are substantial to support the decision-making process? It is known that the aim of the principle of cost effectiveness is to ensure that the most health benefits are obtained from the available resources. However, it has increasingly been recognized that setting health priorities requires not only technical judgments such as those around clinical and cost effectiveness, but also involves social value judgments[30]. Social value judgments might be defined as judgments made on the basis of moral or ethical values of a particular society[30]. In this sense, criteria for patients' inclusion in the Brazilian guidelines are against the constitutional universal right to health and means, tearing the principle of universality of access to health. In addition, Karen Van Nuys *et al.*[31], using a model to simulate the progression of a population susceptible to hepatitis C through infection and several stages of the disease, demonstrated that treating 5 percent of the infected population annually regardless of the patients' disease stages, would also return substantial social benefits and would be much more affordable, so treating patients at earlier stages of liver disease generated more value than waiting to treat them when liver damage has progressed.

Outcomes found in this study, when explored on the perspective of what does the incorporation of high cost medicines by developing countries mean and the decision-making process related to the necessity of developing strategies for the better management of the introduction of new high priced medicines. In Europe, for example, the concerning about the impact of new and emerging health technologies on health, health services and/or society resulted in the development of models to support the adoption and the use of new medicines for the benefit of patients[32,33].

It is relevant to mention that, shortly after BOC and TVR incorporation, the FDA approved SOF (2013)[34]. Thus, the possibility of using new direct-acting drugs in a non-interferon-based regimen for a shorter period and with effectiveness rates above 90%[9-11], may have led to a significant decrease in triple therapy prescriptions starting in 2014. The literature also describes that acquisition of these new medications was facilitated in Brazil, with a good negotiated price when compared with others countries[35].

We also estimated the number of individuals that could have been treated, considering the quantities purchased. However, the available records do not allow us to determine how many patients were effectively treated and, consequently, how much of the drug remains.

Thus, our results bring a discussion that goes beyond the outcomes of therapy effectiveness and safety, contributing to the future medical and social as well as economic analysis

of regulatory activities and other decisions in the field of medication policy and treatment of hepatitis C.

The retrospective nature of the study and the reliance on medical records from routine clinical practice represent limitations of the study. Data on genetic profile, comorbidities and demographic characteristics such as skin color could not be fully recovered. Moreover, the multicenter character of the study also contributed to these losses, once each center has a different way to manage its services, which reflects the amount of information found in medical records. However, the main quality of the present study is the reasonable representation of real-life experience with triple therapy in Brazil and the importance of discussing the strength of scientific evidence that based the construction of the Brazilian guidelines for the HCV infection treatment.

CONCLUSIONS

The present study demonstrates the complexity of the decision-making process in the context of the incorporation of new health technologies, especially those of high cost. The therapeutic and social benefits, the system sustainability and the return of the industry investment in the development of technologies are elements of a difficult solution equation.

The decision to incorporate BOC and TVR was not unanimous, and due to the high cost of treatment, the clinical protocol limited treatment to patients in the more advanced stages of the disease. In clinical practice, this strategy did not bring significant therapeutic or social advantages over previous treatment and increased costs for the health system. Thus, this scenario suggests the necessity of the skillful use of implementation strategies of new pharmaceutical technologies to enhance the adoption and sustainability of a clinical program or practice that really benefits the population and the health care system.

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AUTHORS' CONTRIBUTIONS

Lenyta Oliveira Gomes: collected and analyzed the data, contributed to the study design and wrote the manuscript; Marina Rodrigues Teixeira; Júnior André da Rosa; Alberi Adolfo Feltrin; João Paulo V. Rodrigues; Mariane D'Avila Vecchi; Jane Meire M. Carneiro: collected and analyzed the data; Lúcia de Araújo C. B. Noblat; Silvana Gama F. Chachá; Ana de Lourdes C. Martinelli; Leonardo Regis L.

Pereira; Marysabel Pinto T. Silveira; Carine Raquel Blatt; Mareni Rocha Farias: contributed to the study concept and design, and supervision. All authors critically reviewed the manuscript for important intellectual content and approved the final draft for submission.

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