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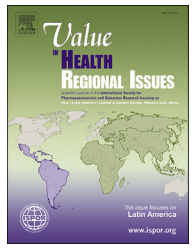

Economic Evaluation

Effectiveness and Cost-Effectiveness of Triple Therapy With Telaprevir and Boceprevir for Chronic Hepatitis C: A Decision Analysis From the Brazilian Public Health System Perspective

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ABSTRACT

Objectives: Because of the lack of evidence regarding long-term effectiveness and cost-effectiveness of first-generation direct-acting antivirals for chronic hepatitis C (CHC) treatment in Brazil, we performed a cost-utility analysis comparing standard dual therapy (peginterferon plus ribavirin [pegIFN/RBV]), boceprevir, and telaprevir for CHC patients. **Methods:** We developed a state-transition Markov model simulating the progression of CHC. Long-term outcomes included remaining life expectancy in life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER). Short-term outcomes included sustained virological response rates (SVR). Direct medical costs were obtained from Brazilian databases. A lifelong time horizon was considered and a 5% annual discount rate was applied for costs and clinical outcomes. A willingness-to-pay threshold of approximately $20 000 per QALY was used. We performed multiple sensitivity analyses. **Results:** For short- and long-term scenarios, therapy with boceprevir was dominated by telaprevir, which was more effective than standard dual therapy (75.0% vs 40.4% SVR rate, 13.47 vs 12.59 LYs, and 9.74 vs 8.49 QALYs, respectively) and was also more expensive ($15 742 vs $5413). The corresponding ICERs were $29 854/SVR, $11 803/LY, and $8277/QALY. Based on our model, triple therapy with telaprevir was the most cost-effective treatment for the Brazilian health system. Despite a lack of data regarding the Brazilian population, we incorporated as many applicable parameters as possible. **Conclusions:** Telaprevir is more effective and cost-effective than boceprevir. Our model may be applied for other settings with a few adjustments in the input parameters.

Keywords: costs and cost analysis, decision making, hepatitis C, protease inhibitors

Introduction

The burden of chronic hepatitis C (CHC) in Brazil is significant, with approximately 2.5% of the population chronically infected with the hepatitis C virus (HCV), 64.9% of which are infected with HCV genotype 1.[1] In 2011, the US Food and Drug Administration (FDA) approved the first direct-acting antivirals (DAAs) boceprevir and telaprevir for treatment in combination with pegylated interferon (pegIFN) and ribavirin (RBV) for patients infected with CHC genotype 1, which represents a more effective treatment than pegIFN plus RBV.[2] Considering the severity of CHC as a cause of progressive liver disease worldwide, and the high cost of

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available treatments, a great impact on public health expenses is expected.[3]

Although second-generation DAAs and interferon-free regimens have been approved by the Brazilian Ministry of Health,[4] until now no systematic evaluation of the long-term effectiveness and cost-effectiveness of these agents from the perspective of the Brazilian public health system was conducted. Therefore, our aim was to perform a decision-analytic cost-utility analysis comparing the regimens with boceprevir and telaprevir, standard dual therapy, and no treatment, because the DAAs are more expensive and have a greater efficacy than the therapy with pegIFN plus RBV. The model built in the present study may be applied for different perspectives besides the Brazilian public health system, including countries where the access to these and new DAAs therapies are limited.[5]

Methods

Model Overview

We developed a Markov state-transition model using TreeAge Pro software (TreeAge Software, Inc., Williamstown, MA, USA) to simulate the progression of CHC in patients infected with HCV genotype 1. We followed international modeling guidelines for model development.[6,7]

We considered a lifelong time horizon for the analysis, and a 5% annual discount rate was applied for all costs and clinical outcomes according to the Brazilian Guideline for Health Technology Assessment.[8] We adopted the perspective of the public health system of Brazil (SUS).

The model predicted long-term outcomes related to the disease and its treatment, including life expectancy measured in life-years (LYs), quality-adjusted life expectancy measured in quality-adjusted life-years (QALYs), and the corresponding incremental cost-effectiveness ratios (ICER). The adopted short-term efficacy measure was the sustained virological response (SVR) rate (ie, absence of HCV RNA in the patient's serum 24 weeks after discontinuing the treatment).[2] The analysis was based on a hypothetical cohort of patients derived from an observational study in Brazil,[9] which included patients with an initial age of 52 years, 65% of which were male.

Model Structure

A state-transition Markov model comprising the treatment strategies standard dual therapy, triple therapy with boceprevir, triple therapy with telaprevir, and no treatment was developed (Fig. 1). The model comprised the following health states: different stages of liver fibrosis according to the METAVIR fibrosis score (F0 to F4), SVR stratified by fibrosis score (SVR F0 to F4), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), first year after liver transplantation (LT), post–liver transplantation (PLT), and death. Patients could transition between these health states in annual cycles.

In the hypothetical cohort, CHC patients could begin in states F0, F1, F2, F3, or F4, and if treated, patients could achieve SVR or not. Patients who did not achieve SVR could progress to the next fibrosis stage (ie, F0 to F1, F1 to F2, and so on) following the natural course of the disease. Patients starting in F3 could also progress to HCC, and patients starting in F4 could progress to HCC or DCC. A progression to HCC from F3 patients who achieved SVR was considered, as well as progression to HCC or DCC from F4 patients who achieved SVR. DCC patients could develop HCC. Both DCC and HCC patients could receive a liver transplant or die of liver-related causes. Patients who received a liver transplant could move to states of post–liver transplantation or liver-related death.

We considered the following assumptions: after the end of treatment, patients with an initial METAVIR score of F0 to F2 who achieved SVR did not experience further disease progression, remaining in their respective SVR state until death from other causes. Patients who achieved SVR from fibrosis stage F3 could still progress to HCC, and those who had a fibrosis score of F4 could progress to HCC or DCC. Progression through the natural disease course was assumed for those patients who did not achieve SVR. Liver-related mortality was applied for DCC, HCC, LT, and PLT states.

Antiviral Treatment Options

According to guidelines for treatment of CHC genotype 1, boceprevir should be administered for 44 weeks, together with PegIFN/RBV, after a lead-in phase of 4 weeks with PegIFN/RBV only. Telaprevir should be given for 12 weeks together with PegIFN/RBV, followed by 36 weeks of PegIFN/RBV only. Standard dual therapy consists of the administration of PegIFN/RBV for 48 weeks.[10,11]

Model Input Parameters

Natural disease course

We obtained the baseline distribution of patients according to fibrosis stage from a cross-sectional study conducted by our group in Brazil (F0 = 7%, F1 = 12%, F2 = 24%, F3 = 19%, and F4 = 38%) (data not published). Because of the lack of data on CHC progression in the Brazilian population, information regarding the probability of transition from one health state to another was derived from the international literature (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.02.005). Data on mortality from causes other than CHC were collected from the Brazilian Agency for Geography and Statistics life table, which provides age- and sex-specific mortality rates for the general Brazilian population.[12] The probabilities concerning disease progression were derived from the published literature (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.02.005).

Efficacy of antiviral therapy

We conducted a systematic literature review to identify randomized clinical trials evaluating the efficacy of boceprevir and telaprevir combined with PegIFN+RBV based on SVR rates. We searched in the electronic databases PubMed, International Pharmaceutical Abstracts (IPA), the Cochrane Library, SCIELO, and Scopus in September 2015. Two studies assessing SVR rates according to the METAVIR score were used as the source of efficacy data for boceprevir and telaprevir in the model.[13,14] The SVR rates of standard dual therapy were obtained from a large randomized clinical trial.[15] For the no treatment arm, the SVR rates were assumed to be zero.

To evaluate the effectiveness of the treatments in terms of QALYs, a utility value was assigned to each health state in the model. Because of the lack of local data, utility values were derived from the international literature (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.02.005).

Cost data

We included only direct medical costs. The procedures related to disease management, considering each evaluated state, were obtained from the literature and the Brazilian guidelines.[11,16-22] The source used for costing these procedures was the government reimbursement procedures list (SIGTAP),[23] and the cost of medication was acquired from the official government source,

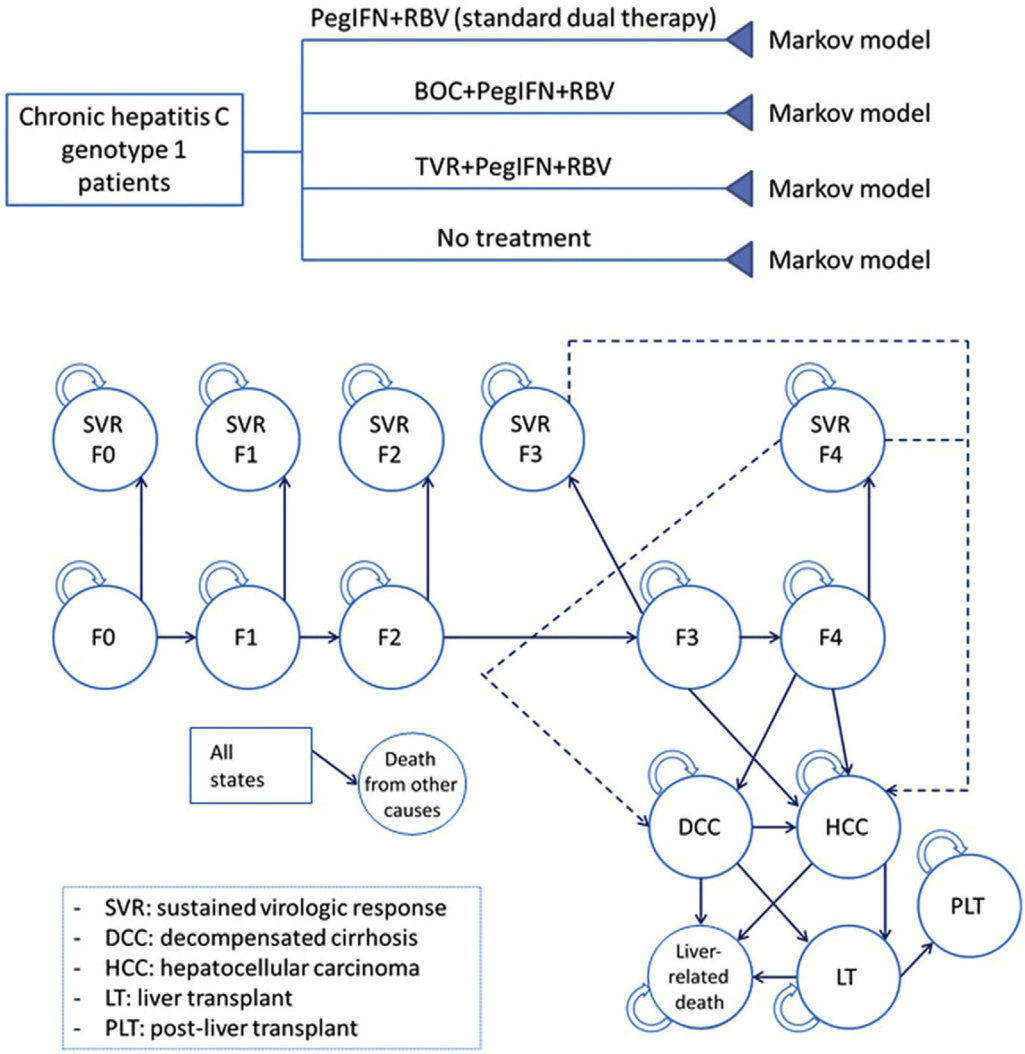

Fig. 1 – Model schematic. Decision tree with the different treatment strategies and diagrammatic representation of the Markov model. The different health states of chronic hepatitis C are represented by circles. The possible transitions between health states, which can occur each year, are represented by arrows. The dashed lines indicate that the states F3, F4, and SVR F4 may all progress to DCC or HCC states. Death can occur from any health state in the model. BOC indicates boceprevir; DCC, decompensated cirrhosis; F0-F4, METAVIR fibrosis score; HCC, hepatocellular carcinoma; LT, liver transplantation (first year); PegIFN, pegylated interferon; PLT, post–liver transplantation; RBV, ribavirin; SVR, sustained virological response; TVR, telaprevir.

"Banco de Preços em Saúde," searching for the available presentations of the therapies and using the column "weighted average." For PegIFN the average price was calculated considering the available forms (ie, 2a or 2b).[24] Unitary costs of the drugs were multiplied by the amount of pills per day, and then the annual cost of the medical treatment was calculated following the dosage regimen indicated in the Brazilian guidelines.[10] For procedures, the cost of each item included in hepatitis C management was multiplied for its frequency in the period of 1 year. Appendix Table 2 (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.02.005) presents the annual treatment cost for disease management, considering each treatment arm and each disease state. Costs were converted from Brazilian reais to US dollars according to the Brazilian Central Bank quotation for 2016 ($1.00 = R$4.00). Drug costs were adjusted for inflation according to the Broad Consumer Price Index (*Índice de Preços ao Consumidor Amplo*) updated for April 2017.

Analytical Strategy

For each treatment strategy, we estimated both the health and economic outcomes. We then performed incremental cost-effectiveness analyses. The main cost-effectiveness measure was the cost per QALY gained (cost-utility analysis), and the secondary measures included the cost per LY gained and cost per SVR gained. Because Brazil does not have an official willingness-to-pay (WTP) threshold, we considered an amount 3 times the gross domestic product per capita of the country based on the recommendations of the WHO-CHOICE (World Health Organization—CHOosing Interventions that are Cost-Effective) project.[25]

Sensitivity Analysis

Multiple deterministic 1-way sensitivity analyses were performed to assess the effect of parameter uncertainty on the results.

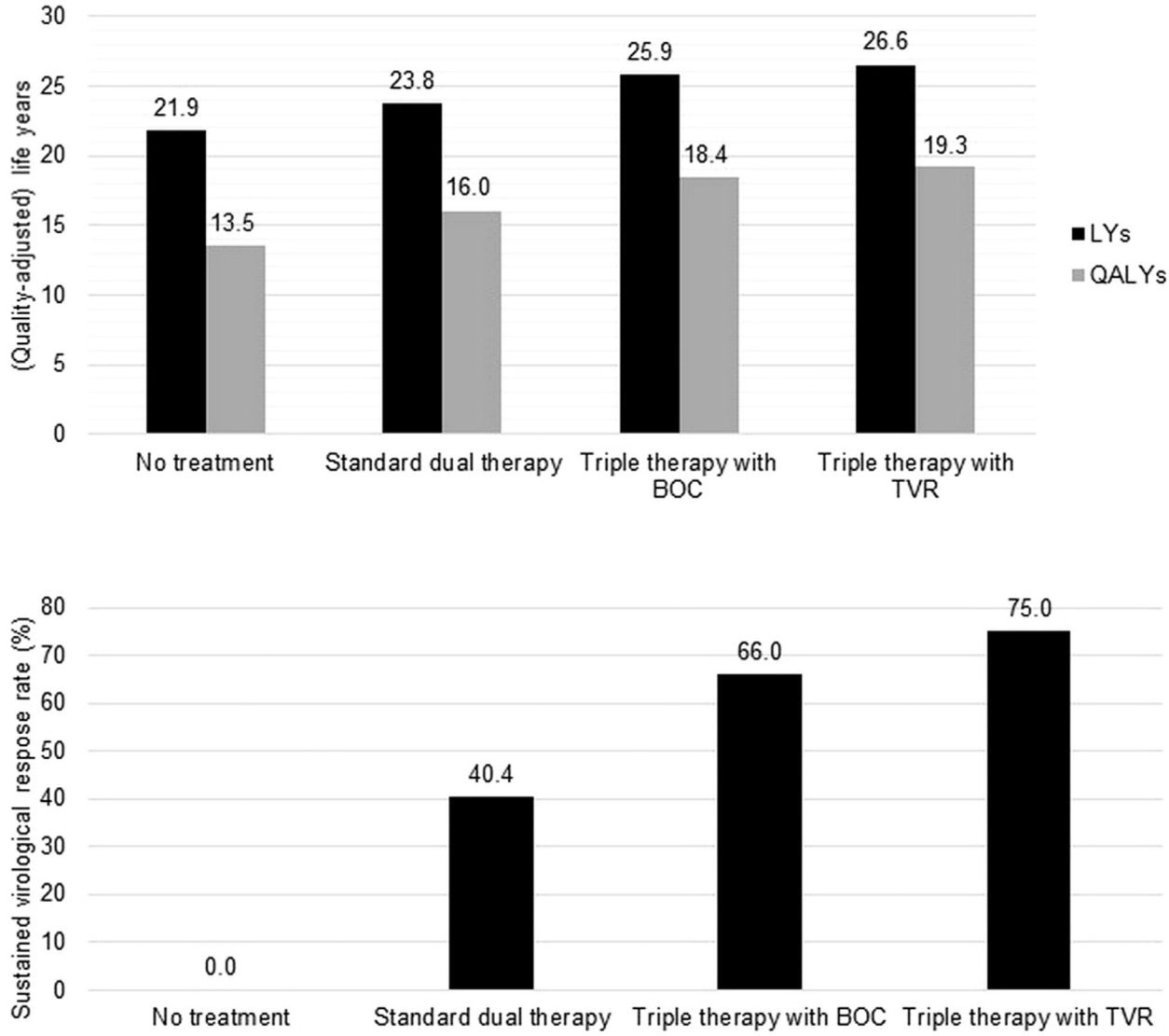

Fig. 2 – Comparison of clinical effectiveness parameters of the antiviral treatment strategies. BOC indicates boceprevir; LYs indicates life-years; QALYs, quality-adjusted life-years; SVR, sustained virological response rate; TVR, telaprevir.

The results were presented in a Tornado diagram. We varied the following parameters: transition probabilities, SVR rates and utilities based on 95% confidence intervals, medication cost (±20%), and discount rate (0% and 10%).

A probabilistic sensitivity analysis (second-order Monte Carlo simulation) was also performed. Cost parameters were varied following the statistical gamma distribution, whereas the probability parameters followed the beta distribution, and 10 000 iterations were applied for the model. Results of the probabilistic analysis were summarized in a scatterplot and in a cost-effectiveness acceptability curve (CEAC).

A technical validation was performed, based on the model's complexity, to check the consistence of the mathematical calculations and its compliance with the specifications of the developed model. The model building and its validation followed the ISPOR-SMDM Modeling Good Research Practices Task Force recommendations.[7,26]

Results

Systematic Review

From the electronic literature search, we retrieved 2158 references. After duplicates were removed (n = 440), 1718 studies were screened for their titles and abstracts, of which 1629 were excluded because they did not fulfill the inclusion criteria. A total of 89 clinical trials were selected for full-text screening. Data regarding efficacy outcomes were extracted from 10 studies, from which 4 were randomized clinical trials (1 for telaprevir[13] and 3 for boceprevir[14,27,28]) that reported data on SVR according to the METAVIR fibrosis score. Nevertheless, only one study that assessed boceprevir[14] was used in the model because this was the only study to report data on treatment-naïve patients. The IDEAL study, published by McHutchison et al. in 2009,[15] was chosen for the extraction of efficacy data for the standard dual therapy

Table 1 – Base-case analysis: cost, efficacy parameters (SVR rates, LYs, and QALYs), and incremental cost-effectiveness ratios (ICERs).

Treatment strategies	Cost (2017 $)	SVR (%)	LYs	QALYs	ICER/SVR (2017 $)	ICER/LYs (2017 $)	ICER/QALYs (2017 $)
No treatment	2212	0	12.01	7.56	0	0	0
pegIFN + RBV	5413	40.4	12.59	8.49	7922	5460	3424
TVR + pegIFN + RBV	15 742	75.0	13.47	9.74	29 854	11 803	8277
BOC + pegIFN + RBV	18 083	66.0	13.25	9.41	Dominated	Dominated	Dominated

BOC indicates boceprevir; ICER, incremental cost-effectiveness ratio; LYs, life-years; PegIFN, pegylated interferon; QALYs, quality-adjusted life-years; RBV, ribavirin; SVR, sustained virological response; TVR, Telaprevir.

because this is a large randomized clinical trial that has been included in previous cost-effectiveness analyses.[29-32] All efficacy parameters included in the model are presented in Appendix Table 3 (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.02.005).

Long-Term Effectiveness

Among the compared strategies, triple therapy with telaprevir provided the highest long-term effectiveness (26.6 LYs and 19.3 QALYs). This was followed by triple therapy with boceprevir (25.9 LYs and 18.4 QALYs), standard dual therapy with PegIFN plus RBV (23.8 LYs and 16.0 QALYs), and finally no treatment (21.9 LYs and 13.5 QALYs) (Fig. 2).

Incremental Cost-Effectiveness

The base-case results of the incremental cost-effectiveness analysis are shown in Table 1. Regarding SVR, triple therapy with boceprevir was the dominated strategy because triple therapy with telaprevir achieved a higher SVR at a lower total cost. Among the nondominated strategies, triple therapy with telaprevir was more expensive than the standard dual therapy ($15 742 vs $5413) and also more effective (SVR rate of 75% vs 40.4%). The ICERs for standard dual therapy and triple therapy with telaprevir were $7922 and $29 854 per SVR gained, respectively.

Similar results were observed for the long-term analyses based on life expectancy and quality-adjusted life expectancy. Treatment with boceprevir was the dominated strategy. Triple therapy with telaprevir showed higher long-term effectiveness when compared with standard dual therapy (13.47 vs 12.59 LYs and 9.74 vs 8.49 QALYs), resulting in ICERs of $11 803/LYs and $8277/QALY. The regimen with telaprevir can be considered cost-effective from the perspective of the Brazilian public health system because the ICER was found to be lower than the WTP threshold.

Sensitivity Analyses

Triple therapy with telaprevir remained cost-effective in all scenarios considering the ICER per QALY as the main outcome for the analysis. The tornado diagram (Fig. 3) presents the impact of varying parameter values on the ICER in $/QALYs for triple therapy with telaprevir compared with standard dual therapy (nondominated strategies). The ICER was most sensitive to the annual discount rate.

Regarding probabilistic sensitivity analysis, the results suggest that the triple therapy with telaprevir presents the highest probability of being the most cost-effective among the evaluated treatments. The scatterplot is shown in Figure 4. The CEAC analysis showed that, with a threshold of up to approximately $5000, standard dual therapy would be the most cost-effective. From this value on and as it increases, the likelihood of triple therapy with telaprevir be the most cost-effective among the evaluated treatments increases. When considering the willingness to pay threshold used in the cost-utility analysis ($20 000), the probability of triple therapy with telaprevir be the most cost-effective is approximately 100%. CEAC results are presented in Figure 5.

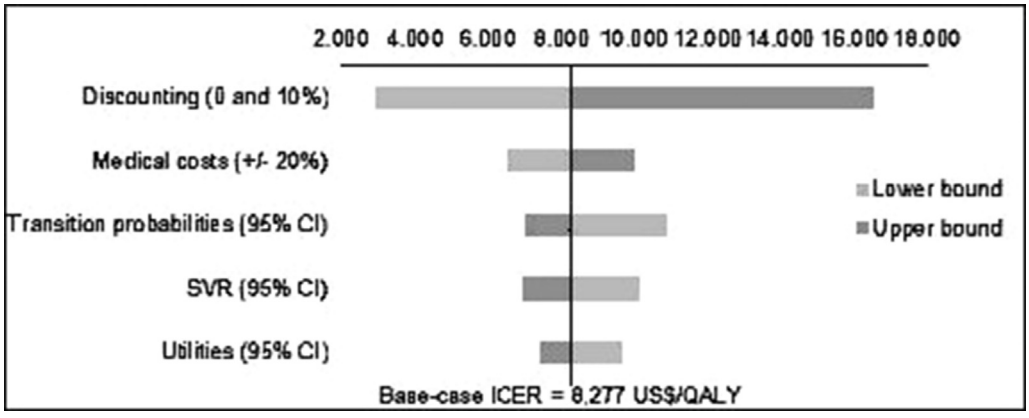

Fig. 3 – Tornado diagram for the incremental cost-effectiveness ratio of triple therapy with telaprevir versus standard dual therapy (ICER in $/QALYs). Costs were varied over a range of ±20%. Transition probabilities, SVR, and utilities were varied according to the lower and upper limit values of their respective confidence intervals (95% CI). Discounting was applied at 0% and 10%. ICER indicates incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SVR, sustained virological response.

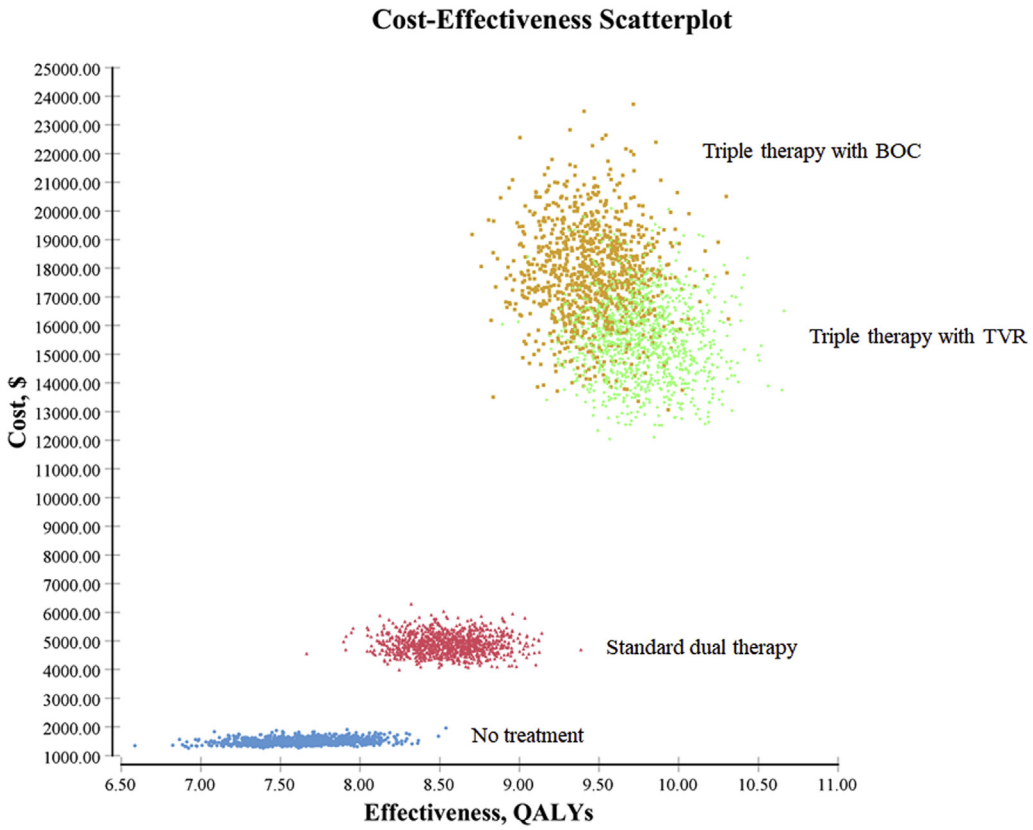

Fig. 4 – Probabilistic sensitivity analysis—scatterplot. BOC indicates boceprevir; QALYs, quality-adjusted life-years; TVR, telaprevir.

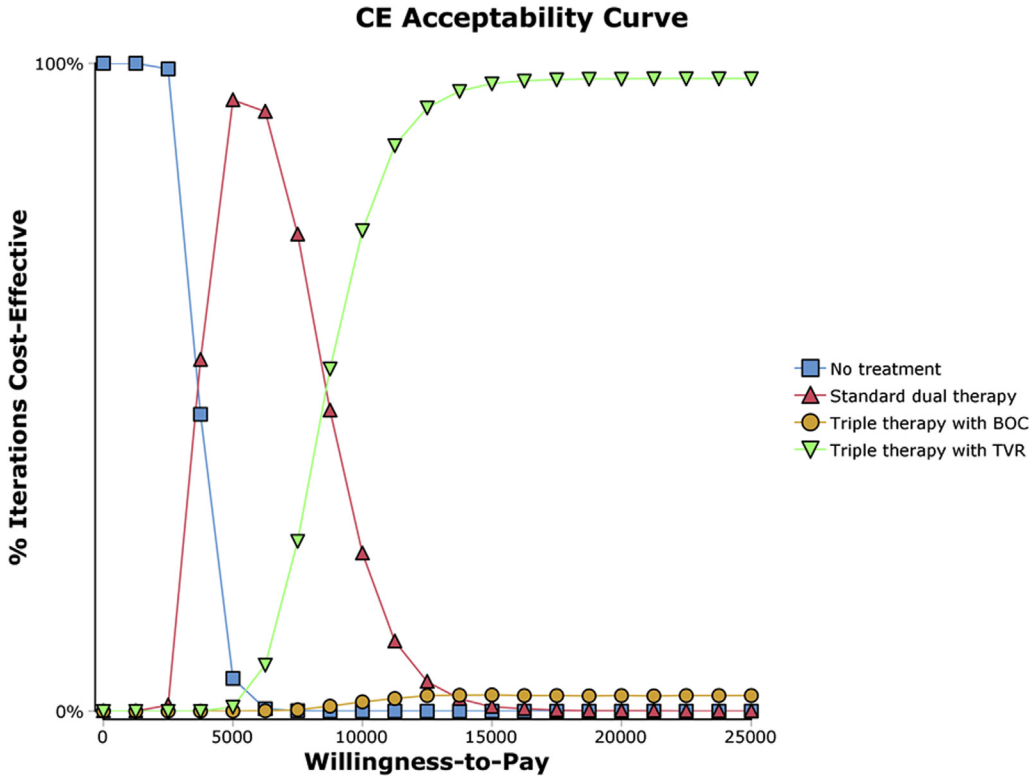

Fig. 5 – Cost-effectiveness acceptability curve (CEAC). BOC indicates boceprevir; TVR, telaprevir.

Discussion

We developed and applied a Markov state-transition model that considered the natural course of CHC to evaluate the cost-effectiveness of telaprevir or boceprevir plus PegIFN and RBV compared with standard dual therapy with pegylated interferon and ribavirin. To our knowledge, this is the first cost-utility analysis of the first-generation DAAs to be conducted from the perspective of the Brazilian public health system.

According to the results of our model, triple therapy with telaprevir results in an ICER of $8277/QALYs ($11 803/LYs) and could be considered cost-effective when a WTP threshold of $20 000 per QALY gained was applied. Therefore, from the perspective of the Brazilian public health system, triple therapy with telaprevir can be considered suitable for the treatment of patients with chronic HCV genotype 1 infection. Recent economic studies conducted in Brazil have been applying a WTP threshold of less than one time the gross domestic product.[33] If this scenario was applied in our analysis, cost of triple therapy with telaprevir would be above the WTP threshold (approximately $7000 per QALY). Nevertheless, WHO recommendations state that interventions that cost more than 3 times the gross domestic product are not considered cost-effective,[34,35] and the price of telaprevir treatment does not exceed this threshold. In addition, the CEAC shows that from a WTP of $10 000, triple therapy with telaprevir could be considered cost-effective. Hence, it can be observed that despite telaprevir not being a highly cost-effective alternative, it is a fitting choice from the perspective of the Brazilian public health system.

According to the Brazilian clinical guidelines on first-generation DAAs, published in 2013, only HCV genotype 1-monoinfected patients with a METAVIR fibrosis score of F3 or F4, or those with a score of F2 who had been diagnosed over 3 years before with previous failure of treatment with pegIFN plus RBV,[10] were eligible for treatment with protease inhibitors. A few years later, a newer generation of DAA therapies was also incorporated in Brazil, which is now available for the whole population.[36] As new therapies for hepatitis C are emerging and the resources are scarce, the model here developed may be applied in further analyses conducted under the Brazilian public health perspective. In addition, the results of the present study are relevant for comparative economic analyses that may be conducted with the new DAAs. For countries where boceprevir and telaprevir are still in use,[37,38] our model may be adjusted for investigations under different perspectives.

As with all model-based cost-effectiveness analyses, our study has several limitations. First, only direct medical costs were considered. Second, the SVR rates were derived from randomized clinical trials, which may present higher efficacy results than those observed in a real-world setting, and therefore the cost-effectiveness of the evaluated treatments may be overestimated. Third, the utility values were derived from the international literature and may not perfectly represent the Brazilian population. Nevertheless, when considering the application of the model for an analysis under a different perspective, these input parameters may be used without major adjustments. In order to fit the model to make it as applicable as possible to Brazil, all available data from Brazil were used. We consider this as a strength of our analysis. In addition, results from the sensitivity analyses showed that the triple therapy with telaprevir remained the most cost-effective option over a wide range of transition probabilities and utility values, indicating the robustness of our results. Another limitation is that the side effects of antiviral treatments were not considered in terms of a temporary disutility, and costs related to the treatment of adverse events associated with the protease inhibitors were not considered. Nevertheless, a cost-effectiveness analysis conducted by Chan et al.[29] in which the impact of erythropoietin for the treatment of adverse events associated with protease inhibitors was considered, an impact on the ICERs was only observed for the boceprevir branch. In addition, other studies have shown that despite boceprevir and telaprevir being associated with different types of adverse events that occur at different frequencies, the overall cost of managing these side effects was similar.[31] The magnitude of the influence of costs associated with side effects on the cost-effectiveness of these therapies may be better evaluated through observational studies, which may provide more accurate data regarding adverse events associated with the first-generation protease inhibitors and their management. Furthermore, the possibility of spontaneous remission from the F0 stage was not modeled, which could slightly overestimate the efficacy of all antiviral treatments. Nevertheless, because only 7% of the cohort in the model started in the F0 fibrosis stage, and the probability of spontaneous remission is very small and difficult to accurately assess, the influence of this limitation on the final results is not likely to be relevant. Finally, as with all models, our model is a simplification of reality.

Our analysis was conducted considering treatment-naïve patients, who may have a better response to antiviral treatment according to results from clinical trials. Therefore, future research should be conducted considering treatment-experienced patients. In addition, future research to assess the quality of life of Brazilian patients with genotype 1 CHC infection will provide more accurate values for evaluating the cost utility of these therapies, thereby improving the analysis in terms of uncertainty.

Despite the limitations, the major strength of our model is that it incorporates as much data from the Brazilian population as possible, and therefore this model should be suitable for further cost-effectiveness analyses conducted from the Brazilian healthcare perspective. Moreover, the developed model may be applied for other settings, with a few adjustments in the input parameters.

Conclusions

Our findings suggest that triple therapy with telaprevir is associated with greater short-term efficacy and long-term effectiveness outcomes, although it comes at a higher cost when compared with the other currently available antiviral treatment regimens. Considering a WTP threshold of $20 000, however, triple therapy with telaprevir can be considered cost-effective in the Brazilian public health system and should be chosen over boceprevir when treating patients with chronic HCV genotype 1 infection, especially where these therapies are still broadly used. Our model allows the cost-effectiveness to be updated when new data or treatments become available and to evaluate the cost-effectiveness of other DAAs under different perspectives.

Author Contributions

Helena H. L. Borba built the Markov model, searched for input parameters, conducted the cost-effectiveness analysis, and wrote the article. Ursula Rochau and Gaby Sroczynski assisted in the Markov model building and with the cost-effectiveness analysis execution. Astrid Wiens supervised the project, assisted in the sensitivity analysis, and wrote the article. Uwe Siebert supervised the project and assisted in the Markov model building and with the cost-effectiveness analysis execution. Vinicius L. Ferreira helped with the search for the input parameters and in the sensitivity analysis. Eimy Minowa participated in the project development and provided assistance in the model building and analyses execution. Roberto Pontarolo supervised the project and participated in the article writing.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2019.02.005.

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