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Cost-effectiveness of nucleoside/nucleotide analogues in chronic hepatitis B

ABSTRACT

OBJECTIVE: To conduct a cost-effectiveness analysis of drug alternatives with rescue therapy in case of relapse due to viral resistance for the treatment of patients with chronic hepatitis B (CHB).

METHODS: Hypothetical cohort of patients with CHB, HBeAg-negative, without clinical or histological evidence of cirrhosis, detectable HBV DNA, histological diagnosis of the disease, positive serum HBsAg for longer than six months, high levels of alanine aminotransferase (ALT) (twice as high as the upper limit of normality) and mean age of 40 years. A Markov model was developed for chronic hepatitis B (HBeAg- negative) with a 40-year time horizon. Costs and benefits were discounted at 5%. Annual rates of disease progression, costs due to complications and the efficacy of medicines were obtained from the literature. One-way and probabilistic sensitivity analysis evaluated uncertainties.

RESULTS: Initiation of treatments with entecavir resulted in an increase of 0.35 discounted life-years gained compared to lamivudine. The incremental cost-effectiveness ratio was R$ 16,416.08 per life-years gained. In the sensitivity analysis, the incremental cost-effectiveness ratio was more sensitive to variation in the probability of transition from chronic hepatitis B to compensated cirrhosis, discount rate and medicine prices (± 10%). In the probabilistic sensitivity analysis, the acceptability curve showed that beginning treatment with entecavir was the most cost-effective alternative in comparison with the use of lamivudine.

CONCLUSIONS: The availability of entecavir is economically attractive as part of early treatment for patients with chronic hepatitis B without HIV co-infection.

DESCRIPTORS: Hepatitis B, Chronic, therapy. Recurrence. Hepatitis B vírus, drug effects. Nucleosides, therapeutic use. Cost-Effectiveness Evaluation.

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INTRODUCTION

Chronic hepatitis B (CHB) is a serious public health problem which affects between 350 and 400 million people worldwide.[2] A population based prevalence study of hepatitis B infection in Brazil revealed endemic levels > 1% across all the capital cities of each region and of the Federal District. The overall prevalence of HbsAg in the Brazilian state capitals was 0.37% (95%CI 0.25;0.50). The prevalence of this marker was 0.055% (95%CI 0.012;0.10) in the ten to 19 year old age group and of 0.6% (95%CI 0.41;0.78) for the 20 to 69 year old age group. The North showed the highest results for both age groups.[a] Treatment, when prescribed, is critical in avoiding progression and complications of the disease such as compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma.[a]

Treatment costs become significantly higher with the high morbidity and mortality of patients in advanced stages of the disease, as serious hepatic complications increase the complexity of treatment and the risk of death.[23]

In Brazil, until 2009, the guidelines from advocated interferon and lamivudine for the treatment of CHB. Currently, drugs such as adefovir, entecavir and tenofovir are also included.[b]

A systematic review[1] showed adefovir, entecavir and telbivudina effectiveness to be similar to or greater than lamivudine's. entecavir may be prescribed as an alternative to lamivudine in treating first time patients with positive and negative HbeAg, due to the low potential for resistance. Adefovir treatment results in a decline in the levels of DNA of the hepatitis B virus (HBV) and has been shown to be effective in first time patients with positive and negative HbeAg and resistance to lamivudine. telbivudina is one of the most recent antivirals to be available to treat CHB, it is more powerful than lamivudine in inhibiting viral replication, however, its use leads to strong antiviral resistance.[1]

Treatment of CHB aims at reducing the progression of the disease, increasing survival and improving the patients' quality of life. This study aimed at analysing the cost-effectiveness of the alternative drugs with rescue therapy in relapses due to viral resistance.

METHODS

We formed a hypothetical cohort of patients with CHB; HBeAg negative, without clinical evidence or history of cirrhosis, detectable HBV DNA; histological diagnosis of the disease; HBsAg positive in the serum for more than six months, high levels of alanina transferase (higher than two times the upper limit of normal [ULN]); and an average age of 40 years old. The Markov model, with annual cycles and a timeframe of 40 years, was constructed and long term treatment with adefovir, entecavir, telbivudina or lamivudine was evaluated. The patients received rescue therapy when relapse due to viral resistance occurred (adefovir was added to the treatment of patients who started on lamivudine, entecavir or telbivudina and entecavir for those who started on adefovir treatment).

Economic analyses can be developed prospectively and together with the results of clinical research, provided that they are designed to simulate maximum effectiveness through pragmatic clinical trials. However, CHB develops over decades, making prospective studies, which require a large number of patients as well as a long time period accompanying them, difficult to carry out. Economic analysis used a mathematical model for decision making and was based on information available from published studies in order to estimate clinical results and the cost of treatment.

Undetectable levels of HBV DNA (< 300-400 copies/mL) were adopted as the measure of effectiveness. This is considered to be the most appropriate prognostic marker of progression of liver disease.[22] The data on the effectiveness of the drugs was obtained from random and controlled clinical studies which addressed the natural history of the disease.

The model chosen consisted of six stages of health: CHB (initial state of health), compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, resistance and death. Resistance to treatment drugs was included in the model to reflect those patients who showed no response to treatment (Figure 1). Patients started at the CHB stage without clinical or histological evidence of cirrhosis.

The calculation of probabilities of transition followed the natural history of the disease and was based on the literature. An annual rate of 9.0%[11] of CHB progressing to compensated cirrhosis and 0.5% to hepatocellular carcinoma was assumed. In the case of patients who responded to treatment and at low risk of progression to compensated cirrhosis, this rate was deemed to be 1.3%.[20]

The annual rate of progression from compensated cirrhosis to CD was deemed to be 5.0%, based on observational study of patients with compensated cirrhosis accompanied for an average of 4.3 years. For patients

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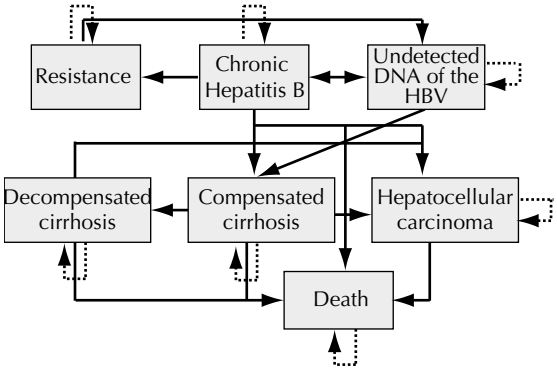
[b] Ministério da Saúde. Secretariat of Health Monitoring. Department of DST, Aids and Viral Hepatitis. National Programme for the Prevention and Control of Viral Hepatitis. Clinical Guidelines for the Treatment of Chronic Viral hepatitis B and Coinfections. Brasília (DF). 2009.



Adapted from Veenstra & Spackman. 2008.[27]

Figure 1. Diagram of the transition states of the Markov model for treating chronic Hepatitis B.

with CD, the annual rate of progression to hepatocellular carcinoma was deemed to be 2.5%.[8]

The annual levels of mortality according to stage were as follows: CHB (0.35%),[26] compensated cirrhosis (5.0%),[18] hepatocellular carcinoma (37.2%)[21] and decompensated cirrhosis (39.0%).[5]

We assumed the following premises and parameters in the model:

- Patients who showed a response to treatment (defined as negative results for HBV DNA in the *Polymerase Chain Reaction* – PCR test) had a lower risk of developing cirrhosis and hepatocellular carcinoma.[22]
- Patients who did not respond to the initial treatment received the same drug therapy throughout the period of the cohort, provided they do not develop resistance.
- In the case of virologic relapse due to resistance occurring (> 1 log of HBV DNA), patients received rescue therapy. Adefovir was added to the treatment of patients who started on lamivudine, entecavir or telbivudina and entecavir was added to those who had started with adefovir.[10]
- Continued response to the treatment was deemed to be 10.0%[13,16] and the same value applied to rescue therapy.
- We assumed there was no resistance to the combined rescue therapy.
- Rates of response to treatment were assumed to be similar from the second to fifth year for initial therapy. The rate of response to rescue therapy was deemed to be 52%[6] and continued response to the rescue therapy to be 10.0%[13,16] (Table 1).

Reduction in HBV DNA (< 300-400 copies/mL) is associated with biochemical remission, histological

Table 1. Annual probability according to the treatment used in the model.

Parametres	Estimates	References
ETV		
HCB-response (year 1)	90.0 (86.0;96.0)	16
HCB-response (year 2-5)	42.0 (37.0;47.0)	16
Resistance, year 1	0.2	10
Resistance, year 2	0.5	10
Resistance, year 3	1.2	10
Resistance, year 4	1.2	10
Resistance, year 5	1.2	10
LAM		
HCB-response (year 1)	73.0 (68.0;78.0)	16
HCB-response (year 2-5)	29.0 (24.0;34.0)	16
Resistance, year 1	24.0	10
Resistance, year 2	38.0	10
Resistance, year 3	49.0	10
Resistance, year 4	67.0	10
Resistance, year 5	70.0	10
ADV		
HCB-response (year 1)	51.0 (46.0;71.0)	12
HCB-response (year 2-5)	15.0 (10.0;20.0)	13
Resistance, year 1	0	10
Resistance, year 2	3	10
Resistance, year 3	11	10
Resistance, year 4	18	10
Resistance, year 5	29	10
TBV		
HCB-response (year 1)	88.3	15
HCB-response (year 2)	82	20
Resistance, year 1	4	10
Resistance, year 2	17	10
Resistance, year 3	-	
Resistance, year 4	-	
Resistance, year 5	-	
Rescue therapy		
Resistance-response	52.0	6
Durability of the response to the treatment	10.0	13.16

improvements and the prevention of complications as well as reduced risk of drug resistance.[10] The percentage of patients with undetectable levels of HBV DNA (< 400 copies/mL) was 73.0% for lamivudine after one year and 29.0% from the second to the fifth year.[16] This percentage was 51.0%[12] after one year of treatment with adefovir and 15% from the second to the fifth year.[13] The reduction in HBV DNA was 90.0% after one year of treatment with entecavir and 42.0% of the patients

who continued to receive treatment showed a response from the second to the fifth year.[16] The reduction in HBV DNA was 88.3%[15] after the first year of treatment with telbivudina and 82.0% in the second year.[19] Due to limited data available on the time of treatment, we used the conservative estimate of 15% rate of reaction to treatment from the sixth to the final year of the cohort, which corresponds to the lowest rate of response to treatment using one drug (adefovir).

The rates of relapse were above 90.0% after six months of treatment with entecavir, adefovir and lamivudine.[13,16] Treatment over a long period of time improves the durability of the treatment, but clinical data are limited. Thus, we considered the relapse rate until the end of the cohort to be 90.0%. In the event of resistance, which may occur from the first year of treatment onwards, patients received rescue therapy, with a response rate deemed to be 52.0% and relapse rate of 90.0%.[6] There was assumed to be no resistance to the rescue therapy.[17]

In this study, direct costs were analysed and calculated in real (R$).

The cost of the drugs was based on the table of prices of the CMED (Chamber of Drug Market Regulation) on 22/3/2011. We used the average of factory prices (FP) before the ICMS (Tax on Circulation of Goods and Services) and the CAP (Coefficient of Price Adequacy) of 24.38%. The unit prices of the drugs were: lamivudine 150 mg (R$ 2.93), adefovir 10 mg (R$ 12.97), entecavir 0.5 mg (R$ 12.95) and telbivudina 600 mg (R$ 13.76).

The annual cost per patient with compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma were taken from the 2005 study by Castelo et al,[4] which evaluated direct costs of CHB in Brazil. These costs included: fees, doctors, laboratory tests, diagnostic and therapeutic procedures, hospital admissions and spending on non-antiviral medicine. The estimate of costs was based on SUS pay-out tables. The costs were updated for 2011 and converted into real (exchange rate US$ 1 = R$ 1.66 22/3/2011). Annual costs of the five stages of CHB development were calculated to be: CHB (R$ 1,092.59), compensated cirrhosis (R$ 1,561.95), decompensated cirrhosis (R$ 9,751.41) and hepatocellular carcinoma (R$ 2,108.80).

The Markov model was used to estimate the clinical benefits in years added to life (YAL) and the costs of the alternative drugs over the timeframe. The comparison between the treatment options was measured by the ratio of incremental cost-effectiveness (RICE). The cost-effectiveness threshold used was that suggested by the World Health Organization,[b] i.e., from one to three times the Gross Domestic Product (GDP) *per capita* (R$ 21,252.00 to R$ 63,756.00; reference year: 2011) per disability-adjusted life year (DALY) prevented. YAL was deemed to be proxy as DALY was not estimated. A reduction of 5% per year was applied to costs and results.

Sensitivity analyses were carried out in order to determine the impact of the RICE estimate. We conducted one-way analysis using a Tornado diagram, altering the individual values: discount rates (0%, 5% and 10%), cost of the drugs (± 10%) or effectiveness of the treatment (maximum and minimum values of the probabilities of transition). Probabilistic sensitivity analysis was developed and an acceptability curve was generated using Monte Carlo simulation. We applied triangular distribution to the probabilities of the measures of effectiveness, based on the maximum and minimum ranges for the parameters used.

We used decision analysis software (DATA, version 1.3.1 Tree Age software, INC, Williamstown, Massachusetts).

This study incorporates the 'Economic evaluation of nucleoside/nucleotide analogue drugs – adefovir dipivoxil, entecavir, telbivudina – in the treatment of chronic hepatitis B virus' project, submitted to edital MCT/CNPq/MS-SCTIE-DECIT/CT – Saúde nº 033/2007.

RESULTS

The accumulated incidence of compensated cirrhosis over ten years was 26.38% in patients who started on entecavir, 26.7% in those who started on telbivudina, 27.9% of those treated with lamivudine and 28.9% of those on adefovir. The accumulated incidence of resistance was 0.4% in patients who started on entecavir

Table 2. Results of the cost-effectiveness analysis.

Treatment Initial	Rescue therapy	Cost (R$)	Custo incremental (R$)	YAL	Incremental effectiveness	RCE (R$/ GYL)	RICE
LAM	LAM+ADV	52,621.60		12.07		4,359.41	
ETV	ETV+ADV	58,344.40	5,722.79	12.42	0.35	4,697.83	16.416.08
ADV	ADV+ETV	78,988.71	20,644.31	11.92	-0.5	6,627.84	(Dominated)
TBV	TBV+ADV	80,481.95	22,137.55	12.31	-0.11	6,536.35	(Dominated)

Reduction of 5% on the costs and effects
YAL: years added to life; RCE: ratio of cost-effectiveness; RICE: ratio of incremental cost effectiveness; ETV: Entecavir; ADV: Adefovir; TDF: tenofovir; LAM: lamivudine; TBV: telbivudina

and was greater for patients who started on adefovir (21.0%), telbivudina (22.4%) and lamivudine (27.5%).

The costs of the treatment strategies were shown including the costs of the disease, incremental costs (difference of the costs between the therapy studied and that which had the lowest cost), effectiveness, incremental effectiveness and the cost-effectiveness ratio (RCE). RICE is the difference between costs divided by the difference between the effectiveness of the treatment compared with the reference strategy. The negative ratio meant that the strategy was more expensive and less effective than the reference strategy.

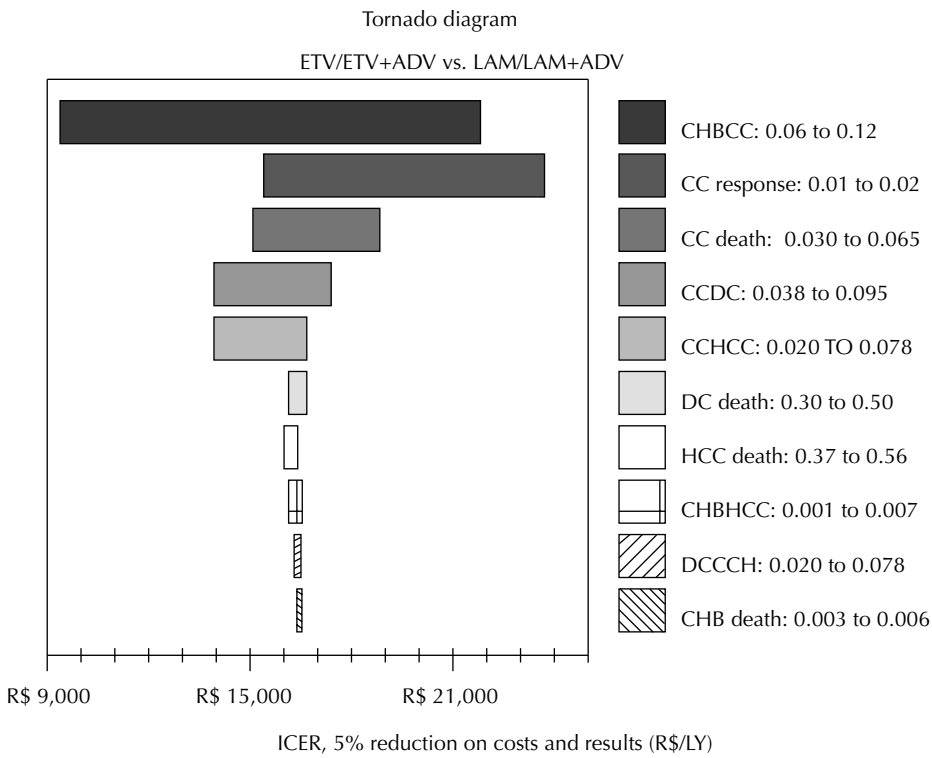
Treatment starting with entecavir resulted in more YAL (12.4), with an increase of 0.3 YAL compared to those who started on lamivudine (Table 2). RICE was R$ 16,416.08 per YAL, comparing treatments starting with entecavir and lamivudine. The strategies (begin treatment with adefovir or telbivudina) were shown to be less cost-effective.

Response to treatment occurred in 20.4% of patients who started on entecavir, in 18.1% of those who were treated using telbivudina, 13.4% of patients on lamivudine and 11.1% of those on adefovir. The RICEs decreased when discount rates of 0%, 5% and 10% were applied in the one-way sensitivity analysis. When considering 10.0% increases or decreases in costs, incremental cost-effectiveness ratios of R$ 18,057.68 and R$ 14,774.47 respectively were found for patients who started on entecavir compared with those who started on lamivudine.

Staring treatment with entecavir signifies an average spend of R$ 249,476.09 per response to treatment. Starting with lamivudine meant spending R$ 259,871.86, and the difference between the options was R$ 10,395.77.

RICE estimates were more sensitive to variation in the probability of transition from CHB to compensated cirrhosis (RICE varying between R$ 9,417.00 and R$ 21,914.00) and to the response for compensated cirrhosis in the Tornado diagram. For the other probabilities, the variation was small (Figure 2).

In the probabilistic sensitivity analysis, starting treatment with entecavir was the option which showed 100.0% probability of being the most cost-effective, within the threshold of cost-effectiveness acceptable for Brazil, compared with treatment with lamivudine. Treatment starting with entecavir offered better net benefits in YAL.



HCB: chronic hepatitis B; CC: compensated cirrhosis; CD: decompensated cirrhosis; CHC: hepatocellular carcinoma; response: response to the treatment

Figure 2. Tornado diagram.

DISCUSSION

In the last few years, lamivudine has been the anti-viral most commonly used by SUS for treating CHB, with high rates of resistance and low effectiveness in controlling the viral load but also with a low unit price thanks to it being mainly produced in official pharmaceutical laboratories. This study compares treatment starting with the drugs adefovir, entecavir and telbivudina to treatment which started with lamivudine. The choice of lamivudine as the comparison drug was in order to make the results more useful and relevant to the perspective of the study.

Treatment starting with entecavir compared to that starting with lamivudine stimulated a significant reduction in the number of CHB complications. More than 20.0% of patients who started on entecavir showed a response in this period and showed a lower level of resistance and lower rates of compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma in addition to RICEs within the thresholds of cost-effectiveness acceptable for Brazil.

In a timeframe of ten years, differences in favour of entecavir can be observed in the average cost of treating and obtaining a response. In other words, in the medium term, using entecavir, less is spent for each measurement of favourable results.

There are studies which analyse the cost-effectiveness ratio of anti-viral therapy in treating CHB. However, they show methodological differences (the drugs being compared, the timeframe, perspective, modelling) and heterogeneity of the simulated population.[25]

Costa et al undertook a study with a ten-year-timeframe comparing entecavir with lamivudine in HBeAg positive and negative patients.[7] Those who developed resistance to lamivudine had adefovir added to their treatment. The study used the following three parameters to judge the treatment's success: percentage of patients who attained undetectable levels of viral load, YAL and the quality of life adjusted to those years gained (QALY). Entecavir was shown to be more effective and produced RICE within the cost-effective threshold acceptable in Brazil, in contrast to lamivudine, showing itself to be more cost-effective.

Calcagno et al compared entecavir and lamivudine in HBeAg positive and negative patients.[3] The analysis took into consideration different perspectives of financing in Argentina (private, social security, social and the perspective of public health). Entecavir was deemed to be more cost-effective than lamivudine in HBeAg positive and negative patients.

Beginning treatment with entecavir was the most cost-effective alternative compared with treatment with lamivudine, according to the probabilistic sensitivity analysis in this study. The option of starting treatment with entecavir showed RICE within the cost-effective threshold acceptable in Brazil in the one-way sensitivity analysis, with different discount rates and variations in cost (10% higher or lower). Even taking into account the differences between the studies, the results of the sensitivity analysis were consistent with the observations of the literature for HBeAg positive and negative patients.[3,7,23]

Adherence to the treatment, the natural history of the disease, failure to use rates of natural mortality apart from the use of estimates obtained from the literature and the extrapolation of the rates for rescue therapy are all limitations of this study. Low levels of adhesion to the treatment may reduce patients' response to it, compromising its effectiveness against the progression of the disease. A systematic revision of studies on the effectiveness of these drugs has shown the occurrence of at least one adverse event; however, this was not considered in the modelling.[1] Moreover, tenofovir, the drug currently recommended by the Ministério da Saúde[3] as the first option for treating patients who are carriers of CHB without cirrhosis, was not included as it did not have authorization from ANVISA (National Agency of Health Monitoring) to be used in the treatment of hepatitis B.

In economic models, it is never possible to include all the possibilities of the technologies being analysed. In spite of the limitations, they are an approximation of reality.

Differences in economic modelling are observed regarding the rates of progression of CHB in the more advanced stages. Studies such as this which encompass patients at different stages of CHB under treatment show the same clinical progression and rates of progression as those of patients who do not receive treatment, according to the natural history of the disease.[24,27] Others use reductions of the rates of progression from CHB to compensated cirrhosis for the first year of treatment or during the first four years of treatment.[22,23] Although the drugs for treating CHB do not alter the rates of progression, their use increases the chance of patients obtaining responses (negative HBV DNA), reducing the number of individuals who progress to more advanced stages of the disease. Thus, both approaches have an impact on the cost-benefit ratio of the treatments.

Estimates of the effectiveness of rescue therapy after one year of treatment, for patients resistant to the initial treatment, are not available. This analysis, as with previous examples, should be treated with caution, as the benefits of rescue therapy and the impact of resistance may be overestimated.[23] Moreover, estimates in the literature referring to the efficacy/effectiveness used may not reflect the reality of the population of

Brazil, as international studies are the main sources of research for the drugs used in treating CHB.

Tenofovir, which efficacy and safety have been little studied, has shown proven effectiveness and low levels of resistance in HBeAg negative patients and those infected with chronic HBV without HIV co-infection. This option shows itself to be cost-effective as a first choice compared to administering lamivudina.[14] Economic evaluation studies in Brazil are needed to reinforce this evidence.

Although the eradication of the hepatitis B virus from the organism is rarely achieved using current treatment options, there is a consensus in the literature on the benefits of early treatment in supressing the viral load and the consequent reduction in risk of compensated cirrhosis and hepatocellular carcinoma.[24] The availability of entecavir as part of an early treatment strategy is economically attractive for patients diagnosed with CHB without co-infection.

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