Chronic Hepatitis B Treatment: The Cost-Effectiveness of Interferon Compared to Lamivudine

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ABSTRACT

Objective: To perform a cost-effectiveness evaluation from the perspective of the Brazilian National Health System of alternatives strategies (i.e., conventional interferon, pegylated interferon, and lamivudine) for the treatment of patients with chronic hepatitis B who present elevated aminotransferase levels and no evidence of cirrhosis at the beginning of treatment. Methods: A Markov model was developed for chronic hepatitis B (hepatitis B antigen e [HBeAg] positive and negative) with 40 years’ 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: For HBeAg positive patients, peginterferon (48 weeks) resulted in an increase of 0.21 discounted life-years gained compared to interferon (24 weeks). The incremental cost-effectiveness ratio (ICER) converted to US dollars using the 2009 purchasing power parity conversion factor was US$100,752.24 per life-year gained. For HBeAg negative patients, conventional interferon (48 weeks) compared to lamivudine provided more life-years gained and ICER of US$15,766.90 per life-year gained. In the sensitivity analysis, the ICER was more sensitive to variation in the probability of transition from chronic hepatitis B to compensated cirrhosis, discount rate, and medicine prices. Cost-effectiveness acceptability curve for HBeAg positive (pegylated interferon vs. conventional interferon) and negative (conventional interferon vs. lamivudine) showed that conventional interferon was cost-effective until three times the gross domestic product per capita. Conclusions: For patients with chronic hepatitis B with elevated aminotransferase levels in the pretreatment and no cirrhosis who were HBeAg positive, pegylated interferon (48 weeks) provided more life-years gained when compared to conventional interferon (24 weeks), and the ICER surpasses the country’s buying power, which makes conventional interferon the chosen alternative. For HBeAg negative patients, conventional interferon (48 weeks) compared to lamivudine provided more life-years gained at a favorable ICER. Keywords: chronic hepatitis B, cost-effectiveness, interferon, lamivudine, peginterferon.

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Introduction

Hepatitis B is one of the most common infectious diseases worldwide. An estimated 350 million people worldwide are chronically infected with hepatitis B virus (HBV) [1]. In Brazil, at least 15% of the population has been in contact with HBV and 1% present with chronic disease [2]. Persistently high HBV DNA levels are associated with an increased risk of cirrhosis and hepatocellular carcinoma (HCC) [3,4], which contributes to the increase of treatment costs due to morbidity [5].

Until recently and according to the Clinical Protocols and Therapeutic Guidelines for High Cost Medications of the Brazilian Ministry of Health [6], pharmacological options for the treatment of chronic hepatitis B were restricted to interferon and lamivudine. Currently, three antiviral medications (tenofovir, entecavir, and adefovir) have extended the treatment alternatives for the control of HBV action [7].

In a systematic review [8], it was observed that interferon (IFN) presented the advantages of long-term response in hepatitis B antigen e (HBeAg) positive patients, a short treatment duration and absence of resistance. The main advantages of pegylated interferon (PEG-IFN) were its extended biological effect and the lower number of treatments it required. Both treatment options showed the disadvantages of limited use in patients with a lower alanine aminotransferase (ALT) level at pretreatment or with a decompensated liver. Their association with several adverse events and the inconvenience of subcutaneous injection.

The first nucleoside analogue to be approved and used for HBV was lamivudine (LAM) [9], which is associated with minimal adverse events, low maintenance response rates, and a need for long-term therapy [10]. Its greatest limitation is the selection of resistant mutants, with patients becoming resistant after a year of treatment [11].

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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The objective of this study was to perform a cost-effectiveness evaluation from the perspective of the Brazilian Public Health System (SUS) of alternative strategies (IFN, PEG-IFN, and LAM) for the treatment of patients HBeAg positive and negative (i.e., antibodies to HBeAg), who present high ALT levels and no evidence of cirrhosis at the beginning of treatment. This group of patients was chosen because it is considered to represent the most prevalent and clinically relevant chronic HBV infection.

**Methods**

Decision analysis software (DATA, version 1.3.1, Tree Age software, Inc., Williamstown, MA) was used for the cost-effectiveness analysis aimed at evaluating a hypothetical cohort of patients with chronic HBV infection with a histological diagnosis of the disease, positive for serum hepatitis B surface antigen for more than 6 months, with detectable HBV DNA levels and high ALT levels (more than twofold the upper normal limit [UNL]) and no clinical or histological evidence of cirrhosis. Clinical research shows differences in the age profile among HBeAg positive and negative patients [12,13]. As a result, two models were built, considering the average age at the onset of treatment as 32 years for HBeAg positive patients [12,14] and 40 years for HBeAg negative patients [14]. A Markov model was used with 1-year cycles and both models evaluate short-course and longer duration treatments with time-horizon of 40 years, given that most of the patients in the cohort would be dead after this period.

Ideally, economic analysis should be established prospectively, and together with the results of clinical research. The disease progression involves decades and it is difficult to realize prospective studies. The model parameters, including efficacy/effectiveness measures were obtained from a specific systematic review [8] and from review of selected studies.

The efficacy measures used were: 1) HBeAg positive patients: HBeAg seroconversion; and 2) HBeAg negative patients: response to treatment [low levels of HBV DNA (< 300–400 copies/mL) and normalisation of ALT levels] [13]. The long-term results were modelled using the stages in the Markov model considering the annual failure in the durability of HBeAg seroconversion and treatment response.

In this study, like previous economic analyses of antiviral treatment for chronic hepatitis B [15], HBeAg seroconversion was used as a treatment-stopping criterion. However a patient could experience a relapse and return to the chronic hepatitis B stage used as a treatment-stopping criterion. However a patient could experience a relapse and return to the chronic hepatitis B stage. In this study, like previous economic analyses of antiviral treatment for chronic hepatitis B [15], HBeAg seroconversion was used as a treatment-stopping criterion. However a patient could experience a relapse and return to the chronic hepatitis B stage used as a treatment-stopping criterion. However a patient could experience a relapse and return to the chronic hepatitis B stage. In this study, like previous economic analyses of antiviral treatment for chronic hepatitis B [15], HBeAg seroconversion was used as a treatment-stopping criterion. However a patient could experience a relapse and return to the chronic hepatitis B stage. In this study, like previous economic analyses of antiviral treatment for chronic hepatitis B [15], HBeAg seroconversion was used as a treatment-stopping criterion. However a patient could experience a relapse and return to the chronic hepatitis B stage. In this study, like previous economic analyses of antiviral treatment for chronic hepatitis B [15], HBeAg seroconversion was used as a treatment-stopping criterion. However a patient could experience a relapse and return to the chronic hepatitis B stage.

**HBeAg negative**

All HBeAg negative patients in the model started at chronic hepatitis B disease stage with no cirrhosis. The model consisted of six disease stages (Fig. 1B in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011). All the efficacy assumptions for LAM were based on observational studies [12,19,20]. The rate of seroconversion observed in the fourth year (5%) [20] was used from the fifth year onward (Table 1 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011).

In all therapeutic alternatives, after treatment cessation, all patients could experience a relapse. Van Nunen et al. [21] and Wang et al. [22] demonstrated a 35% relapse for LAM in patients with ALT levels greater than or equal to two to five times the UNL 6 months after the treatment; that rate was considered until the fourth year of treatment. For the fifth year, a relapse of 25% was estimated considering the potential long-term impact on the durability of seroconversion [21,22]. Spontaneous seroconversion rates of 9% were considered for patients in the beginning of the treatment with PEG-IFN and IFN [18] (Table 1 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011).

There was limited published data on the annual loss of response following treatment with PEG-IFN, so conservative relapse rates of 8% were used in the analysis for IFN and PEG-IFN [21], despite PEG-IFN has showed fewer relapses than conventional IFN (Table 1 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011). All the efficacy assumptions for LAM and PEG-IFN are similar to what was used by Veenstra et al. [14]; thus, relapse rates for INF and PEG-IFN were obtained in the same study. The annual rates of disease progression or effectiveness measures were described in Table 2 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011.

All HBeAg positive patients: IFN dosed at 9 to 10 MU three times a week (24 weeks), PEG-IFN alfa 2a (180 µg) once a week (48 weeks) or long-term LAM (100 mg) daily (LAM use after 4 years of treatment in patients who did not undergo HBeAg seroconversion did not bring any added benefit; however, in the Markov model, these patients continued to receive LAM and the cost was calculated in subsequent years). The model doesn’t assume rescue therapy in case of treatment failure associated with emergence of drug-resistant virus.
The costs

Only direct costs were taken into account in this study. All costs were originally calculated in the national currency (Brazilian real [BRL]). These values were converted to US dollars using the 2009 purchasing power parity (PPP) conversion factor according to the International Monetary Fund. It was assumed 2009 PPP conversion factor (US$1 = 1.56 BRL).

Prices of the medication therapies

Prices were based on the list of medication prices from the Medication Market Regulating Chamber (Câmara de Regulação do Mercado de Medicamentos) on November 13, 2009. The average factory price was used with a state tax on goods and services of 0% and the price adjustment coefficient of 24.92%, which is a mandatory minimum discount that affects the factory price of some medications purchased by public entities. The average prices were of US$398.52 (US$78.76–US$106.85) for IFN, US$578.69 (US$338.69–US$730.02) for PEG-INF and US$1.39 (US$0.43–US$2.16) for LAM. The calculation of the minimum and maximum prices used the lowest and the highest price found in the Medication Market Regulating Chamber table and then applied the price adjustment coefficient. Because there was no price variation for the PEG-INF, the same variation found for the IFN was used.

Annual costs due to chronic hepatitis B complications

Annual costs per patient with compensated cirrhosis (CC), decompensated cirrhosis, and HCC were obtained from the study by Castelo et al. [30] that evaluated the chronic hepatitis B costs in 2005 in Brazil with a Delphi panel of specialists. The direct costs included those generated by medical fees, lab exams, diagnostic and therapeutic procedures, hospitalizations, and medications. Data on costs were predominantly obtained from SUS billing tables and medication prices. The annual costs of the evolving chronic hepatitis B stages were updated to 2009 and estimated as follows: chronic hepatitis B (US$870), CC (US$1243), decompensated cirrhosis (US$7763), and HCC (US$1679).

Cost-effectiveness analysis

The Markov model was used to estimate the clinical benefits in life-years gained (LYG) and the costs of the medication alternatives in the time horizon period. The comparison among the treatment alternatives was measured by the incremental cost-effectiveness ratio (ICER). The cost-effectiveness threshold developed by the World Health Organization [31] is one to three gross domestic product (GDP) per capita for an additional disability adjusted life year prevented. A discount rate of 5% per year was adopted for the costs and results.

A unidirectional sensitivity analysis was conducted to determine the impact in the ICER estimate. This analysis was carried out by changing individual inputs: therapy response at the first year of treatment (interval confidence), prices of the medication (lowest, highest), discount rates (0%, 5%, and 10%) or magnitude of treatment effectiveness in a Tornado analysis. A probabilistic sensitivity analysis was conducted and generated a cost-effectiveness acceptability curve using Monte Carlo simulation methods. Triangular distributions were assigned to probability based on the parameter ranges (minimum, maximum) listed in Table 2 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.012.

Results

The clinical results and economic estimates for each medication alternative (IFN, PEG-INF, and LAM) for chronic hepatitis B treatment are presented in Table 3 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.012.

In HBeAg positive patients, it was observed that PEG-INF (48 weeks) resulted in more LYG compared to IFN (24 weeks), with a difference of 0.21. The ICER was US$100,752.24 per LYG. The LAM strategy was dominated. In the case of HBeAg negative patients, it was observed that IFN (24 weeks) presented an ICER of US$15,766.90 per LYG compared to LAM, with a difference of 0.45 LYG. The LAM strategy and PEG-INF were dominated.

For HBeAg positive patients, the treatment with LAM resulted in an average of 13.58 LYG compared to 14.25 LYG (IFN) and 14.46 LYG (PEG-INF). The accumulated incidence of CC across 10 years was 18%, 15%, and 14%, respectively. For HBeAg negative patients, the treatment with IFN results in an average of 13.12 LYG compared to 12.93 LYG (PEG-INF) and 12.67 LYG (LAM). The incidence accumulated of CC in 10 years was 22.7%, 23.3%, and 26%, respectively.

Sensitivity analysis

For both groups, when the discounts (0%, 5%, and 10%) were applied to the costs, the ICER estimates decreased.

For HBeAg positive patients, when the worst and the best scenarios (minimum or maximum values of the seroconversion rates) were modelled for the first year of treatment, there was no affect on the ICER comparing PEG-INF versus INF.

For HBeAg negative patients comparing INF versus LAM, when the best scenario (maximum value of response) was used for the first year of treatment, we observed a reduction in the ICER US$4894.87. Concerning the worst scenario, the ICER was not altered. For HBeAg positive patients comparing PEG-INF versus INF, when medicines minimum prices were applied to the medications, there was a decrease in the ICER US$57,541.40 and the ICER increased (US$128,248.29) when maximum prices were applied. The same phenomenon was observed for the HBeAg negative patients comparing INF versus LAM, with ICERs of US$4895.94 and US$24,507.22, respectively.

The Tornado analysis demonstrated that the ICER estimates were more sensitive to the variation in the probability of chronic hepatitis B evolving to CC, seroconversion to CC and response to CC (Figs. 2 and 3 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011).

For HBeAg positive patients, the cost-effectiveness acceptability curve generated from the PSA for the discounted incremental cost-effectiveness ratio indicated that INF was cost-effective compared with PEG-INF until three GDP per capita. To willingness to pay up than US$104,487.20, using the 2009 PPP conversion factor, PEG-INF has up than 50% to be cost-effective compared with INF. For HBeAg negative patients, INF was cost-effective compared with LAM at the Brazilian threshold.

Discussion

In this study, for HBeAg positive patients, PEG-INF when compared to the IFN showed a little better result, but presented an ICER above the current Brazil cost-effectiveness threshold. The ICER was more sensitive to variation in the progression probability of the chronic hepatitis B to CC and seroconversion for CC. Therapy response did not impact the sensitivity analysis and can be related to the small seroconversion interval observed in the literature. Greater variation in the ICER was noticed when medication price and discount rate was varied. In probabilistic sensitivity analysis, INF was cost-effective compared with PEG-INF until three GDPs per capita.

Using a Markov model system and data from clinical research, Sullivan et al. [32] evaluated the ICER of treatment with PEG-INF compared to that of LAM in HBeAg positive patients from the perspective of Taiwan. Treatment with PEG-INF was considered more cost-effective considering factors such as disease progression,
LYG, therapy cost, and effectiveness. The ICER was sensitive to the same variations observed in this study and was considered favorable because it was within the buying power parameters of that country. Veenstra et al. [14] observed that even thoughpeg-IFN was a more expensive alternative than LAM, it provided better results in terms of health and cost-effectiveness within the buying power constraints of the United Kingdom.

In our study, for HBeAg negative patients, INF compared to LAM demonstrated more LYG and ICER within the buying power of the country. The PEG-IFN alternative was dominated. In the sensitivity analysis, we observed that varying the interval of the transition probabilities caused less variation in the ICER. Greater variation in the ICER was observed when medications price and discount rate varied. In PSA, INF was cost-effective even for values up to three GDPs per capita.

The results of our study show that the progression to CC in HBeAg negative patients was higher than in HBeAg positive patients and that LAM resulted in greater progression in both groups. Lacey et al. [16] observed similar results and concluded that short-term treatment with IFN, PEG-IFN, or LAM presented limited influence on the disease progression.

Comparing PEG-IFN with LAM in HBeAg negative patients, Veenstra et al. [27] demonstrated that PEG-IFN had incremental benefits on life expectancy and quality of life with an acceptable ICER in Taiwan. Kanwal et al. [28] verified that IFN was more cost-effective compared to LAM in HBeAg negative patients. The authors emphasized that IFN could reduce costs because it eliminated the need for longer therapy and that it could be effective when it did not present viral resistance.

Some limitations to our study can be identified and they pertain to treatment compliance, patient profiles, natural history of the disease, annual costs, time-horizon, no natural mortality rates, and the estimates obtained in the literature. All long-term modeling studies are inherent uncertainties in projecting long-term results.

The modelling did not consider the occurrence of problems in compliance with LAM long-term antiviral treatment, which can generate worse results than those observed in the clinical trials. The same can be considered in the treatment with IFN due to adverse events. Low adherence rates to the treatment can reduce the therapy response, thereby risking the treatment’s effectiveness on the disease progression.

The profile of the patients included in our study does not allow for the extrapolation of the results to patients with a different profile. However, that choice was considered the most prevalent and clinically relevant form of chronic HBV infection. High levels of ALT in the pretreatment is a predictable factor for the response at the end of the treatment and that IFN may be adverse to patients in advanced stages of the disease [18].

We assumed that patients in different stages of chronic hepatitis B present the same clinical course and progression rates as nontreated patients. This condition is consistent with several published analyses of cost-effectiveness, where the patients without response and nontreated patients progress in a similar manner [28,32,33].

In addition, the estimates in the literature are limited and international studies that are mainly focused on Asian populations are the main sources of findings on the medications used in the treatment of chronic hepatitis B.

Conclusions
This analysis suggests that for HBeAg positive patients with high levels of ALT in the pretreatment and without cirrhosis or HCC at the beginning of the treatment, PEG-IFN (48 weeks) provided more LYG when compared to IFN (24 weeks), but the ICER surpasses the country’s buying power, which makes IFN the chosen alternative for those patients. For HBeAg negative patients, INF (48 weeks) compared to LAM (long-term) provided more LYG at an acceptable ICER to the country. The sensitivity analyses show that the ICER was more sensitive to variation in the probability of transition from chronic hepatitis B to CC, discount rate, and medicine prices. Our findings suggest that interferon could be considered the chosen alternative in health care systems with limited resources.

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Supplemental Materials
Supplemental material accompanying this article can be found in the online version as a hyperlink at doi:10.1016/j.jval.2011.05.011 or if hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES


