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

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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, it was observed that interferon (48 weeks) compared with long-term lamivudine presented an increase of 0.45 discounted 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.

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 [16]. For HBeAg negative patients, sustained remission was also not considered common [17].

The model did not assume any explicit consideration in regard to LAM resistance. However, some effects of resistance to the medication were captured with the reduction in long-term seroconversion rates [15].

HBeAg positive

The model consisted of six disease stages (Fig. 1A in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011). The model structure was adapted from the model of Crowley et al. [18].

All patients in the model started at the chronic hepatitis B disease stage with no cirrhosis and received treatment alternatives. The model evaluated short-term treatment for HBeAg positive patients: IFN dosed at 9 to 10 MU three times a week (24 weeks), PEG-INF 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.

Efficacy measures were obtained for 1 year of treatment considering results from clinical research in patients with ALT levels greater than or equal to twice the UNL, HBeAg seroconversion rates for IFN (24%) [18], LAM (19%) [12], and PEG-IFN (32%) [12]. The seroconversion estimates sustained for LAM for the second, third, and fourth year of treatment were 10%, 6%, and 5%, respectively, 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-INF, so cconservative 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-INF are similar to what was used by Veenstra et al. [14]; thus, relapse rates for INF and PEG-INF 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.

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). The treatment alternatives considered were IFN at a dosage of 9 to 10 UM three times a week (48 weeks), PEG-IFN (48 weeks) once a week, or long-term LAM daily (until the patient responds to treatment).

To obtain efficacy measures, the estimates for sustained combined response (suppression of HBV DNA and ALT normalization) 6 months after the treatment was stopped were derived from the randomized controlled trial by Marcellin et al. [13] that compared PEG-IFN with LAM (48 weeks). The response rates for PEG-IFN were 36% at the end of treatment and at follow-up and 69% for LAM at the end of treatment. There is some data in the literature on relapse rates after 6 months of treatment with LAM, but two studies pointed out that the combined response rates were around 11% to 20% 1 to 2 years after treatment [23,24]. These authors reported relapse rates of 83% after 6 months and after a year of follow-up [23,24]. Based on these data, a conservative annual rate of relapse of 80% for LAM was considered. For IFN, a complete response rate to the treatment of considered 60% [25].

There are no long-term data on combined response for PEG-IFN and there are few for IFN. One study suggested that 50% of patients treated with IFN experienced relapse between 6 months and 32 months post treatment [26]. Considering that there were no relapses 6 months after treatment with PEG-IFN [13], a relapse of 25% was assumed after 6 months of treatment [27]. Spontaneous relapses of 6% were considered [28,29]. These estimates were obtained from Veenstra et al. [27]. The annual rates of disease progression or effectiveness measures are described in Table 2 in Supplementary Materials found at: doi:10.1016/j.jval.2011.05.011.