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Cost-Effectiveness Analysis of Antiviral Treatments for HBeAg-Positive Chronic Hepatitis B in Canada

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ABSTRACT

Objective: To conduct a cost-effectiveness analysis of currently available nucleos(t)ide antiviral treatments (lamivudine, telbivudine, entecavir, and tenofovir) for chronic hepatitis B in Canada. **Methods:** Markov modeling was used to project the lifetime health benefits and costs associated with the antiviral treatments. The hypothetical patient population was hepatitis B e antigen–positive chronic hepatitis B–infected patients aged 34 years. Quality-adjusted life-years were used as a measure of effectiveness. Long-term cumulative incidence of liver complications was also projected. Treatment effectiveness data were derived from the literature; meta-analysis was conducted when there was a large variance in reported effectiveness data. Costs were obtained from a cost analysis of treating chronic hepatitis B–related complications in Canada. Stochastic parameter uncertainty was examined in probabilistic sensitivity analysis by using second-order Monte Carlo simulation. Alternative modeling assumptions were assessed in scenario analysis. One-way sensitivity analysis was used to explore each parameter's impact on the uncertainty of the results. **Results:** In the base-case analysis, telbivudine was dominated by entecavir and tenofovir. Tenofovir strictly dominated lamivudine, telbivudine, and entecavir. Over the 72-year period of the model, the expected life expectancy (undiscounted) of lamivudine, telbivudine, entecavir, and tenofovir was 35.71, 36.94, 37.65, and 37.99 years, respectively. Tenofovir had the highest expected quality-adjusted life-years at 11.86 (discounted) in all comparisons. Scenario and sensitivity analyses proved the robustness of the base-case results. The projected 10-year cumulative incidence of cirrhosis and hepatocellular carcinoma was 11.40% and 3.05%, respectively, for tenofovir, which is significantly lower than that for lamivudine. **Conclusion:** Tenofovir generated the best results compared with all other therapies under evaluation.

Keywords: antiviral treatments, chronic hepatitis B, cost-effectiveness analysis, Markov modeling, probabilistic sensitivity analysis.

Introduction

In Canada, the estimated number of hepatitis B virus (HBV)-infected individuals is 5.2% in immigrants, 0.7% to 0.9% in Canadian-born individuals, and 4% in aboriginals [1,2]. The projected seroprevalence of HBV in Canada is close to 1.26% [2]; therefore, there are approximately 430,000 Canadians infected with HBV. With 20% to 25% mortality rate among untreated cases [2], chronic hepatitis B (CHB) infection has severe long-term outcomes and requires complex algorithms for management. The Ontario Burden of Infectious Disease study [3] estimated that 346 deaths per year in Ontario are directly attributable to chronic HBV infection, and an increasing burden to the health system is expected because of new cases of cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Although antiviral treatments for CHB do not provide a complete cure except for rare cases [2], timely treatment can significantly prevent the progression of liver damage from HBV by slowing down or stopping the virus from reproducing. Oral nucleos(t)ide analogues (NAs) have become the preferred first-line treatment for most genotypes of hepatitis B due to relatively few adverse effects compared with those of interferons. During the past 5 years, a new generation of NAs has become available.

Lamivudine (LAM) was the first oral agent to be approved for the treatment of HBV infection in Canada, and until 2006 it was the only NA available. Although it is no longer recommended by the Canadian Consensus Guidelines as the first-line choice for the treatment of high viral load CHB (HBV DNA $> 2 \times 10^7$ IU/mL) because of its low genetic barrier to developing resistance [2], it is still the most commonly prescribed NA in clinical practice in Ontario. According to a national survey, in 2009 77% of treatment-naive patients with public funding received LAM in Ontario [4]. In contrast, the consensus guidelines recommended telbivudine (LdT) for patients with both low and high viral load; however, the use of LdT in Canada was rare (2% in 2007 and 1% in 2009), mainly because of provincial reimbursement restrictions and nonsuperiority of LdT over other agents [4].

Entecavir (ETV) was recommended by the consensus guidelines as a first-line therapy for all patients regardless of viral load. It was considered the most potent agent available before tenofovir disoproxil fumarate (TDF) was officially licensed for hepatitis B [2]. New evidence has suggested that both TDF and ETV are the most

Note: This study was done when the principal investigator was affiliated to McMaster University.

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effective therapies for CHB [5,6], and the recent update of the American Association for the Study of Liver Diseases (AASLD) practice guideline (2010) has recommended TDF or ETV as the first-line oral antiviral medications for CHB. From 2007 to 2009, clinical practice in Canada showed a 525% increase in TDF use and 211% increase in ETV [4].

To date, there has been no economic evaluation studying recently available nucleos(t)ide antiviral treatments for CHB from a Canadian perspective. Therefore, this study aimed to conduct an economic evaluation of these agents in Canada, using LAM as the reference.

Methods

Overview

A cost-effectiveness analysis was conducted to evaluate LdT, TDF, and ETV compared with LAM. A Markov model was chosen as the preferred structure for the analysis because of the chronic and recursive nature of chronic infection of HBV, which requires long-term follow-up to capture the relevant clinical and economic end points. The outcome measures used in the model were life-years, quality-adjusted life-years (QALYs), and costs associated with the treatments and disease progression. The analysis took the perspective of Ontario Ministry of Health and Long Term Care; therefore, only direct medical costs associated with CHB infection were considered. The time horizon of the model was the patients' lifetime. Clinical and economic outcomes were discounted at an annual rate of 5% [7], as this is the recommended rate by Canada's HTA agency. Microsoft Office Excel 2007 was used to conduct the analysis.

Patient population and treatment regimens

A hypothetical cohort of 1000 adult patients with the following baseline characteristics was chosen to go through the model:

- Hepatitis B e antigen (HBeAg)–positive chronic HBV infection without other coinfections and complications
- 34 years of age
- 72% males
- Mean serum alanine transaminase (ALT) level ranging from 100 to 200 IU/L
- Mean serum HBV DNA concentration ranging from 10^7 to 10^{10} copies/mL
- No prior treatment with anti-HBV nucleos(t)ides.

The characteristics of this patient cohort were based on efficacy trials from which key disease transition probabilities were derived. The model employed 72 yearly cycles, since 99.99% of the patient cohort has died by that time on the basis of the Ontario life table [8].

Treatment regimens included in the model were LAM (Epivir) 100 mg daily, LdT (Sebivo) 600 mg daily, TDF (Viread) 300 mg daily, and ETV (Baraclude) 0.5 mg daily, all administered orally. For patients who developed viral resistance to their initial treatments, the model employed rescue combination therapies recommended by the Canadian and AASLD guidelines, because they are consistent with the most effective care. In the case of LAM resistance, adefovir (ADV) (Hepsera, 10 mg) or TDF was added; the same add-on therapies were also used for LdT-resistant patients; for patients resistant to TDF, LAM was added; for ETV resistance, ADV was used as the add-on therapy [2,4,9].

Markov model

Chronic infection with HBV can transition through multiple pathways. The diagram of disease transition under treatment is presented in Figure 1. The patient cohort enters the model in the CHB state. While receiving antiviral therapies, patients could experience serum HBeAg seroconversion (i.e., the loss of HBeAg and the gain of anti-HBe), representing that progressive liver damage has been largely controlled but that they remain at risk of cirrhosis and HCC [10-15]. Hepatitis B surface antigen (HBsAg) clearance could also occur, indicating a cure of CHB. It is possible to develop viral resistance on long-term nucleos(t)ide treatment. Rescue therapies were administered to patients entering the resistance state. All patients except those who have lost HBsAg remain at the risk of developing cirrhosis and HCC over the long term. However, for patients who did not seroconvert but achieved viral suppression, the risk of developing cirrhosis and HCC may be reduced. During severe disease stages including decompensated cirrhosis and HCC, a liver transplant may be indicated. All states could lead to death. Because Markov models cannot hold memory of the disease transition history, several temporary states (not all shown in Fig. 1) were built to enable the assignment of state-specific transition probabilities and to adjust utilities and costs.

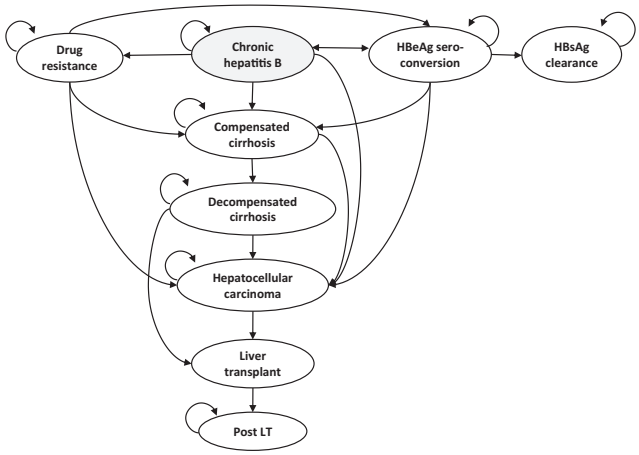

Fig. 1 – Health state transition diagram for the Markov model. HbeAg, hepatitis B e antigen; HbsAg, hepatitis B surface antigen; LT, liver transplant.

Key modeling assumptions

1. International guidelines on the therapy of hepatitis B suggest that finite duration of treatment with NAs is a reasonable option and recommend that treatment may be stopped after HBeAg seroconversion and an additional 6 to 12 months of consolidation therapy to maximize the durability of treatment response [2,9]. The model employed the recommended treatment strategy and 12-month consolidation therapy after the confirmed appearance of anti-HBe.
2. It was assumed that 60% of LAM-resistant and LdT-resistant patients receive ADV add-on and that 40% of these patients receive TDF add-on, according to the ratio of patients receiving these rescue therapies in clinical practice in Canada [2,4,9]. We did not consider alternative therapies that accounted for less than 10% in Canadian clinical practice and that were not recommended by international guidelines.
3. Hundred percent durability of HBeAg seroconversion was assumed during consolidation therapy. When off treatment, serologic durability varied across antivirals. In the case of serologic relapse, which means HBeAg seroconversion reverses and is considered a reactivation of hepatitis B [2], reinstitution of the initial antiviral treatment was applied to patients who had not developed viral resistance [9].