VALUE IN HEALTH ▮ (2015) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom

Sarah L. Bermingham, BSc, MSc[1,], Ralph Hughes, BSc, MSc[2], Elisabetta Fenu, MPharm, MSc[2], Laura M. Sawyer, BSc, MSc[3], Elizabeth Boxall, PhD, FRCPath, FFPH[4], Patrick T. Kennedy, MB, BCH, BAO, BMedSci, MRCP, MD[5], Geoff Dusheiko, MD, MB, BCh[6], Grant Hill-Cawthorne, MA, MB, BChir, MRCP[7], Howard Thomas, BSc, MB, PhD, FRCP[8]*

[1]*Symmetron Limited, Toronto, Ontario, Canada;* [2]*Royal College of Physicians, National Clinical Guideline Centre, London, UK;* [3]*Symmetron Limited, Borehamwood, UK;* [4]*Virology Laboratory, Health Protection Agency, Microbiology Services Division, Heartlands Hospital, Birmingham, UK;* [5]*Barts and The London School of Medicine and Dentistry, London, UK;* [6]*UCL Institute of Liver and Digestive Health, Royal Free Hospital, London, UK;* [7]*Marie Bashir Institute for Infectious Diseases and Biosecurity, Sydney School of Public Health, University of Sydney, Sydney, Australia;* [8]*Section of Hepatology and Gastroenterology, Department of Medicine, Imperial College, London, UK*

ABSTRACT

Background: Seven drugs are licensed for the treatment of chronic hepatitis B (CHB) in the United Kingdom. Which initial treatment, secondary therapy, and whether antivirals should be given alone or in combination are questions of considerable uncertainty. **Objective:** The aim of this model was to undertake a comprehensive economic evaluation of all antiviral treatments for CHB to recommend the most cost-effective therapeutic sequence. **Methods:** We developed a probabilistic Markov model to compare the cost-effectiveness of all clinically relevant antiviral treatment sequences for nucleos(t)ide-naive adults with hepatitis B e-antigen (HBeAg)-positive or HBeAg-negative CHB. Relative rates of HBeAg seroconversion and viral suppression were obtained from a network meta-analysis. Data on mortality, antiviral drug resistance, durability of response, adverse events, and costs were obtained from published literature. Results are reported in terms of lifetime costs, quality-adjusted life-years (QALYs), and expected net benefit. **Results:** In the base-case analysis, pegylated interferon alpha-2a (peg-IFN α-2a) followed by tenofovir disoproxil fumarate was most effective and cost-effective in HBeAg-positive patients, with a cost of £7488 per QALY gained compared with no treatment. In HBeAg-negative patients, peg-IFN α-2a followed by entecavir was most effective and cost-effective, with a cost of £6981 per QALY gained. The model was robust to a wide range of sensitivity analyses. **Conclusions:** Peg-IFN α-2a followed by tenofovir disoproxil fumarate or entecavir is the most effective antiviral treatment strategy for people with both variants of CHB. At a cost of less than £10,000 per QALY gained, these sequences are considered cost-effective in England and Wales. The results of this analysis were used to inform 2013 National Institute for Health and Care Excellence guideline recommendations.

Keywords: antiviral treatment, chronic hepatitis B, cost-effectiveness analysis, interferon-alpha, nucleosides, nucleotides.

Introduction

Chronic hepatitis B (CHB) is an infectious disease that affects approximately 400 million people worldwide [1]. The hepatitis B virus (HBV) infects liver cells and may lead to an immune response in which infected cells are killed but the virus is not eliminated. Over time, this can lead to cirrhosis, hepatocellular carcinoma (HCC), and death [1].

There are two molecular variants of HBV, which are defined according to the presence or absence of the hepatitis B "e" antigen (HBeAg). Over the course of infection, HBeAg-negative CHB may arise because of the selection of precore or other HBV mutant strains affecting the expression of HBeAg [2]. This variant is more frequently observed in older patients and is associated with worse outcomes than HBeAg-positive CHB [3].

Currently, seven drugs are licensed for the treatment of adults with CHB. Interferon-alpha (IFN-α) and pegylated interferon alpha-2a (peg-IFN α-2a) are injected subcutaneously, whereas nucleosides (lamivudine [LAM], entecavir [ETV], and telbivudine) and nucleotides (adefovir [ADV] and tenofovir [TDF]) are administered orally.

Interferon amplifies the immune response with the aim of achieving seroconversion and is administered over a 24- or 48-week course. Nucleos(t)ide analogues (NAs) inhibit viral

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

* *Address correspondence to:* Sarah L. Bermingham, Symmetron Limited, 20 Camden Street, Toronto, Canada M5V 1V1.
E-mail: s.l.bermingham@gmail.com.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2015.05.007

replication and must be continued long-term. Although interferon may reduce the probability of requiring NA treatment, it is costly and associated with significant adverse effects. NAs are associated with relatively few adverse outcomes, but the effectiveness of some drugs is limited by high rates of antiviral resistance.

Patients may receive treatment of finite duration with IFN-α or peg-IFN α-2a before starting NA therapy, or they may initiate a long-term course of NA treatment de novo. If patients develop resistance to an NA, they may be switched to a complementary "rescue therapy" with a drug that does not share cross-resistance. Alternatively, they may receive "add-on" therapy as a means of controlling multidrug resistance.

The choice of initial therapy, rescue therapy, and whether rescue therapy should be given alone or in combination are issues of considerable uncertainty. Several economic evaluations have considered parts of this question in isolation, but none has simultaneously assessed all available alternatives in both HBeAg-positive and HBeAg-negative populations [4]. The aim of this model was to undertake a comprehensive economic evaluation of all antiviral treatments for CHB to recommend the most cost-effective therapeutic sequence. This model was developed by the guideline development group (GDG) of the 2013 National Institute for Health and Care Excellence (NICE) guideline Diagnosis and Management of Chronic Hepatitis B in Children, Young People and Adults [5]. The results of this analysis were used to inform recommendations within the guideline.

Methods

Model Overview

We developed a probabilistic Markov cohort model using TreeAge 2009 to estimate lifetime costs in 2011 British pounds and quality-adjusted life-years (QALYs) from a UK National Health Service (NHS) and personal social services perspective. Costs and QALYs were discounted at the standard annual rate of 3.5% [6]. Total net benefit (NB) was used to rank order the cost-effectiveness of each antiviral treatment strategy.

Figure 1 illustrates the key health states used to represent the natural history of CHB and possible transitions between them. Baseline population characteristics and baseline transition probabilities are reported in Table 1. The model structure and baseline transition probabilities were informed by our review of previously published CHB models [7–9]. Structural decisions and probability estimates were discussed with clinical experts from the GDG to ensure that the assumptions and choice of data were directly relevant to the United Kingdom (see Appendix Tables 4 and 5 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.007). Relative estimates of effectiveness are reported in Table 1 and described below.

Patients entered the model as NA-naive adults with either HBeAg-positive or HBeAg-negative CHB. Approximately one-fifth of HBeAg-positive patients had evidence of active cirrhosis at baseline, compared with one-third of the HBeAg-negative population [12]; the remaining patients had active CHB that required treatment. *Active CHB* was defined as the presence of HB surface antigen (HBsAg) for at least 6 months and HBV DNA of more than 2000 IU/ml. Consistent with the epidemiological literature, the average age at the start of treatment was 31 years for HBeAg-positive and 40 years for HBeAg-negative patients [12]. Most of the patients in both populations were male [12]. People coinfected with HIV and treatment-experienced patients with LAM-resistant HBV were excluded from the model.

At the end of each cycle, patients could remain in each health state, achieve spontaneous or treatment-induced responses (HBeAg seroconversion or viral suppression), or experience a reactivation of the disease [17]. Patients could also develop

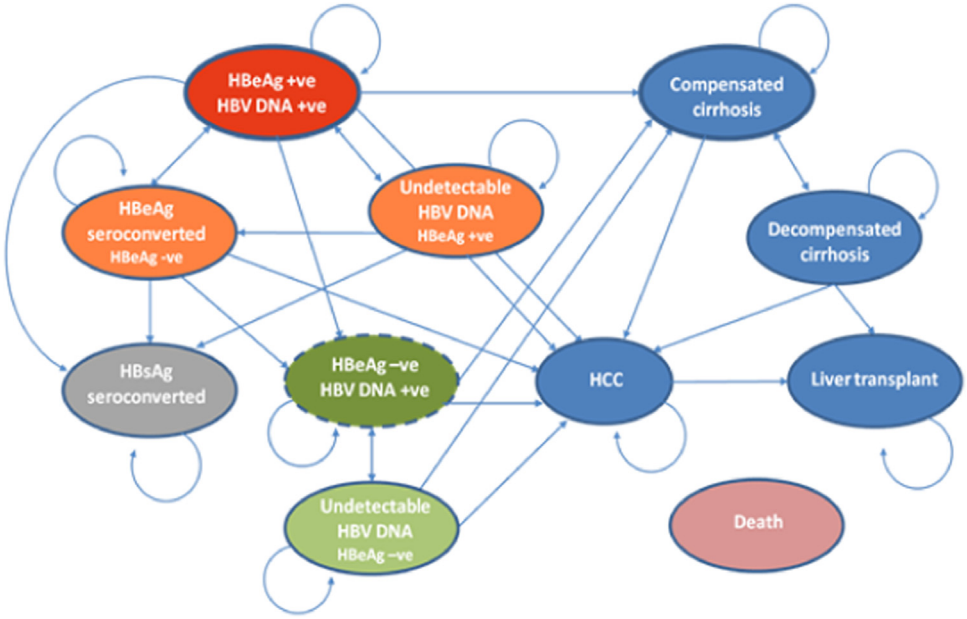

Fig. 1 – Natural history of CHB. A Markov model was developed to extrapolate the impact of short-term serologic and virologic changes on long-term outcomes in patients with either HBeAg-positive or HBeAg-negative CHB. Linear arrows indicate transitions between health states may occur at each cycle. Circular arrows indicate residual probabilities (i.e. one minus the sum of all other transition probabilities from that health state). All individuals were exposed to a background rate of mortality in each health state (not shown).