

Economic Evaluation of Drug Treatments for Patients with Chronic Hepatitis B (CHB): Results from a Systematic Review

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Abstract

The treatment of chronic hepatitis B (CHB) could reduce liver inflammation and progression of hepatic cirrhosis and hepatocellular carcinoma which could prolong survival and improve quality of life of patients. The cost of treatment is very expensive; therefore economic evaluation studies are needed. This study aimed to review economic evaluation studies on drug treatment options for patients with CHB. Studies assessing both costs and outcomes of two or more drug treatments for patients with CHB were included. These studies published during 2000-2010 were searched through the Pubmed and Cochrane databases. The results showed that seventy-two abstracts were reviewed and only 26 articles were included. Most studies were analyzed based on the perspectives of health care system or third party payer which considered only direct medical costs. The outcomes were measured in terms of life years saved and/or quality-adjusted life year gained. Markov model was more frequently used compared to decision tree model. Probabilistic and one-way sensitivity analyses were mainly applied to test parameter uncertainty. Most studies showed that entecavir or pegylated interferon was more cost-effective compared with lamivudine. The results were relatively varied due to the differences in time horizon and variables used in the models such as drug resistance rate, efficacy on viral suppression, and drug prices. Moreover, most studies did not consider drugs' side effects which could lead to higher costs and worse outcomes.

Key words: Chronic hepatitis B, economic evaluation, cost-effectiveness analysis, cost-utility analysis

INTRODUCTION

Hepatitis B is an infectious disease of the liver caused by hepatitis B virus (HBV). It is transmitted through blood to blood contact, sexual contact, or mother to child. An estimated 350 million people or more than one third of the world's population have been infected with the HBV¹. About 5% of the populations are chronic carriers of HBV, and nearly 25% of all carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) causing more than one million deaths every year¹. In Thailand, an estimated 4-5 million people are chronically infected with HBV with the prevalence rate higher than 8%¹. Chronic liver diseases and HCC associated with HBV infections are one of the most important public health problems in high-prevalence regions and cause an increase in economic burden and decrease in quality of life of patients²⁻³.

Current HBV infection can be detected by the presence of hepatitis B surface antigen (HBsAg) in the serum. Infected individuals develop an acute infection, which may or may not result in symptoms. In most individuals, infection will resolve and HBsAg disappears from the serum, but the viruses persist in some patients who become chronically infected with hepatitis B⁴. More than 95% of those infected with HBV during adulthood make a full recovery and acquire immunity from future infection, while less than 5% of infected adults and more than 90% of infected neonates will develop chronic hepatitis B (CHB).

Drug treatments for CHB can reduce viral replication to the lowest possible level and maintain it through the long term. The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to compensated cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death⁵⁻⁶. Currently six CHB medications including both oral (i.e., lamivudine, adefovir, entecavir and telbivudine) and intravenous (i.e.,

conventional interferon and pegylated interferon) dosage forms have been licensed by the Thai Food and Drug Administration (FDA). However, only lamivudine has been included in the National List of Essential Drugs (NLED) but not other medications for patients with CHB. The cost of treatment is very expensive; therefore economic evaluation studies are needed. This study aimed to review economic evaluation studies on drug treatment options for patients with CHB in order to provide the evidences for policy decision making.

MATERIALS AND METHODS

Literature review

A systematic review was conducted to identify full health economic evaluation studies (i.e., cost-effectiveness, cost-utility, cost-benefit analyses) comparing treatment options in patients with CHB and published between 2000 and January 2010. These studies were searched through the Pubmed and Cochrane databases using the key words as follows: (cost effective* OR cost utilit* OR cost benefit OR cost evaluation* OR economic evaluation*) AND (hepatitis B OR liver inflam*) AND (lamivudine OR zeffix OR epivir OR adefovir* OR viread OR entecavir* OR baraclude OR tenofovir* OR viread OR telbivudine OR sebivo OR interferon* OR intron* OR peginterferon* OR pegintron* OR pegasys OR PEG OR thymosin OR zadaxin) NOT vaccin* NOT transplant* NOT malignan*

The studies comparing interventions that are currently available for the treatment of CHB patients (i.e., lamivudine, adefovir, entecavir, telbivudine, tenofovir, interferon, pegylated interferon) with palliative care or no treatment were included. Outcomes of this review focused on both the choices of method used and results of economic evaluation.

Study selection

The inclusion and exclusion criteria used for study selection are shown in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Studies comparing both cost and outcome of the treatment of patients with CHB • Publication date during 2000-2010 	<ul style="list-style-type: none"> • Studies related to only cost or outcome analysis • Studies related vaccination • Studies related mutation analysis of drug resistance • Studies that consider target populations which are patients with hepatocellular carcinoma, cirrhosis, malignant, hepatitis C, or transplantation).

Data abstraction

For the data collection process, a data extraction sheet was developed (based on the Centre for Reviews and Dissemination's data extraction template). The data extraction sheet for each study is available from the author on request. A summary of the considered data items can be found. Information was extracted from each included study on: (1) author, year, country, (2) disease and patient group, (3) objective, (4) intervention, (5) perspective, (6) source

of data, (7) outcome, (8) method, (9) discounting rate, (10) sensitivity analysis, and (11) incremental cost-effectiveness result.

Methodological quality assessment

The methodological quality assessment of included economic evaluation studies and systematic review studies was assessed using Drummond's criteria (Table 2)⁷ Study quality was assessed and data were extracted by one reviewer. Items were scored as positive, negative, or unclear.

Table 2. Drummond's criteria for evaluating economic evaluation studies

Criteria
1. Was a well-defined question posed in an answerable form?
2. Was a comprehensive description of the competing alternatives given
3. Was there evidence that the programme's effectiveness had been established?
4. Were all the important and relevant outcomes and costs for each alternative identified?
5. Were outcomes and costs measured accurately in appropriate units
6. Were the outcomes and costs valued credibly?
7. Were outcomes and costs adjusted for different times at which they occurred
8. Was an incremental analysis of the outcomes and costs of alternatives performed?
9. Was a sensitivity analysis performed?
10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?
11. Were the conclusions of the evaluation justified by the evidence presented?
12. Can the results be applied to the local population?

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A).

RESULTS AND DISCUSSIONS

Literature search

The primary literature search by electronic databases identified 72 citations. After screening of all titles and abstracts, only

32 articles were identified. Of all 32 full articles, 26 articles comparing both costs and outcomes of two or more drug treatments for patients with CHB were included⁸⁻³³. The result of systematic literature search is shown in Figure 1.

Figure 1. Result of systematic literature search

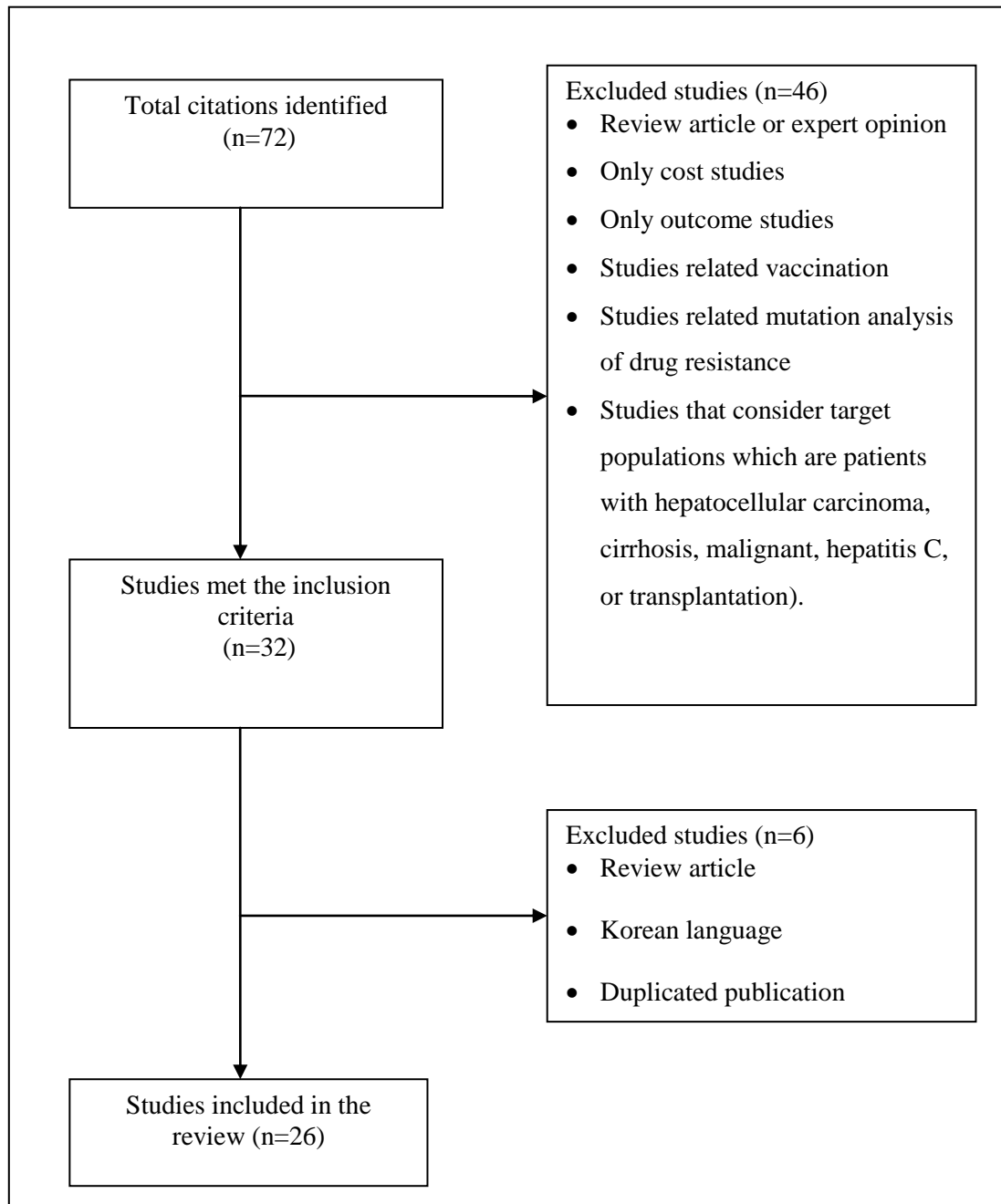


Table 3. Paper extraction according to Drummond checklists

No	Study	1. Was a well-defined question posed in an answerable form?	2. Was a comprehensive description of the competing alternatives given	3. Was there evidence that the programme's effectiveness had been established?	4. Were all the important and relevant outcomes and costs for each alternative identified?	5. Were outcomes and costs measured accurately in appropriate unit	6. Were the outcomes and costs valued credibly?	7. Were outcomes and costs adjusted for different times at which they occurred	8. Was an incremental analysis of the outcomes and costs of alternatives performed?	9. Was a sensitivity analysis performed?	10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	11. Were the conclusions of the evaluation justified by the evidence presented?	12. Can the results be applied to the local population?
1	Chen W. (2009)	+	+	+	+	+	+	N/A	+	N/A	+	+	-
2	Jones J. (2009)	+	+	+	+	+	+	+	+	+	+	+	+
3	Buti M. (2009)	+	+	+	+	+	+	N/A	+	N/A	-	+	-
4	Costa Am. (2008)	+	+	+	+	+	+	+	+	+	+	+	+
5	Calcagno JL.(2008)	+	+	+	+	+	+	N/A	+	+	+	+	-
6	Spackman D. 2008	+	+	+	+	+	+	+	+	+	-	+	-
7	You JH. (2008)	+	+	+	+	+	+	N/A	+	N/A	-	+	-
8	Yuan Y. (2008)	+	+	+	+	+	+	+	+	+	+	+	+
9	Lacey L. (2008)	+	+	+	+	+	+	+	+	N/A	+	+	-
10	Veenstra DL. (2008)	+	+	+	+	+	+	+	+	+	+	+	-
11	Veenstra DL. (2008)	+	+	+	+	+	+	N/A	+	+	+	+	-
12	Yuan Y. (2008)	+	+	+	+	+	+	+	+	+	+	+	+
13	Arnold E. (2008)	+	+	+	+	+	+	N/A	+	N/A	+	+	+

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A)

Table 3. Paper extraction according to Drummond checklists (cont.)

No	Study	1. Was a well-defined question posed in an answerable form?	2. Was a comprehensive description of the competing alternatives given	3. Was there evidence that the programme's effectiveness had been established?	4. Were all the important and relevant outcomes and costs for each alternative identified?	5. Were outcomes and costs measured accurately in appropriate unit	6. Were the outcomes and costs valued credibly?	7. Were outcomes and costs adjusted for different times at which they occurred	8. Was an incremental analysis of the outcomes and costs of alternatives performed?	9. Was a sensitivity analysis performed?	10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	11. Were the conclusions of the evaluation justified by the evidence presented?	12. Can the results be applied to the local population?
14	Veenstra DL. (2007)	+	+	+	+	+	+	N/A	+	+	+	+	+
15	Lacey LF. (2007)	+	+	+	+	+	+	+	+	+	-	+	+
16	Sun X. (2007)	+	+	+	+	+	+	N/A	+	N/A	+	+	+
17	Veenstra DL. (2007)	+	+	+	+	+	+	+	+	+	+	+	+
18	Larry L. (2007)	+	+	+	+	+	+	N/A	+	N/A	-	+	+
19	Buti M. (2006)	+	+	+	+	+	+	+	+	+	+	+	+
20	Kanwal F. (2005)	+	+	+	+	+	+	N/A	+	+	+	+	+
21	Pwu RF. (2002)	+	+	+	+	+	+	+	+	+	+	+	-
22	Aggarwal R. (2002)	+	+	+	+	+	+	-	-	+	-	+	-
23	Orlewska E. (2002)	+	+	+	+	+	+	N/A	+	+	-	+	-
24	Crowley S. (2002)	+	+	+	+	+	+	N/A	-	N/A	-	+	-
25	Brooks EA. (2001)	+	+	+	+	+	+	N/A	-	N/A	-	+	-
26	Crowley (2000)	+	+	+	+	+	+	N/A	+	N/A	-	+	-

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A).

Quality assessment

Most studies clearly described the objectives, competing alternatives and specified the cost and outcome measures. It could be seen that about 69% (18 out of 26) of all studies passed 9 out of 12 Drummond's criteria.

Characteristics of the selected studies

Sixteen studies were conducted in Europe and America, whereas eleven studies were performed in Asia. It was found that disease and patient groups in all studies were classified into four groups which are patients with HBeAg positive (6 articles), HBeAg negative (3 articles), both HBeAg positive and negative (7 articles) and cannot define HBeAg status (10 article). Regarding the perspective, most studies were analyzed based on the perspectives of health care system (13 articles) or third party payer (10 articles) and only two articles performed based on patient's perspective.

Direct medical costs such as cost of drugs, lab, admission, diagnosis and professional fees were included in all studies. Since there were two studies performing based on patient's perspective, they collected both direct and indirect cost (i.e., productivity loss). The outcomes were measured in terms of life years saved (LYs) and/or quality-adjusted life year gained (QALYs). Incremental cost effectiveness (ICER) was used to interpret the results of cost-effectiveness analysis. In term of time horizon, three articles used lifetime and one article used 40 years which used Markov model to analyse the data. In addition, two articles used 10 years, one article used 4 years and one article used one year which used decision tree model. Data were generally obtained from systematic review, published literature and clinical trials. Markov model (11 articles) was more frequently used compared to decision tree model (5 articles). Both Markov and decision tree models used in three articles but the models were not presented in seven articles. Discounting rate of 3% (8 articles) and 5% (1 article) were used for both cost and outcome.

Only one article used 6% for discounting cost and 1.5% for outcome but others articles did not present discounting rate. Probabilistic (7 articles) and one-way (4 articles) sensitivity analyses were mainly applied to test parameter uncertainty. Two articles were test both one-way and probabilistic sensitivity analyses.

The cost-effectiveness outcome

All of ten studies (i.e., seven studies in America, two studies in Asia and one study in Australia) showed that entecavir was more cost-effective when compared with lamivudine. Two studies which are in America and Europe showed that adefovir was more cost-effective when compared with lamivudine. One study showed that telbivudine was more cost-effective when compared with lamivudine. One study showed that tenofovir was more cost-effective when compared with entecavir, telbivudine, adefovir. Two studies showed that interferon was not cost-effective when compared with lamivudine. One study showed that interferon was more cost-effective when compared with lamivudine and adefovir. Three studies (i.e., two studies in Asia, one study in Europe) showed that pegylated interferon was more cost-effective when compared with lamivudine. One study showed that pegylated interferon was more cost-effective when compared with interferon. For combination treatment, two studies showed that lamivudine increased life expectancy and reduced the lifetime risk of cirrhosis and carcinoma when added with interferon. Moreover, three studies showed that medications treatment of CHB with antiviral therapy for a long term treatment decreased the rate of disease progression and were highly cost-effective compared with a short-term treatment.

Based on the systematic review, it was found that studies' results were relatively varied due to the differences in time horizon and variables used in the models such as, efficacy on viral suppression, resistance rate and price of the medications for CHB. In addition, most studies were supported by

pharmaceutical industries. For example, five articles were supported by Bristol Myers Squibb and the result showed that entecavir was superior than other drugs^{11,14,18,32-33}. One article was supported by Glaxo Wellcome and the result showed that lamivudine was more cost-effective than interferon and this study used only one year of time horizon which might cause a difference in efficacy for treatment CHB if the study used a longer time horizon²⁹. In addition, most studies did not consider drugs' side effects such as suppression of granulocytes, platelets, and lymphocytes which could lead to higher costs and worse outcomes.

CONCLUSIONS

Recently, lamivudine has been included in the National List of Essential Drugs (NLED) but not other medications for patients with CHB. The results in this study suggested that there has been no study related to cost-effectiveness analysis of the treatment in patients with CHB in Thailand yet. The cost-utility analysis of drug treatments among patients with CHB in Thailand would be required to investigate for future research as it would be useful information for making decision on whether which drug should be included in the NLED.

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