Original Article

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Clinical Efficacy of Chronic Hepatitis B Treatment for Patients with HBeAg-Positive Indirect Comparison: Indirect Comparison Meta-Analysis

N. Tantai[1,2,4], P. Lerdkiattikorn[1,2,4], U. Chaikledkaew[2,4], T. Tanwandee[3], P. Weerayingyong[4] and Y. Teerawattananon[4]*

[1] *Department of Pharmacy, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[2] *Division of Social and Administrative Pharmacy, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand*
[3] *Division of Gastroenterology, Department of medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[4] *Health Intervention and Technology Assessment Program (HITAP), Ministry of Public Health, Nonthaburi, Thailand*

Abstract

This study was aimed to assess the clinical efficacy in terms of HBeAg seroconversion among existing treatment options for HBeAg positive CHB patients using indirect comparison meta-analysis. A systematic review of randomized controlled trials (RCTs) of treatments for patients with HBeAg-positive CHB was performed through the Pubmed and Cochrane databases. The clinical studies were included only if they assessed the efficacy amongst the following treatment options namely i) lamivudine, ii) entecavir, iii) Telbivudine, iv) Adefovir, v) Tenofovir, vi) Pegylated interferon and vii) Palliative care. Indirect or mixed-treatment comparison meta-analysis with random effect model was employed to combine results of several studies. The meta-analysis was carried out using the WinBUGS14 software. Odds ratio (OR) and its 95% credible interval (CI) were presented. Heterogeneity test was applied for testing the variation of study outcomes between studies. There were 294 abstracts reviewed with 14 relevant RCTs included in the analysis. Based on the meta-analysis results, PEG2a yielded the best efficacy which was about five times more likely to increase HBeAg seroconversion rate (OR=5.36, 95%CI=2.17-10.46) than telbivudine (OR=4.29, 95%CI=2.05-7.68), tenofovir (OR=4.17, 95%CI=1.41-9.23), entecavir (OR=3.85, 95%CI= 1.96-6.72), lamivudine (OR=3.52, 95%CI=1.81-6.09) and adefovir (OR=3.03,95%CI=1.57-5.31). There was a significant increase in HBeAg seroconversion rate in patients with HBeAg positive CHB receiving antiviral treatment when compared with palliative care.

KEYWORDS: Chronic hepatitis B, Efficacy, Meta-analysis, HBeAg-positive, HBeAg-seroconverion

INTRODUCTION

Clinical efficacy of chronic hepatitis B (CHB) treatment can be assessed by histologic improvement, biochemical responses and virologic responses. HBeAg seroconversion, one of the virological responses, is an indicator for discontinuing CHB treatment. Many randomized controlled trials (RCTs) have investigated the clinical efficacy of available treatments specifically recommended for HBeAg positive CHB patients. However, there has been no study investigating the clinical efficacy in terms of HBeAg seroconversion among all available

***Corresponding author:** Division of Social and Administrative Pharmacy, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand, Tel: 66-2-644-8677 ext 5317, Fax: 66-2-644-8694, Email: usa.chi@mahidol.ac.th

treatment options for patients with HBeAg positive CHB. This study was aimed to assess the clinical efficacy in terms of HBeAg seroconversion among existing treatment options for HBeAg positive CHB patients using indirect comparison meta-analysis.

MATERIALS AND METHODS

Literature review

A systematic review of randomized controlled trials (RCTs) of treatments for patients with HBeAg-positive CHB was performed through the Pubmed and Cochrane databases using the key words as follows: (efficac* OR effectiv* OR "relative risk" OR "meta analysis" OR "RR") (efficac* OR effectiv* OR "relative risk" OR "meta analysis" OR "RR") AND ("RCT" OR randomi* OR "clinical trial*") AND (entecavir OR peginterferon* OR pegintron* OR "PEG" OR pegylated OR lamivudine OR telbivudine OR adefovir OR tenofovir) AND ("hepatitis B" OR "chronic hepatitis B" OR "HBV") AND ("HBeAg" OR "HBsAg" OR seroconvers* OR seroclearanc*). The clinical studies were included only if they assessed the efficacy amongst the following treatment options namely i) lamivudine, ii) entecavir, iii) telbivudine, iv) adefovir, v) tenofovir, vi) pegylated interferon and vii) palliative care.

Study selection

The RCT or meta-analysis studies comparing interventions (i.e., lamivudine, adefovir, entecavir, telbivudine, tenofovir or PEG) with palliative care or no treatment were included. The studies on the patients aged at least 18 years with HBeAg positive CHB who required the treatment based on the following criteria (i.e., patients who had detectable serum HBsAg for at least 6 months, serum ALT level 1.5 -10 times the upper limit of the normal range for at least 3 months, an evidence of chronic hepatitis on liver biopsy and a detectable level of serum Hepatitis B viral DNA) were included. In addition, the studies measuring outcome as HBeAg seroconversion rate, the studies with treatment duration for one year, the studies with publication date during 1995-2010 and only English language studies were incorporated. The studies without recommended dose for CHB and the studies of patients with advanced liver diseases such as decompensated cirrhosis and HCC were excluded.

Data analysis

Indirect or mixed-treatment comparison meta-analysis with random effect model was employed to combine results of selected studies based on inclusion criteria. The meta-analysis was carried out using the WinBUGS14 (Medical Research Council and Imperial College of Science, Technology and Medicine, United Kingdom) software program. Odds ratio (OR) and its 95% credible interval (CI) were presented. Heterogeneity test was applied for testing the variation of study outcomes between studies.

RESULTS AND DISCUSSION

Based on systematic reviews, 294 abstracts were reviewed and 14 relevant RCTs were included in the analysis [1-14]. None of 14 RCTs included all seven treatment options. Fourteen articles were evaluated by Jadad score's criteria. Thirteen articles had Jadad score equal or greater than 3 [1-3, 5-14]. There were two studies comparing lamivudine with placebo [5-6], five studies comparing lamivudine with entecavir [3-4, 7-9], two studies comparing lamivudine with telbivudine [10, 12] and one study comparing lamivudine with PEG 2a [2]. There were four studies comparing adefovir with placebo (1 study) [1], entecavir (1 study) [13], telbivudine (1 study) [11] or tenofovir (1 study) [14]. Table 1 and Figure1 present the odds ratio of HBeAg seroconversion rate and its 95% credible interval (CI) of all treatments compared with palliative care. There are statistical significance differences in odds ratio of HBeAg seroconversion rate between each treatment and palliative care.

Patients with HBeAg positive CHB receiving lamivudine, adefovir, entecavir, telbivudine, tenofovir or PEG 2a are about three to five times more likely to have HBeAg seroconversion rate compared to those without

treatment. However, the RCT studies of PEG 2b were not included because their dose and treatment duration were different from the studies of other treatments. Although patients with HBeAg seroconversion can stop the treatment, their CHB disease progression may have been the same as those without HBeAg seroconversion and still receiving the treatment. Not only HBeAg seroconverion but also histologic improvement as well as virologic and biochemical responses should be considered when assessing clinical efficacy.

Table 1. Odds ratio of HBeAg seroconversion rate of all treatments compared with palliative care

Treatment	Odds ratio (95% CI)
PEG 2a	5.36 (2.17-10.46)
Telbivudine	4.29 (2.05-7.68)
Tenofovir	4.17 (1.41-9.23)
Entecavir	3.85 (1.90-6.72)
Lamivudine	3.52 (1.81-6.09)
Adefovir	3.03 (1.57-5.31)

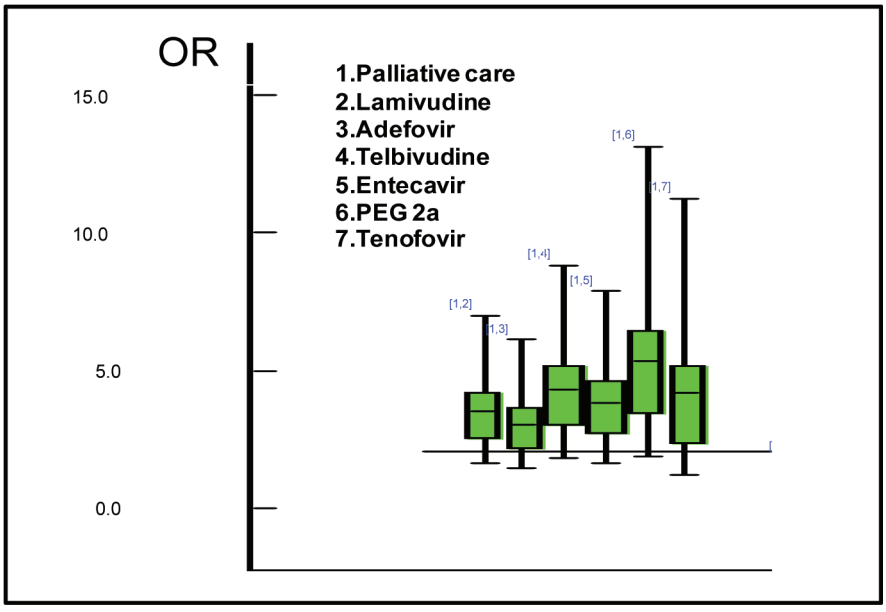

Figure 1. Box plot for the odds ratio of HBeAg seroconversion rate of all treatments compared with palliative care

CONCLUSION

There was a significant increase in HBeAg seroconversion rate in patients with HBeAg positive CHB receiving antiviral treatment when compared with palliative care. Pegylated interferon yielded the highest HBeAg seroconversion rate among existing treatment options.

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