Original Article

Mahidol University Journal of Pharmaceutical Sciences 2013; 40 (2), 45-50

Systematic Review of Economic Evaluation of Drug Treatments in Pulmonary Arterial Hypertension (PAH)

W.Thongsri[1], U. Chaikledkaew[1] and Y. Teerawattananon[2]*

[1] Social and Administrative Pharmacy Excellence Research (SAPER) Unit, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, 10400, Thailand
[2] Health Intervention and Technology Assessment Program (HITAP), Ministry of Public Health, Nonthaburi

Abstract

Pulmonary arterial hypertension (PAH) is a rare disease but PAH treatment cost is very high. Nowadays, there has been no cost-effectiveness information related to PAH treatments in Thailand. The aim of this study was to systematically review economic evaluation studies of drugs treatment in PAH. Studies reporting in term of clinical outcomes and costs during January 1990 to October 2012 were searched through PubMed and Cochrane databases.

Seventeen articles were reviewed and only six full text articles were included. Six studies were conducted in developed countries. Populations in most studies were not specific to any type of PAH. Perspectives in all studies were healthcare payer and healthcare system. Compared interventions included sildenafil, iloprost and bosentan. Time horizon was either short-term or long-term period. Most studies used Markov model approach. Costs were estimated according to the perspective of study. Costs were discounted at different rates in each study. In term of clinical effectiveness, most studies showed that bosentan and sildenafil had more effective than iloprost. Sensitivity analyses were performed in all studies. Most studies showed that bosentan and sildenafil had lower cost and higher quality-adjusted life year (QALYs) gained compared to other drugs. The results of this systematic review suggested that drug treatments for PAH would be cost-effective in developed countries. However, the cost-effectiveness analysis of drug treatments for PAH should be further investigated in Thailand due to a difference in socioeconomic infrastructure from developed countries.

Key word: Economic Evaluation, Pulmonary arterial hypertension, Pulmonary artery hypertension, Systematic review, Drug treatments for PAH

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare condition with narrowing coronary arteries in the lungs. The major symptoms such as swelling, syncope and angina can get worse as the disease progressed and right heart failure developed [1]. If the progression of the disease becomes advanced, it can be fatal to the patient. Patients with moderate or severe disease progression will have high risk mortality. The disease can be classified as either idiopathic PAH (iPAH) or PAH caused by other health problems such as connective tissue disease (PAH-CTD) and congenital heart disease (PAH-CHD) which are a major cause of PAH in Thailand[2, 3]. In Thailand, the respective incidence rate and prevalence of (PAH–CHD) is 0.4 per million per year and 2 per million, whereas the incidence rate and prevalence of PAH associated with scleroderma—which accounts for the majority of (PAH-CTD)—is 0.36

***Corresponding author:** Social and Administrative Pharmacy Excellence Research (SAPER) Unit, 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

per million per year and 2.5 per million, respectively. The specific medications discovered for the treatment of PAH such as anticoagulation therapy, diuretics, oxygen and digoxin were prescribed to PAH patients with the aim for supportive care [1, 4]. It was found that a median survival of PAH patients receiving supportive care ranged from 2 to 3 years after treatment [1].

Recently, pulmonary selective drugs specifically licensed for the treatment of PAH (i.e., inhaled iloprost, bosentan, beraprost and sildenafil) have become available in Thailand [5]. These drugs can directly reduce pulmonary arterial pressure and result in improving functional class; quality of life (QOL) and survival of patients [1, 4]. However, these drugs are very expensive, ranging from approximately 600 to 20,000 baht per day [6]. This, therefore, can lead to financial difficulty for patients accessing to drug.

Currently only pulmonary selective drugs included in the National List of Essential Medicines (NLEM) as for the first line treatment is sildenafil, while others drugs (e.g., iloprost and bosentan) have been proposed to be included in the NLEM as the second-line treatment. Nevertheless, in this country there has been no economic evaluation information related to these drugs available. The objective of this study was to systematically review and summarize the previous published economic evaluation studies. This is particularly important for making decision whether PAH treatment would be cost-effective and cost-effectiveness study of PAH should be further performed.

MATERIALS AND METHODS

A systematic literature was conducted to identify economic evaluation studies of drug treatments (i.e., bosentan, iloprost, beraprost and sildenafil) in pulmonary arterial hypertension (PAH) published from January 1990 to October 2012 and searched from electronic databases including PubMed and the Cochrane Library. Searching terms used for PubMed database were as follows: "Hypertension, Pulmonary/drug therapy" [Mesh] AND "Cost-Benefit Analysis"[Mesh] AND ("sildenafil" OR "bosentan" OR "iloprost" OR "beraprost"). Key words used for Cochrane database were as follows: "Hypertension, Pulmonary" [Mesh] AND "Cost-Benefit Analysis"[Mesh] OR "iloprost" OR "bosentan" OR "Sildenafil" OR "beraprost"

The following inclusion criteria were used to select relevant studies. Original study with full-text of full economic evaluations (i.e., cost-effectiveness or cost-utility analyses) studies related to PAH treatments in English language were included. Therefore, studies evaluating only costs (i.e., cost of illness or cost analysis) or clinical outcomes of the interventions were excluded. Figure 1 shows the systematic review process.

Assessment

The authors screened titles and abstracts of studies based on the inclusion and exclusion criteria. Selected studies were included for the full review. Data were extracted using data extraction form in Microsoft Excel 2010. Data included study characteristic, citation, publication year, setting, objective study population, intervention, comparator, perspective, time horizon, model used, clinical effectiveness, type of cost, discounting, results and sensitivity analysis.

RESULT AND DISCUSSION

According to systematic review of economic evaluation of drug treatments in PAH, seventeen articles were reviewed and only six full text articles were included [6-11]. Table 1 present six articles in details. Six studies were conducted in the United Kingdom (UK) [6, 10], the United State (US) [7, 9], Australia and Spain [8, 11]. Target populations in two studies were specific to iPAH and PAH-CTD [8, 10], while those the other studies did not mention about type of PAH. Perspective

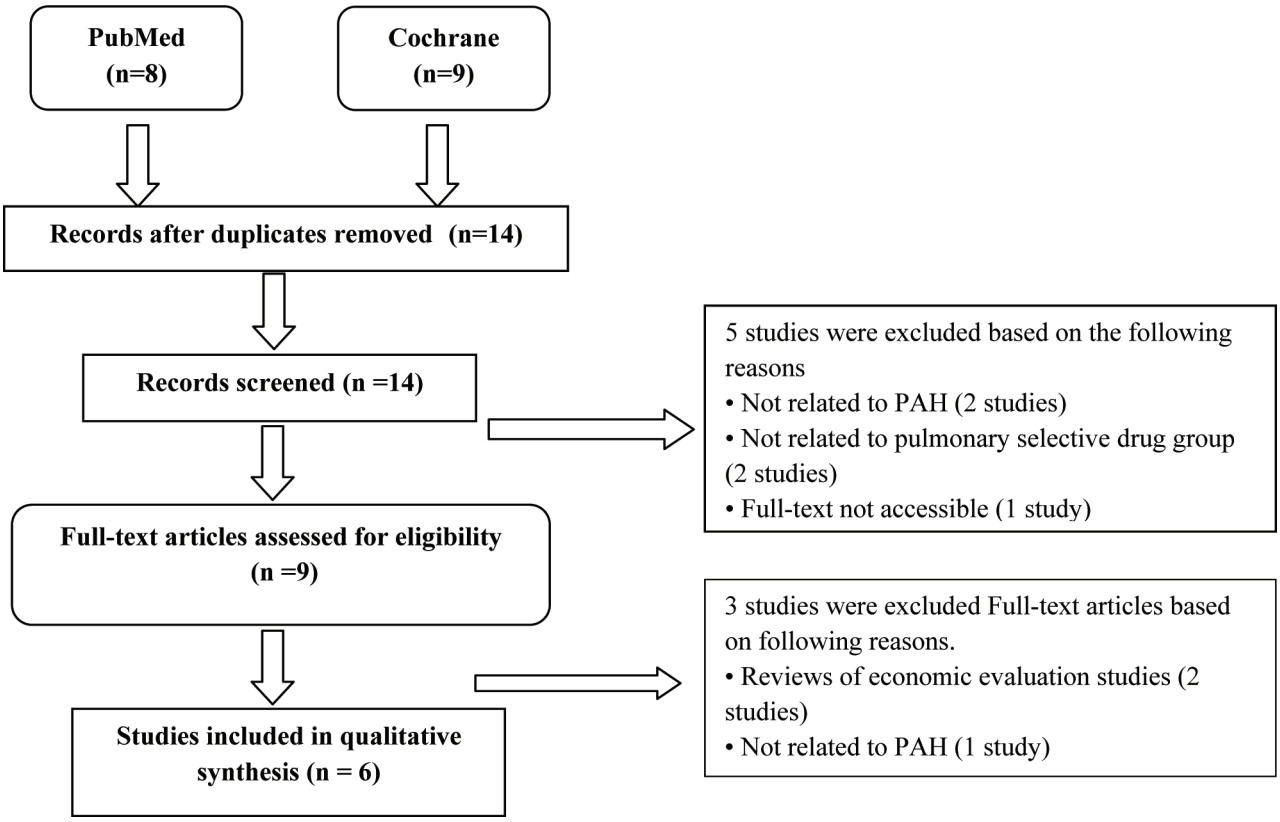

Figure 1. The systematic review process

used in these studies was healthcare payer [7-9] (3 studies) and healthcare system [6, 10, 11] (3 studies). Compared interventions included sildenafil, iloprost and bosentan. Nevertheless, beraprost was not found as a compared intervention in any economic evaluation studies. Time horizon used in these studies was 1 year [7, 9] (2 studies), 3 years [11] (1 study), 15years [8] (1 study) and lifetime period [6, 10] (2 studies). The cost-effective analysis (CEA) [8] (1 study) and cost-utility analysis (CUA) [6, 7, 9-11] (5 studies) were mostly used. Markov model (5 studies) and Monte-Carlo simulation [8] (1 study) were applied to evaluate cost and outcome. Only direct medical costs were estimated in accordance with perspective used. In term of clinical effectiveness, most studies showed that bosentan and sildenafil were more effective than iloprost. Costs have been discounted at the rate of 3% [11] (1 study), 3.5% [6, 10] (2 studies) or 5% [8] (1 study) per annum. Probabilistic sensitivity analysis (PSA) [11] (1 study) and one-way sensitivity analysis [6-11] (6 studies) were used.

Results of cost-effectiveness analysis were presented in Table 1. All studies reported both cost and clinical outcome in term of incremental cost-effectiveness ratio (i.e., cost per quality-adjusted life year (ICER/QALY) or cost per life year gained (ICER/LYG), or cost saving (per 100 patients/year). The results showed that bosentan and sildenafil were likely to be less costly and resulted in a greater increase in QALYs gained when compared to other drugs. Moreover, the ICER results of bosentan compared to other drugs were A $55,927/LYG [8], £27,000/QALY [6] and £30,000/QALY [10]. Four studies in the UK, USA, and Australia indicated that bosentan was more cost-effective compared with other drugs in their contexts. In addition, one study demonstrated that bosentan was cost

Table 1. Results of systematic review

Data	Highland et al. (2003) [7]	Wlodarczyk et al. (2006) [8]	Chen et al. (2009)[6]	Garin et al. (2009)[9]	Stevenson et al.(2009) [10]	Roman et al. (2012) [11]
Conduct study	USA	Australia	UK	USA	UK	Spain
Study population	PAH in (FC) III or IV	iPAH	PAH of (FC) III	PAH of (FC) III or IV	iPAH or PAH-CTD (FC) III	PAH of (FC)III
Intervention	bosentan	bosentan	epoprostenol, iloprost, bosentan,sitaxentan and sildenafil	bosentan, treprostinil, epoprostenol, iloprost, sildenafil, sitaxentan and ambrisentan	bosentan	iloprost,epoprostenol, treprostinil
Comparator	treprostinil, epoprostenol	supportive care	supportive care	other treatments	supportive care	other treatments in prostacyclin group
Perspective	Healthcare payer	Healthcare payer	Healthcare system	Healthcare payer	Healthcare system	Healthcare system
Method	Cost-utility (Markov model)	Cost-effectiveness (First-order Monte Carlo simulation)	Cost-utility (Markov model)	Cost-utility (Markov model)	Cost-utility (Markov model)	Cost-utility (Markov model)
Time horizon	1 year	5,10,15 years	Life time	1 year	Life time	3 years
Discounting	-	5%	3.50%	-	3.50%	3%
Sensitivity analysis	one-way sensitivity analysis	one-way sensitivity analysis	one-way sensitivity analysis	one-way sensitivity analysis	one-way sensitivity analysis	one-way sensitivity and probabilistic analysis
Outcome	QALYs	ICER*	QALYs	QALYs	QALYs	QALYs
Result	Bosentan was less costly (cost savings of US$3,631,900) and resulted in greater gain in 11 QALYs than epoprostenol and treprostinil for 100 patients in cohort study	ICER at 15 years of A$55,927 dollars for each LYG	Epoprostenol = ICER £277,000/ QALY for FCIII and £343,000/QALY for FCIV patients. In FCIII patients. iloprost = £101,000/QALY, bosentan= £27,000/ QALY, QALY and sitaxentan = £25,000/QALY	Treatment with sildenafil was less costly, resulted in a greater gain in QALYs and ICER of sildenafil was dominant compared with other treatments.	The cost per QALY of bosentan compared with palliative care alone became £30,000 (a potential cost-effectiveness threshold used in the United Kingdom).	ICER of epoprostenol versus iloprost and treprostinil were much above the threshold commonly used in Spain. Iloprost was dominant compared with treprostinil.

saving (US$3,631,900 per 100 patients/ year) [7]. In addition, two studies revealed that the ICER results of sildenafil compared with other drugs were dominant meaning that the intervention was more effective and less costly than other drugs and also cost-effective in the UK and USA [6, 9].

CONCLUSION

Although PAH is orphan disease that occurs, it may devastate social economic of patients. In developed countries, cost-effectiveness studies of PAH treatments have been investigated and their results showed that drug treatments for PAH would be cost-effective based on their context. However, these studies were performed in developed countries. The thresholds of developed countries are extremely higher than those of developing country. For example, the societal willingness to pay in the UK is about £30,000 (approximately 1,500,000 baht)[12], whereas it is about 120,000 baht in Thailand[13]. Therefore, it is impossible to adapt the information from developed countries to Thai context. Therefore, cost-effectiveness study of PAH treatments should be further conducted in Thailand.

REFERENCES

1. McLaughlin VV, Archer SL, Badesch, *et al*: ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009, 53(17):1573-1619.
2. Foocharoen C: Prognostic factors of mortality and 2-year survival analysis of systemic sclerosis with pulmonary arterial hypertension in Thailand. *Int J Rheum Dis* 2011 14(3):282-289
3. Durongpisitkul K: Pulmonary Hypertension Registry. 2009
4. Galie N, Hoeper MM, Humbert M, *et al*: Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009, 30(20):2493-2537.
5. Food And Drug Administration Thailand: Health product e-logistics and lodgment organizer http://wwwapp1.fda.moph.go.th/consumer/conframe.asp (accessed October 2012).
6. Chen YF, Jowett S, Barton P, *et al*: Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation. *Health Technol Assess* 2009, 13(49):1-320.
7. Highland KB, Strange C, Mazur J, *et al* : Treatment of pulmonary arterial hypertension: a preliminary decision analysis. *Chest* 2003, 124(6):2087-2092.
8. Wlodarczyk JH, Cleland LG, Keogh AM, *et al*: Public funding of bosentan for the treatment of pulmonary artery hypertension in Australia: cost effectiveness and risk sharing. *Pharmacoeconomics* 2006, 24(9):903-915.
9. Garin MC, Clark L, Chumney EC, *et al*: Cost-utility of treatments for pulmonary arterial hypertension: a Markov state-transition decision analysis model. *Clin Drug Investig* 2009, 29(10):635-646.

10. Stevenson MD, Macdonald FC, Langley J, *et al*: The cost-effectiveness of bosentan in the United Kingdom for patients with pulmonary arterial hypertension of WHO functional class III. *Value Health* 2009, 12(8):1100- 1105.
11. Roman A, Barbera JA, Escribano P, *et al*: Cost effectiveness of prostacyclins in pulmonary arterial hypertension. *Appl Health Econ Health Policy* 2012, 10(3):175-188.
12. Akehurst R. in Towse A, Pritchard, C. Devlin, N. : Cost effectiveness thresholds: Economic and Ethical Issues. London Kings Fund and Office of Health Economics *p38*; ,2002
13. Food And Drug Administration Thailand: Cost effectiveness thresholds in Thailand. National List of Essential Medicines sub-committee conference (9th/2007) on 20 December 2007 at Food And Drug Administration Thailand. 2007.