

Cost-utility analysis of Macitentan Vs. Bosentan in pulmonary atrial hypertension

Marzieh Nosrati¹, Nikinaz Ashrafi Shahmirzadi^{1,2,3}, Monireh Afzali¹,
Pardis Zaboli⁴, Hasti Rouhani^{2,3}, Haleh Hamedifar², Mirhamed Hajimiri^{2,3}

¹Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran, ²CinnaGen Medical Biotechnology Research Center, Alborz University of Medical Sciences, Karaj, Iran, ³NanoAlvand Co., Avicenna Tech Park, Tehran University of Medical Sciences, Tehran, Iran, ⁴Drug Selection Committee, Iranian Food and Drug Organization, Iran Ministry of Health, Tehran, Iran

ABSTRACT

Objective: Endothelin (ET) receptor antagonists (ERAs) have considerable improvements in pulmonary arterial hypertension (PAH) patients' symptoms. Macitentan, a novel ERA, has more significant positive effects like reduction of morbidity and mortality in PAH patients by 45% and decreases PAH hospitalization. Besides, macitentan was able to improve both the physical and mental aspects of patients' lives. This study aimed to evaluate an incremental cost-utility analysis of macitentan compared with bosentan in PAH patients in the Iranian health care system. **Methods:** We developed a hybrid model consisting of a decision tree in which PAH patients would take and continue either macitentan or bosentan with different probabilities. Subsequently, each patient would enter one of the 4 Markov's, each consisting of 5 states, PAH fraction I, PAH fraction II, PAH fraction III, PAH fraction IV, and death. The cycles and time horizon were considered 3 months and lifetime, respectively. We assessed the impact of each medicine on patients' quality-adjusted life-years (QALYs) and costs, consequently calculated the ICER (Incremental Cost-Effectiveness Ratio). The costs were measured in the dollar (1 dollar is equal to 42000 rials) with the perspective of the payer. The discount rates were assumed 3% for utility and 5% for costs. In addition, a sensitivity analysis was conducted. **Results:** The costs are about 14163 dollars for bosentan and 13876 dollars for macitentan for each patient in a lifetime. The QALY produced per patient by macitentan was 0.81 more than that of bosentan. The calculated ICER was -357.47 which means that for each incremental QALY, the payer is charged less. **Conclusion:** Macitentan is preferable to and dominant over bosentan in both effectiveness and expenditure. Thus, the therapeutic regimen containing macitentan is introduced as a favorable treatment strategy.

Keywords: Cost-effectiveness, economic evaluation, endothelin receptor antagonists, Markov, quality-adjusted life years, sensitivity analysis

Introduction

Pulmonary arterial hypertension (PAH) is a chronic and progressive disease related to small pulmonary arteries and arterioles.^[1] The abnormal proliferation and remodeling of

pulmonary vessels cause pulmonary circulation resistance, due to thrombosis, leading to disability and premature death.^[1-3] PAH patients are identified by the mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, as measured by right heart catheterization (RHC). This disease is a life-threatening situation that reduces the survival of patients with PAH to about 2 or 3 years and would result in progressive pulmonary and heart disease which needs lung transplant.^[3,4] It also remarkably negatively affects the quality of patients' lives

Address for correspondence: Dr. Mirhamed Hajimiri, CinnaGen Medical Biotechnology Research Center, Alborz University of Medical Sciences, Karaj, Iran.
E-mail: H.Hajimiri@nanoalvand.com

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by limiting their daily activities and the consequent social isolation.^[5]

Recent registry data suggest that the epidemiology of this disease has changed significantly during the past three decades. Results from France and the United Kingdom registries for PAH indicated an incidence rate of 1.1–2.4 and a prevalence of 6.6–15.0 cases per million annually.^[6] Data registries found that PAH is more prevalent in women than men (4:1).^[7] Regional information according to the IPAHA (Iranian pulmonary arterial hypertension) registry, established in November 2009 for PAH patients, shows that the number of cases with this disorder in Iran is estimated to be over 137.^[8] In addition, the cost of PAH treatment was estimated dramatically high, and calculated to be \$116,681 in the baseline period and \$98,243 in the follow-up period.^[9]

Therapy for PAH patients has evolved progressively in the past decade.^[4] The medicines for the treatment of PAH target one or more of three biological pathways involved in the pathogenesis of the disease: the prostacyclin, nitric oxide, and endothelin pathways.^[2] Endothelin-1 (ET-1) is one of the vasoconstrictors which shows its pharmacological effects through binding to two types of receptors, ETA and ETB, mainly located in the pulmonary vasculature. Therefore, both of the endothelin and its receptor antagonists would be used in PAH treatment.^[5,7]

The result of short-term clinical trials indicated that endothelin (ET) receptor antagonists (ERAs), like bosentan, macitentan, and ambrisentan, can improve exercise capacity, symptoms, cardiopulmonary hemodynamic variables, and delay time to clinical worsening.^[1] According to the Iranian drug list (IDL), bosentan is the only ERA available in Iran. Macitentan, a new ERA to bosentan with higher receptor binding, improved mortality and morbidity in a placebo-controlled trial named SERAPHIN.^[10] Macitentan must be taken once a day in comparison with bosentan which has to be taken twice a day.^[11] The results of meta-analysis about the adverse event of ERAs suggested that bosentan significantly increased the risk of elevated liver transaminases, but macitentan did not appear to have the same hepatotoxicity as bosentan.^[12] Therefore, macitentan treatment reduces the need for monthly liver function tests. Furthermore, macitentan has higher tissue penetration and achieves a higher reduction in mean pulmonary artery pressures compared to bosentan in pre-clinical studies. According to the results of a long-term Phase III clinical trial,^[10] macitentan, the novel ERA, has reduced the combined endpoint of morbidity and mortality in patients suffering from PAH by 45%^[11] and decreased the PAH hospitalization.^[11] Besides, another study conducted on PAH patients' quality of life demonstrated that bosentan was not effective on quality of life but macitentan was able to improve both physical and mental aspects of their lives.^[13] Therefore, macitentan might be an alternative to bosentan, or even superior.^[11] In spite of being more advantageous, macitentan is a more expensive medicine than bosentan. The objective of this study was to evaluate an incremental cost-utility analysis

of macitentan compared with bosentan in PAH patients in the Iranian health care system.

Methods

Analytical framework

We developed a hybrid model, combined decision tree and Markov, in Microsoft Office Excel for evaluating the cost-utility analysis of macitentan in comparison with bosentan in PAH treatment. Due to macitentan nonexistence in Iranian pharmaceutical market as well as the absence of published clinical study of macitentan in Iran, this model was developed based on the data from a comprehensive report related to PAH pharmacotherapy, published in 2016 in which different indicators like death, changes in functional class (FC), 6MWD (6-minute walked distance), adverse drug reactions, and treatment withdrawal were evaluated.^[13]

The model consisted of a decision tree in which PAH patients would take and continue either macitentan or bosentan with different probabilities. In the case of major adverse effects, supportive care would be administered. Therefore, each patient would enter one of the four Markov's, each consisting of 5 states, PAH fraction I, PAH fraction II, PAH fraction III, PAH fraction IV, and death as an absorbing state. These states were considered according to the classification first time by the New York Heart Association (NYHA) for patients' heart failure following the severity of their symptoms. The schematic model is illustrated in Figure 1. The reason why 3-month cycles were chosen was that this period closely approximates the time of assessing the effectiveness of PAH therapies within the clinical trials. The model assumptions are represented in Table 1. Within every 3-month cycle, probabilities of the transition caused by the improvement in FC, worsening in FC, and death determined the number of individuals who move from one state to another. Tables 2-4 show the model inputs. In this cost-utility analysis (CUA), we assessed the impact of each medicine on PAH patients' quality-adjusted life-years (QALYs) and costs, consequently calculated the ICER (Incremental Cost-Effectiveness Ratio) and finally assessed the ratios. The costs were measured in the dollar (1 dollar is equal to 42000 rials) and the perspective of the study was the payer. Following reliable

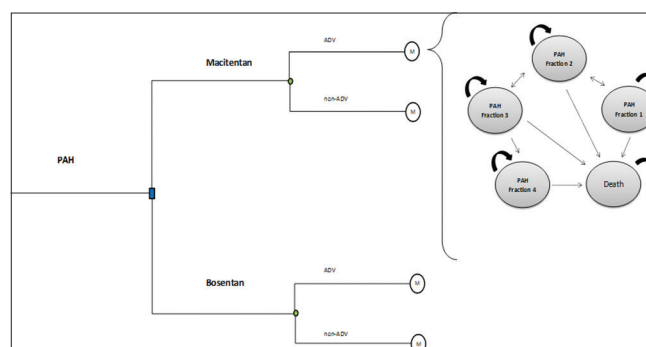


Figure 1: The decision tree-Markov hybrid model

Table 1: The model assumptions

Item	Assumption	Ref.
Cycle duration	90 days	Expert
Time horizon	5 years	Expert/ ^[13]
Outcome	FC improved/ worsen	Expert/ ^[13]
Anemia assessment	once per cycle	Expert
Hepatotoxicity assessment	once per month	^[14,17]
Treatment monitoring tests	once per cycle	Expert
Specialist visit	once per cycle	Expert
Patient's mean weight	70 kg	Expert
Patient's mean age	50 years old	Expert/ ^[13] / ^[10]
Withdrawal	based on major adv. effect	Expert/ ^[13] / ^[10]
Macitentan daily dose	10 mg once daily	^[17]
Bosentan daily dose	125 mg twice daily	^[14]

Table 2: The calculated transition probabilities of patients with PAH during 3 months (each cycle)^[13]

Transition	Bosentan (cycle)	Macitentan (cycle)	Withdrawal (cycle)
FC progression	0.0328	0.016	0.07
FC improvement	0.1267	0.118	0.08
Withdrawal due to adverse effect	0.020	0.026	-

Table 3: The relative risk of mortality in patients with PAH^[13]

State	RR (vs. normal population)
FC I	5.18
FC II	22.35
FC III	39.34
FC IV	57.47

Table 4: The utility of patients with PAH in different functional classes^[13]

State	Utility in macitentan regimen	Utility in bosentan regimen
FC I	0.73	0.73
FC II	0.73	0.670
FC III	0.684	0.600
FC IV	0.520	0.520
Death	0.000	0.000

clinical guidelines, review of similar cost-effectiveness studies, and local expert opinions, the time horizon for based analysis was considered a lifetime. As the time horizon was considered more than one year, discount rates were assumed 3% for utility and 5% for costs.

Patient population

Analysis (about costs and QALY) was conducted for two hypothetical separate cohorts (those receiving macitentan and those receiving bosentan) in which all the patients had PAH and in order to simplify, all the patients entered into this model were assumed to be outpatients in FC II PAH

without any contraindication for these medicines, with the mean age of 50.

Cost variables

Considering the perspective of this study, only the direct medical costs were measured, including the costs of medications, clinic visits, and monitoring.

- Macitentan, bosentan, sildenafil, warfarin, amlodipine, and epoprostenol as the principal therapeutic agents entered the model. Their generic prices in the local market were considered
- PAH patients were essentially considered outpatient
- Clinic visit costs were calculated by considering tariff rates mentioned in the last version of the national tariffs book.^[14] Regarding the recommendation of the local FDA, the coefficients considered for determining the costs consist of 80% of public tariffs and 20% of private tariff^[15]
- PAH patient status has to be regularly examined and also must be monitored for the incidence of adverse drug reactions. Therefore, the costs for echocardiography and 6MWD were considered as well as the costs of monthly liver function test in patients who received bosentan, CBC and hemoglobin levels at the beginning and regularly every 3 months in the duration of treatment in patients who received macitentan and intermittently PT/INR in patients who received warfarin. The prices of these services and laboratory tests were obtained from the last version of the tariff book by considering coefficients consisting of 80% of public tariffs and 20% of the private tariff.

Sensitivity analysis

Sensitivity analysis is necessary to evaluate the effect of parameter and structural uncertainty on the outcomes. In this study, a deterministic sensitivity analysis was conducted in which all variables like expenses, effectiveness probabilities, mortality rates, and utility varied in the range between -20% and +20%.

Model validation

Validity testing is a necessary step because of the conceptual model, assumptions, and different sources of data. In this study, the cross validity of the model was maximized by using published models in various economic evaluation studies conducted in PAH as well as consultation with a clinical expert. Moreover, it was evaluated by a professional committee of Iran Food and Drug Administration (IFDA) consisting of independent pharmacoeconomists as the reviewers of model structure, inputs, and outcomes.

Results

Incremental analysis

According to the assessment in the developed model and from the perspective of payer, the costs are about 14163 dollars for bosentan and 13876 dollars for macitentan for each PAH patient lifetime. Therefore, the therapeutic cost with macitentan was

estimated to be lower than bosentan. The QALY produced per patient by macitentan was 0.81 more than that of bosentan. The calculated ICER was -357.47 which means that for each incremental QALY, the payer is charged less. The result is depicted in Table 5. The results show that macitentan has more utility at a lower cost and dominates bosentan.

Sensitivity analysis

The results of the deterministic sensitivity analysis demonstrated in the Tornado plot can be seen in Figure 2. It was seen that the most effective variables in our sensitivity analysis are the price of medications (bosentan, macitentan, and epoprostenol) and their effectiveness probabilities. However, changes in different variables do not cause the ICER to go over the threshold. In other words, the results of changes in the variables do not influence our conclusion.

Discussion

According to the result of our study, it was found that a therapeutic regimen containing macitentan is a dominant strategy for PAH treatment in comparison with bosentan.

The results of deterministic sensitivity analysis identified considerable uncertainty in calculated ICER regarding the prices of medicines (macitentan, bosentan, and epoprostenol) in our model. However, because the Iranian FDA controls medicines' prices seriously, they tend to be stable; hence, the uncertainty related to prices could be disregarded. The other affecting factor on uncertainties is medicines' effectiveness with a wide confidence interval (macitentan, bosentan, and epoprostenol) in our model. This data is obtained from the meta-analysis which reveals this uncertainty in our model.^[13] Maybe with further clinical studies providing more robust data, we can overcome this uncertainty in our model.

Table 5: Base case results

	Macitentan	Bosentan	Incremental
cost	13,876.16 [§]	14,163.75 [§]	-287.59 [§]
QALY	7.29	6.48	0.80

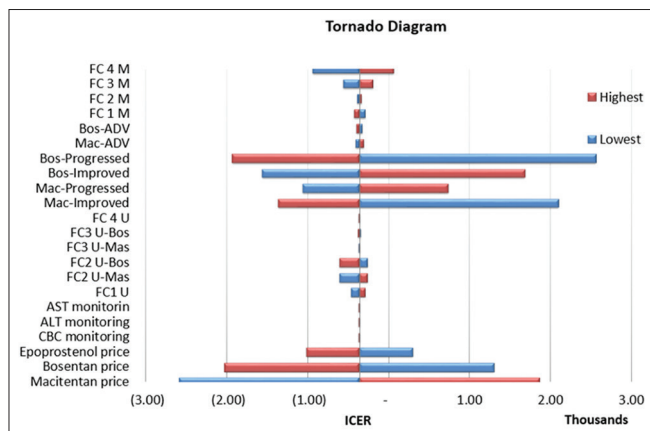


Figure 2: Deterministic sensitivity analysis

Macitentan is more expensive than bosentan but its monitoring cost is lower than that of bosentan resulting in lower overall costs.

The probability of disease progression and functional class (FC) improvement for macitentan was lower than that of bosentan. However, the QALY of macitentan increases and exceeds that of bosentan because patients' status could be stabilized by this drug. The reason is the fact that the rate of decreasing the progression of the disease is more than that of FC improvement. Therefore, in PAH patients who receive macitentan, the disease worsens at a lower rate and an increase in QALY is expected. According to previous studies, macitentan improves patients' utility in every status and reduces their symptoms.^[13]

Previously, the cost-utility analysis of macitentan in comparison with bosentan was conducted in different countries like Canada and Russia.^[13,16] Canadian Agency for Drugs and Technologies in Health has published a comprehensive report and compared the efficacy, safety, and cost-effectiveness of PAH therapeutics alternatives. They use a Markov model for lifetime evaluation and found macitentan with more cost and more QALY from the Canadian Ministry of Health perspective. In the study, the branded price of alternatives has been used.^[13] Moiseeva and Rudakova conducted an economic evaluation from the social perspective in Russia.^[16] They followed a Markov model for 5 years and found macitentan as a cost-effective treatment strategy in comparison with bosentan. The authors used registered prices for estimating comparators' cost.^[16] In current economic evaluation, the generic price of medicines has been enrolled that might affect the results on the cost side. However, the results of economic evaluation studies depend on the study context and economic and therapeutic features. Therefore, it would be necessary to reiterate the study in different countries for their national decision-making. Herein, an economic evaluation was conducted by a developed hybrid model and with regards to the nationally used therapeutic guidelines, expert opinion, and internal costs.

Conclusion

According to the results, macitentan is preferable to and dominant over bosentan in both effectiveness and expenditure in Iran. Moreover, due to the result of sensitivity analysis and Tornado plot, with changes all the variables within the range of ±%20, the ICER stays below the threshold line leading to a reliable result. Consequently, according to the results of cost-utility analysis, a therapeutic regimen containing macitentan is introduced as a favorable treatment strategy. Considering the IPAH registry, a trial or cohort-based economic evaluation would be recommended.

Limitation

The main limitation of our study is that we do not have local clinical data for the development of this model; hence, we had to use the data from the literature.

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Conflicts of interest

This project is financially supported by NanoAlvand co. and the authors declare that the publication of study results was not contingent on the sponsor's approval or censorship of the manuscript.

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