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Cost-utility Analysis of Dornase alfa in comparison with Tobramycin for Managing Iranian Patients with Cystic Fibrosis

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ABSTRACT

Background: Cystic fibrosis (CF) is a progressive, life-threatening, and autosomal disease most prevalent in Europe, North America, and Australia. This genetic disorder does not have curative treatment. Current medications to manage CF, including Tobramycin, are associated with high economic costs to the healthcare system and noticeable out-of-pocket and time costs to patients and their families. Dornase alfa is a recombinant human DNAse and is an advanced therapeutic intervention. It has been indicated in clinical trials that Dornase alfa elevates FEV1 in CF patients and enhances lung function. Therefore, this study was designed to evaluate the cost-utility of Dornase alfa compared with Tobramycin in managing CF patients' symptoms.

Methods: A Markov model was developed based on previous similar studies to determine the cost-utility of Dornase alfa in comparison with Tobramycin. The model's time horizon and the cycles' length were assumed to be ten years and 28 days, respectively.

Results: Based on the cost-utility analysis, from the health system's perspective, Dornase alfa indicated 0.174 higher effectiveness in patients' QALY than Tobramycin and resulted in 27,517,260 Rials reduction in costs in the time horizon of 10 years.

Conclusion: Dornase alfa could be considered a cost-effective strategy in treating CF patients associated with increased benefits compared to Tobramycin.

Keywords: Cystic Fibrosis, Dornase alfa, Tobramycin, Economic evaluation, Cost-utility analysis.

Introduction

Cystic fibrosis (CF) is a progressive, life-threatening, and autosomal disease [1, 2], which is caused by mutations in a cystic fibrosis transmembrane regulator (CFTR) gene [2, 3]. CFTR mutations lead to elevated viscosity of mucous secretion, which influences the airways, pancreas, liver, and gut [4]. The most noticeable changes can be seen in the airways, in which the fundamental genetic deficiency leads to chronic pulmonary infections with very few bacterial pathogens [3]. Paeruginosa is the most widespread isolate [3, 5], and Staphylococcus aureus and Haemophilus Influenzae come next [3].

CF is most prevalent in Europe, North America, and Australia [1, 2] and affects up to one in 2500 newborns in the UK, and the average age at diagnosis is two months. Furthermore, CF is increasingly detected in South and East Asia, Africa, and Latin America, with more usage of newborn screening. On the other hand, the incidence and prevalence of CF have yet to be apparent in many areas, particularly in Iran [4]. Modaresi et al. indicated that CF in Iran is in 17.6% of high-risk children [4].

Although recently developed medications and treatments to manage CF have increased survival age, these improvements are associated with high economic costs to the healthcare system and potentially high out-of-pocket and time costs to care recipients and their families. Because the management of CF includes a high utilization of healthcare resources, from the perspective of the healthcare system and recipients of care, the costs associated with this disease are pretty dramatic [6]. It was demonstrated in a recent study that CF has a constant and wide-ranging economic influence on payers, with noticeable differences in the distribution of expenses and service consumption between younger and older patients and mild versus severe patients [7].

This genetic disorder does not have a curative treatment [8]. Current therapies that are used to slow down the progression of CF include: treating the symptoms and fighting respiratory infections and their consequences [8]. Therefore, developing and delivering medications that increase mucus clearance from the lungs and treat the consequent infection, combined with correcting pancreatic malfunction and undernutrition by multidisciplinary teams, can significantly improve CF patients' quality of life [2]. Non-medical treatments for patients with CF include: recommending nutrition and fitness, medications, and chest physiotherapy to clear the airways [9]. Medical treatments that are available today include inhaled, oral, and intravenous antibiotics such as inhaled Tobramycin, which is used in moderate to severe forms of disease and reduces the exacerbations [2, 10], anti-inflammatory therapies, pancreatic enzymes and supplemental nutrients and vitamins, bronchodilators, agents that promote airway secretion clearance such as inhaled Dornase alfa, hypertonic saline, and mannitol, supplemental oxygen, CFTR modulators like Ivacaftor and Lumacaftor, and lung transplantation [5, 9-12].

One of the treatments for CF patients with lung injuries is Dornase alfa, which is a recombinant human DNAse (rhDNAse), and is a developed therapeutic intervention [13]. Inhalation of Dornase alfa hydrolyses extracellular DNA in elevated levels in lower airway secretions and reduces the viscosity of CF sputum [13-15]. It has been indicated in clinical trials that Dornase alfa increases FEV1 in CF patients five years of age and older with forced vital capacity (FVC) > 40% and improves lung function [9, 13-15].

Since economic evaluation, especially cost-utility analysis is a constant instrument for policymaking in health finance [16], the Food and Drug Administration (FDA) of Iran has suggested making a cost-utility analysis of Dornase alfa in comparison with Tobramycin in the management of patients with CF, in order to add Dornase alfa to Iran Drug List (IDL). Therefore, we designed this study to determine the cost-utility of Dornase alfa versus Tobramycin in treating CF patients.

Methods

Model structure

Since there was no head-to-head clinical trial on Dornase alfa in a systematic review of this study, a network meta-analysis was performed to evaluate the utility of Dornase alfa and Tobramycin. A Markov model was developed based on previous studies on similar medicines [17-19] to determine the cost-utility of Dornase alfa compared to Tobramycin. This model was constructed by Tree Age pro-2019 software. The amount of FEV1 reflects the level of pulmonary obstruction. Therefore, the basic model has consisted of 4 states, and patients were included in the first three states of the model based on the measured FEV1 percentage:

1. FEV1≥70%: mild| 2. 40%≤FEV1≤69%: moderate | 3. FEV1≤40%: severe | 4. Death.

Patients can experience each state, but the transition between different states is based on FEV1 and transition probability for that state. The model's time horizon and the cycles' length were assumed to be ten years and 28 days, respectively.

Model inputs

Efficacy and Safety

Basic transition probabilities for Tobramycin were collected from a similar previous study [19], and results were adjusted and counted for Dornase alfa: Primary distribution of patients in different states is indicated in Tables 1&2 according to baseline characteristics of patients.

Pulmonary exacerbations in CF patients mainly occur in major or minor forms. They are indicated by the reduction in lung function due to pulmonary infections, which decrease patients' quality of life. The incidence rate of exacerbations depends on the state of the disease and differs for each state. The average duration of hospitalization is 14 days in these patients. Patients with minor exacerbations mostly do not need hospitalization and receive oral antibiotics such as ciprofloxacin and azithromycin. The incidence rate of exacerbations is indicated in the table below [19]. (Table 3)

Health-Related Quality of Life

CF patients experience a different quality of life in each state of the disease. Their utility in each state was included as beta distribution. Both minor and significant exacerbations result in a decrease in quality of life and utility in each state of disease. The Panguluri et al. study's results were used for patients' quality of life extraction and the effect of exacerbations on quality of life [19]. (Table4)

These utility results were included in the model with a beta distribution in 28 days.

Resource Use and Costs

In health economics, costs are categorized into three groups: direct costs, indirect costs, and intangible costs. In economic evaluation studies, these costs are chosen and studied based on the perspective of the study. Direct medical costs are the costs that are directly used in disease treatment, like diagnosis, medical therapy, monitoring, rehabilitation, and hospitalization costs. Since this study was based on the health system's perspective, only direct medical costs were included in the analysis.

Direct medical cost – Medicines

The list and price of medicines that are used in CF treatment are indicated in the table below: (Table 5)

Direct medical cost – Medical services

On average, CF patients have a specialist doctor appointment to check their health status every eight weeks. In case of experiencing a significant exacerbation, patients require hospitalization and need nutritionist and psychiatrist appointments.

The cost of specialist appointment: The cost of a lung specialist's appointment was considered 304,800 Rials, and the cost of a psychiatrist's appointment was considered 373,400 Rials (20% of the patient is out of pocket, 80% insurance reimbursement)

The cost of a nutritionist appointment: It was considered 615,139 Rials (2.5 K)

Direct medical cost – Hospital services

The total cost of hospitalization was considered 6,000,000 Rials (20% of patient is out of pocket, 80% insurance reimbursement)

Direct medical cost – Monitoring

A lung function test during monitoring appointments was considered every eight weeks for all CF patients. Lung function test for patients with significant exacerbation is done at admission and discharge from hospitalization and once for patients with minor exacerbation.

Chest radiography is done once for patients with significant exacerbation at hospital admission.

Total blood count tests and cultivation of sputum are done every eight weeks during monitoring for all patients.

In order to advance the lung clearance of patients and increase the excretion of lung secretions in hospitalized patients with significant exacerbation, chest physiotherapy is done three times a day on average, along with antibiotic therapy.

Discount Rate

Since the model's time horizon was more than one year, a discount rate of 7% was used for costs based on Abdoli et al. recommendation [20]. Besides, a utility discount rate of 5% was applied in this study.

Sensitivity analysis

To ensure the robustness of the results, a one-way deterministic sensitivity analysis was performed by varying the key parameters over a variation of ±20%. Then, the Tornado diagram is plotted using sensitivity analysis results. A tornado diagram is a schematic ordering of parameters from the most sensitive to the least.

Besides, all costs were included in the model in expected periods as a gamma distribution, and all probabilities were included as a beta distribution according to the reported standard

deviation (SD). Finally, the probabilistic sensitivity analysis (PSA) was reported.

Results

Cost-utility evaluation

Based on the cost-utility analysis, from the health system's perspective, the average cost to treat CF patients with Dornase alfa was estimated to be 3,804,460,239 Rials per patient in 10 years. While the average cost to treat these patients using Tobramycin was estimated to be 3,831,977,498 Rials per patient in the time horizon of 10 years. (Table 6)

In terms of utility, the average discounted QALY in the Dornase alfa treatment regimen equals 4.6, and the Tobramycin treatment regimen equals 4.40. According to the results, from the health system perspective, Dornase alfa indicated 0.174 higher utility in patients' QALY than Tobramycin. It resulted in a 27,517,260 Rials reduction in costs in the time horizon of 10 years. Therefore, Dornase alfa is more cost-effective than Tobramycin and is cost-effective in treating CF patients in Iran within ten years.

Most costs in the Dornase alfa and Tobramycin treatment regimen were related to the acquisition cost of drugs, 86% of all costs in the Dornase alfa treatment regimen and 81% of all costs in the Tobramycin treatment regimen.

Monte Carlo simulation

Based on the Monte Carlo stimulant, considering the distribution of variables including probabilities and costs, in a 1000 patients' cohort, the average of discounted direct medical costs in the Dornase alfa regimen was estimated to be 3,918,392,729 Rials (SD = 445,090,641) and in Tobramycin regimen was estimated to be 3,941,883,915 Rials (SD = 448,244,926) per patient. Regarding utility, the average discounted QALY in Dornase alfa regimen equals 4.56 (SD= 0.27), and in the Tobramycin regimen equals 4.39 (SD= 0.29). (Chart 1)

Incremental cost-effectiveness scatter plot

Another outcome of the Monte Carlo simulation is a cost-effectiveness scatter plot, which indicates more detailed information in individual comparisons. This curve is used to better understand all the uncertainties and probability distribution and indicates the percentage of points in a good area. (Chart 1)

Points that are in the first, third, and fourth quarter of the chart and are under the threshold line are excellent and cost-effective points.

In the chart, the Monte Carlo stimulation points for CF patients in the Dornase alfa group compared with Tobramycin have been drawn in the threshold of willingness to pay equal to 1 GDP/capita (120,000,000 Rials). According to the results, Dornase alfa is in a good area in 68% of cases and is considered a cost-effective strategy.

Tornado chart

Since the dependent variable is impacted by multi-independent variables, identifying the independent variables with the most significant influences on the dependent variable is challenging. The Tornado chart is one of the best ways to identify the most influential variables in the results. The effective variables, in this case, include the impact rate, the price of Dornase alfa, the price of Tobramycin (Tobi), and the ratio of using Podhaler to Tobramycin nebulizer, respectively. (Chart 3)

One-way sensitivity analysis

Dornase alfa price sensitivity analysis

In Dornase alfa price sensitivity analysis in range of 628,000 to 943,000 Rials, it is indicated that in higher prices than 800,000 Rials, incremental cost-utility would be more than willingness to pay threshold, and Dornase alfa would not be cost-effective. (Chart 4)

Tobramycin Podhaler price sensitivity analysis

In Tobramycin Podhaler price sensitivity analysis of 300,000 to 700,000 Rials, it is indicated that in lower prices than 544,000 Rials, incremental cost-utility would be more than willing to pay threshold, and Dornase alfa would not be cost-effective. (Chart 5)

Ratio of podhaler usage sensitivity analysis

In ratio of podhaler usage sensitivity analysis in range of 10 to 70 percent, it has been shown that in lower percentage than 29.39 percent, incremental cost-utility would be more than willingness to pay threshold, and Dornase alfa would not be cost-effective. (Chart 6)

Two-way sensitivity analysis

Considering the simultaneous sensitivity of the model to the price of Dornase alfa and Tobramycin (Tobi), the two-way sensitivity analysis was performed for the price of both medicines, in order to determine the new cost-effective price of Dornase alfa by changing the price of Tobi. (Chart 7)

Discussion

Dornase alfa is a mucolytic agent that reduces the viscosity and surface adhesion properties of CF sputum, thus enhancing mucus clearance [13]. Previous studies indicated that treatment with dornase alfa is associated with a decrease in the annual rate of reduction in FEV1% predicted in patients with CF and an improvement in lung function compared with control, regardless of age or disease stage [14, 21]. The study of adding

Dornase alfa into CF patients' treatment regimen in Iran was performed to evaluate the cost-utility of Dornase alfa compared to Tobramycin. It was analyzed using a Markov model.

Since there was no head-to-head clinical trial on Dornase alfa in a systematic review of this study, a network meta-analysis was performed to evaluate the utility of Dornase alfa and Tobramycin. Results indicated the impact of Dornase alfa on FEV1 advancement (3.1% CL: -13%, +17%) and elevation of the respiratory capacity of CF patients, which confirms previous studies.

Incremental cost-utility analysis of Dornase alfa and Tobramycin from the health system's perspective showed higher effectiveness of Dornase alfa compared to Tobramycin, equal to 0.174 in patients' QALY. It caused a cost reduction of 27,517,260 Rials per patient in 10 years. Therefore, Dornase alfa is more cost-effective than Tobramycin in treating CF patients in 10 years.

The sensitivity analysis results indicated that the study model is sensitive to crucial variables resulting from Tornado analysis, such as the price of 2 medicines. Besides, results from the cost-utility distribution curve and Monte Carlo stimulant showed that dornase alfa is in the acceptable area in 68% of cases compared with Tobramycin.

Conclusion

In conclusion, Dornase alfa is a cost-effective strategy for treating CF patients. More studies are required to confirm these findings.

Conflict of interest

All authors declare no potential conflicts of interest in conducting the study and publishing the article.

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No funding was received to assist with the preparation of this manuscript.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethical committee of the Tehran University of Medical Sciences (TUMS). All the participants accepted enrollment in the study orally and all of the data that were gathered was considered confidential.

Figure

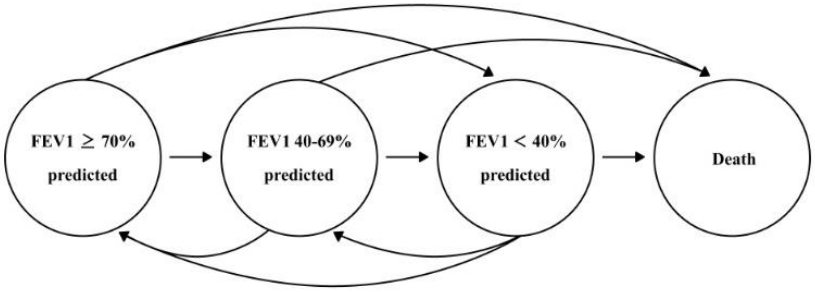

Figure 1: The schematic model of study based on level of FEV_1

Tables

Table 1: Tobramycin and Dornase alfa transition probability matrix

	From/to State of Model	Mild: FEV1>70%	Moderate: 69>FEV1>40	Severe: FEV1<40%	Death	Distribution
Tobramycin	Mild: FEV1>70%	0.58	0.39	0.03	0.00014	Dirichlet
	Moderate: 69>FEV1>40	0.12	0.83	0.05	0.00034	Dirichlet
	Severe: FEV1<40%	0.02	0.29	0.69	0.023	Dirichlet
Dornase alfa	Mild: FEV1>70%	0.62	0.35	0.03	0.00014	Dirichlet
	Moderate: 69>FEV1>40	0.16	0.80	0.04	0.00034	Dirichlet
	Severe: FEV1<40%	0.02	0.33	0.65	0.023	Dirichlet

Table 2: Primary distribution of patients in different states

State	Initial Distribution
Mild	0.15
Moderate	0.65
Severe	0.2

Table 3: Rate of exacerbations in each state in a one-year period

FEV1% predicted severity level	Population	
	Requiring hospitalization (severe)	Treated at home (mild)
FEV1% predicted, <40	2.61	2.64
FEV1% predicted, 40-69	1.36	1.97
FEV1% predicted, >70	0.86	2.18

These rates were converted to 28-days probabilities and were included in the model:

$p = 1 – \exp(-r*t)$

Table 4: Patients' quality of life based on EQ5D questionnaire

Description	Utility Value	Standard Deviation
FEV1% predicted, 70-99	0.864	0.165
FEV1% predicted, 40-69	0.810	0.216
FEV1% predicted, <40	0.641	0.319
Mild Exacerbation	0.060 decrement	0.048
Severe Exacerbation	0.260 decrement	0.341

Table 5: Cost inputs

Product	Unit Cost (Rial)	Administration	Total Cost (Rial per cycle)
Tobramycin (TOBI Podhaler)	563,000 (per 1 pack of inhalation powder 28 mg)	q12h 4 pack of inhalation powder for 28 days then DC for another 28 days	126,112,000
Tobramycin (Bramitob)	455,000 (Respiratory Soloution 300 mg/4mL)	q12h 1 Vial of inhalation solution for 28 days then DC for another 28 days	25,480,000
Tobramycin (Tobamist)	Inhalant respiratory 60 mg/1mL 5mL	q12h 1 Vial of inhalation solution for 28 days then DC for another 28 days	-
Dornase alfa	965,000 (per 2.5mg/2.5ml inhalation solution ampoul)	1 Ampoule nebulized daily	27,020,000
Amikacin	44,000 (per 500 mg vial)	10 mg per kg q8h IV injection for 14 days	1,848,000
Ceftazidime	118,000 (Per 2 gr vial)	2 gr q8h for 14 days	4,956,000
Vancomycin	76,100 (Per 500 mg vial)	10 mg per kg q8h IV injection for 14 days	3,196,200
Ciprofloxacin	1,700 (Per 250 mg capsule)	30 mg per kg q12h orally for 14 days	119,000
Cloxacillin	44,000 (Per 500 mg vial)	1 g q6h IV injection for 14 days	4,928,000

Table 6: A cost-utility evaluation

Strategy	Cost (Rial)	Utility (QALYs)	Incremental Cost	Incremental Utility	ICER
Dornase alfa	3,804,460,239	4.58	-27,517,260	0.17466690	**-157,541,356**
Tobramycin	3,831,977,498	4.40			

Charts

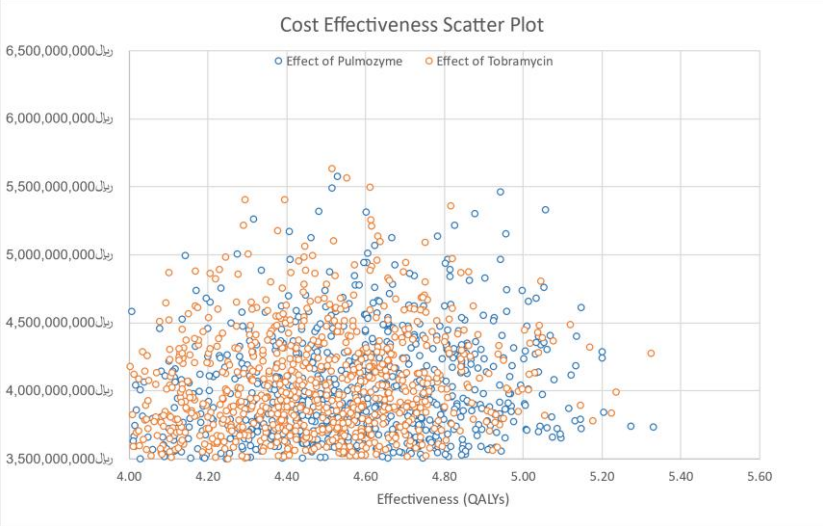

Chart 2: Monte Carlo stimulant

Chart 3: Incremental cost-effectiveness scatter plot

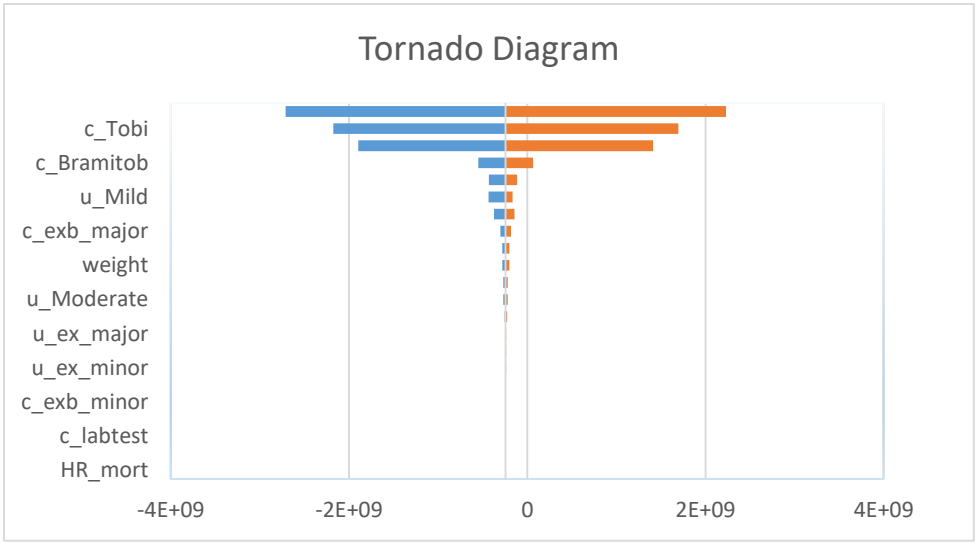

Chart 4: Tornado diagram

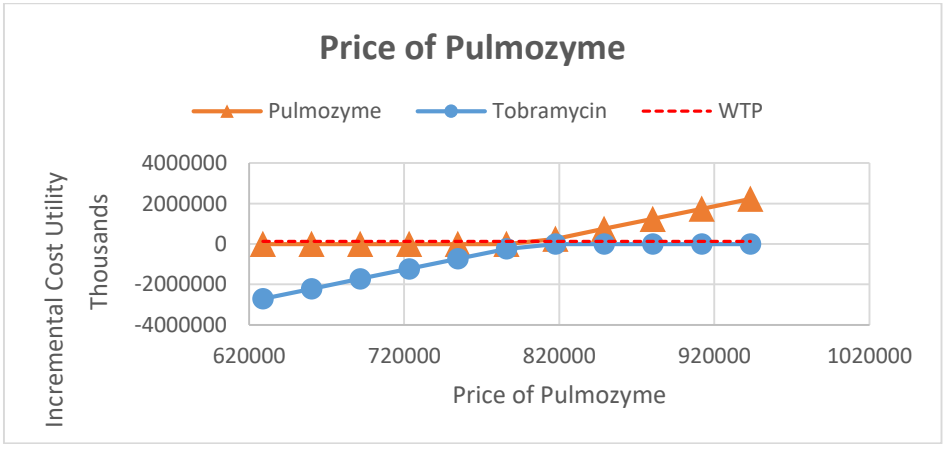

Chart 5: Dornase alfa price sensitivity analysis

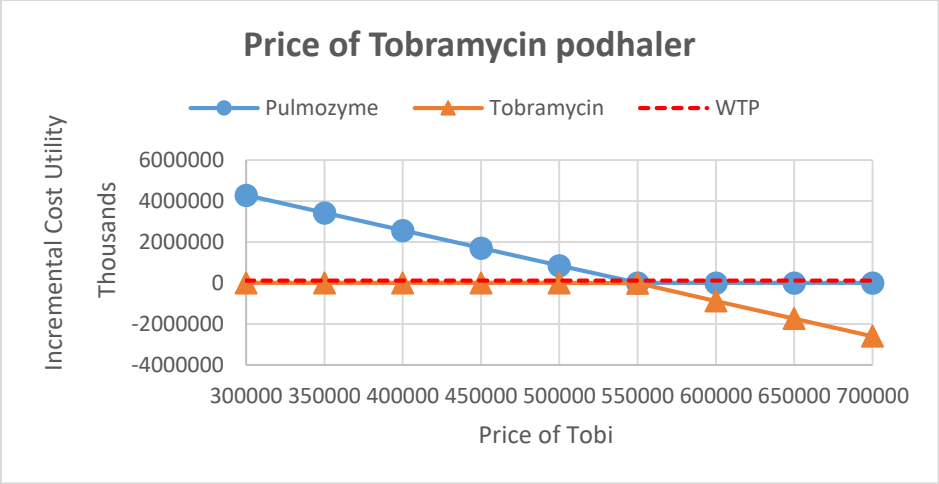

Chart 6: Tobramycin Podhaler price sensitivity analysis

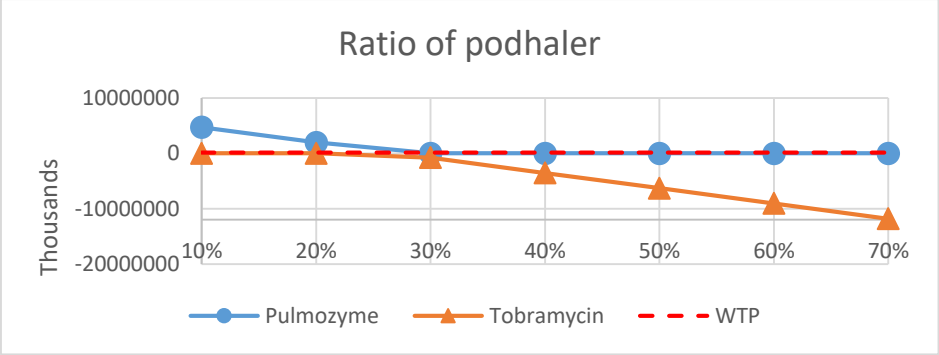

Chart 7: Ratio of podhaler usage sensitivity analysis

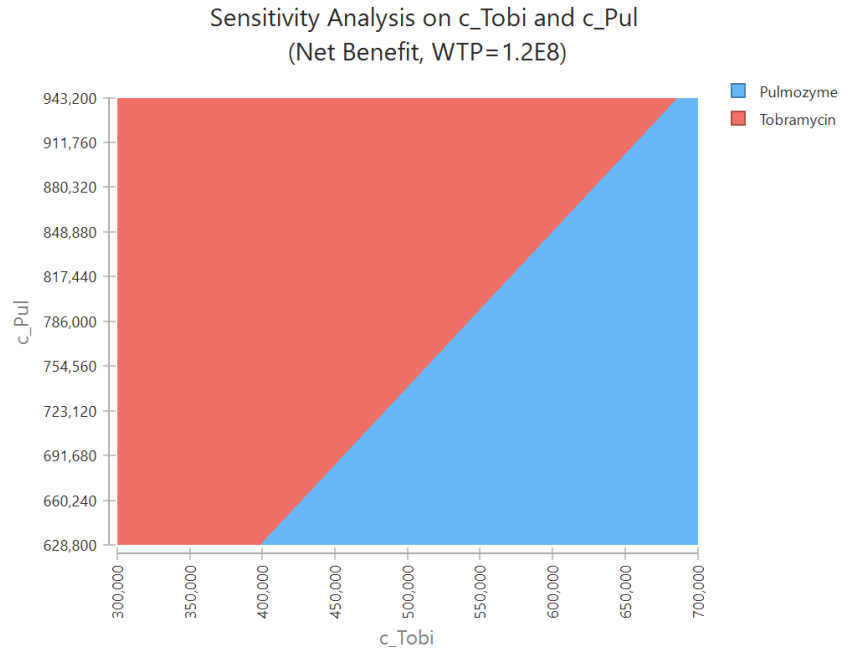

Chart 8: The price of Dornase alfa and Tobramycin two-way sensitivity analysis

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