

ECONOMIC IMPACT LINKED TO THE REDUCTION OF EXACERBATIONS WHEN A TREATMENT REGIME WITH INHALED ANTIBIOTICS IS SWITCHED TO AZTREONAM LYSINE IN PATIENTS WITH CYSTIC FIBROSIS AND CHRONIC PULMONARY INFECTION CAUSED BY PSEUDOMONAS AERUGINOSA

A. Solé¹, J.L. Poveda¹, R. Girón², C. Prados³, J. de Gracia⁴, M.A. Casado⁵

¹ Hospital Universitario y Politécnico La Fe, Valencia, Spain; ² Hospital Universitario de la Princesa, Madrid, Spain; ³ Hospital Universitario La Paz, Madrid, Spain;

⁴ Hospital Universitario Vall d'Hebrón, Barcelona, Spain; ⁵ Pharmacoeconomics & Outcomes Research Iberia, Madrid, Spain

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease that causes complications in several organs, particularly the lungs and the pancreas. With an incidence of 1 in 1,800-25,000 live births, depending on the country [1], CF is the most common fatal autosomal recessive disease in Caucasians [2], affecting about 70,000 people in Europe and the United States of America [1,3].

CF is associated with chronic disabling symptoms such as pulmonary exacerbations, which have a negative impact on health-related quality of life [4] and disease prognosis [5,6]. Exacerbations also have been associated with higher health care costs [7,8].

Development of new inhaled antibiotics and new regimens of administration are increasing the therapy options and diversification for CF patients. CF treatment can ease symptoms, reduce exacerbations and slow the progression of the disease.

Aztreonam lysine (AZLI, Cayston[®]) for inhalation solution, developed for the treatment of CF patients with chronic lung infection by *Pseudomonas aeruginosa* (PA) may avoid exacerbation episodes [9].

The high cost of exacerbation episodes and the emergence of new and expensive treatments to treat CF patients with PA infection oblige the consideration of budget impact models.

OBJECTIVE

To estimate, from the Spanish National Healthcare System (SNHS) perspective, the required reduction of exacerbation episodes in different patient profiles, in order to maintain constant the overall treatment cost, if a inhaled antibiotic treatment is switched to AZLI in patients with CF and chronic pulmonary infection by PA.

METHODS

To characterize the different patient profiles, an annual cost analysis model was developed considering the following costs:

- Drug cost: calculated based on ex-factory prices [10] and considering local mandatory discounts [11].
- Exacerbation episode cost (considering 14 hospitalization days per episode): derived from Diagnosis Related Group (DRG) 740 [12, 13].

All costs were updated to €2014 (Tables 1 and 2).

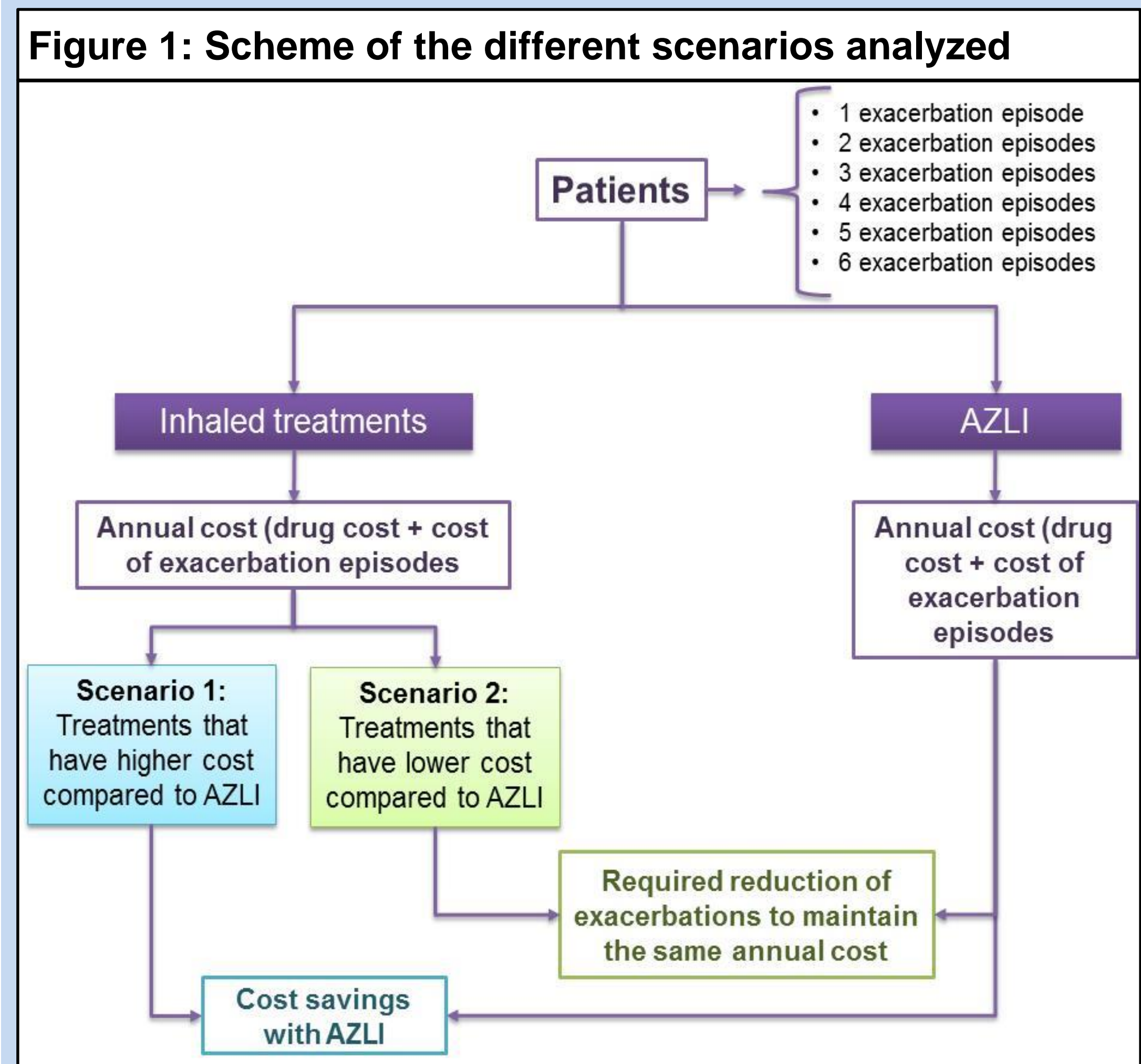
Active ingredient	Current treatment	Presentation form	Units per day	Net price (EUR)*	Annual cost (EUR)	
					On/off	Continuous
Colistimethate sodium	Colistina GES [®]	10 vials (1 MUI [†] =80 mg)	2	55	1,996	3,992
			4		3,992	7,983
	Colobreathe [®]	56 capsule (1.6625 MUI [†] =125 mg)	2	998	6,507	13,015
			4		13,015	26,030
Promixin [®]	30 vials (1 MUI [†] =80 mg)	2	328	3,989	7,978	
		4		7,978	15,955	
Tobramycin	Bramitob [®]	56 containers (300 mg/4 ml)	2	1,167	7,603	15,207
			4		15,207	30,414
Tobramycin	Tobj [®]	56 vial (300mg/5ml)	2	1,167	7,603	15,207
			4		15,207	30,414
Aztreonam lysine	Cayston [®]	84 vials (75 mg)	3	2,080	13,557	-
Exacerbation episodes cost						
Exacerbation - 14 hospitalization days (EUR)						8,729

*Net price = Ex-factory price minus mandatory discount (Royal Decree-Law 8/2010) + VAT
[†]1 MUI = 1 Million International Units
[‡]Cayston[®] is administered in repeated cycles of 28 days of therapy followed by 28 days without treatment.

Considering a switch to AZLI, two scenarios were analyzed (Figure 1):

- Scenario 1 - Treatments that have a higher cost than the cost of AZLI: the cost savings with AZLI were calculated

- Scenario 2 - Treatments that have a lower cost than the cost of AZLI: the reduction of exacerbation in the AZLI arms required to achieve the same overall cost were calculated



- Two sensitivity analysis (SA) were performed:
 - SA₁: considering different drug commercial discounts (table 2)
 - SA₂: rotation of antibiotics (AB) → 6 months of current regime + 6 months of AZLI (on/off)

Active ingredient	Current treatment	Price reductions ^a	Units per day	Net price (EUR)*	Annual cost (EUR)	
					On/off	Continuous
Colistimethate sodium	Colistina GES [®]	15%	2	46	1,696	3,393
			4		3,393	6,786
	Colobreathe [®]	30%	2	699	4,555	9,110
			4		9,110	18,220
Tobramycin	Bramitob [®]	15%	2	279	3,391	6,781
			4		6,781	13,562
	Tobj [®]	30%	2	817	5,322	10,644
			4		10,644	21,288

*Net price = Ex-factory price minus mandatory discount (Royal Decree-Law 8/2010) + VAT
^aPrice reductions applicable to the presentation forms detailed in table 1

RESULTS

- Base case:
 - Switching to AZLI (maintaining the same number of exacerbations) would save overall costs in 4 out of 13 options (Table 3).

Current regimen	New regimen	Savings with AZLI (EUR)
Promixin [®] continuous - 4 units	Cayston [®] alternated (on/off)	2,398
Bramitob [®] continuous		1,649
TOBI [®] continuous		1,649
TOBI [®] alternated with Promixin [®] - 4 units		2,024

- In the remaining options, the required reduction of exacerbations varies depending on the patient's current situation (Table 4) ranging from 110% (one episode/year) to 1% (five or six episodes/year). Reductions below 30% are highlighted in green in Table 4.

Current regimen	Exacerbation episodes per year					
	1	2	3	4	5	6
Colistina GES [®] continuous - 2 units	110%	55%	37%	27%	22%	18%
Colistina GES [®] continuous - 4 units	64%	32%	21%	16%	13%	11%
Promixin [®] Continuous - 2 units	64%	32%	21%	16%	13%	11%
Bramitob [®] alternated (on/off)	68%	34%	23%	17%	14%	11%
TOBI [®] alternated (on/off)	68%	34%	23%	17%	14%	11%
TOBI [®] alternated with Colistina GES [®] - 2 units	45%	23%	15%	11%	9%	8%
TOBI [®] alternated with Colistina GES [®] - 4 units	22%	11%	7%	6%	4%	4%
TOBI [®] alternated with Promixin [®] - 2 units	23%	11%	8%	6%	5%	4%
Colobreathe [®] continuous	6%	3%	2%	2%	1%	1%

- Sensitivity analysis₁ (SA₁):
 - There is 1 out of 13 options in which switching to AZLI would save costs (Table 5).

Current regimen	New regimen	Savings with AZLI (EUR)
Promixin [®] continuous (-15%) - 4 units	Cayston [®] alternated (on/off)	5

- For the remaining alternatives, the required reduction of exacerbations does not change significantly from the base case (Table 6); reductions below 30% are highlighted.

Current regimen	Exacerbation episodes per year					
	1	2	3	4	5	6
Colistina GES [®] continuous (-15%) - 2 units	116%	58%	39%	29%	23%	19%
Colistina GES [®] continuous (-15%) - 4 units	78%	39%	26%	19%	16%	13%
Promixin [®] continuous (-15%) - 2 units	78%	39%	26%	19%	16%	13%
Bramitob [®] (-30%) alternated (on/off)	94%	47%	31%	24%	19%	16%
Bramitob [®] (-30%) continuous	33%	17%	11%	8%	7%	6%
TOBI [®] (-30%) alternated (on/off)	94%	47%	31%	24%	19%	16%
TOBI [®] (-30%) continuous	33%	17%	11%	8%	7%	6%
TOBI [®] (-30%) alternated with Colistina GES [®] (-15%) - 2 units	75%	37%	25%	19%	15%	12%
TOBI [®] (-30%) alternated with Colistina GES [®] (-15%) - 4 units	55%	28%	18%	14%	11%	9%
TOBI [®] (-30%) alternated with Promixin [®] (-15%) - 2 units	55%	28%	18%	14%	11%	9%
TOBI [®] (-30%) alternated with Promixin [®] (-15%) - 4 units	17%	8%	6%	4%	3%	3%
Colobreathe [®] (-30%) continuous	51%	25%	17%	13%	10%	8%

- Sensitivity analysis₂ (SA₂):
 - There are 4 out of 13 options in which rotating AB's with AZLI would save costs (Table 7).

Current regimen	New regimen	Savings with AZLI (EUR)
Promixin [®] continuous - 4 units	Current regime for 6 months followed by Cayston [®] alternated (on/off) for 6 months	1,199
Bramitob [®] continuous		825
TOBI [®] continuous		825
TOBI [®] alternated with Promixin [®] - 4 units		1,012

- For the remaining alternatives, the required reduction of exacerbations are much lower compared to the base case (Table 8) Reductions below 30% are also highlighted.

Current regimen	Exacerbation episodes per year					
	1	2	3	4	5	6
Colistina GES [®] continuous - 2 units	55%	27%	18%	14%	11%	9%
Colistina GES [®] continuous - 4 units	32%	16%	11%	8%	6%	5%
Promixin [®] continuous - 2 units	32%	16%	11%	8%	6%	5%
Bramitob [®] alternated (on/off)	34%	17%	11%	9%	7%	6%
TOBI [®] alternated (on/off)	34%	17%	11%	9%	7%	6%
TOBI [®] alternated with Colistina GES [®] - 2 units	23%	11%	8%	6%	5%	4%
TOBI [®] alternated with Colistina GES [®] - 4 units	11%	6%	4%	3%	2%	2%
TOBI [®] alternated with Promixin [®] - 2 units	11%	6%	4%	3%	2%	2%
Colobreathe [®] continuous	3%	2%	1%	1%	1%	1%

CONCLUSIONS

- In comparison with current treatments, AZLI has demonstrated to bring savings to the SNHS.
- In addition, using AZLI instead of the other available treatments would imply a neutral budget impact if exacerbation episodes can be reduced. This also applies when commercial discounts are considered.
- If a strategy of rotating antibiotics is considered using AZLI there would also be either savings to the SNHS or a neutral budget impact if exacerbation episodes can be reduced.

REFERENCES

- Colombo C, Littlewood J. The implementation of standards of care in Europe: state of the art. *J Cyst Fibros* 2011; 10 (Suppl 2): S7-S15
- Flume PA, Van Deventer DR. State of progress in treating cystic fibrosis respiratory disease. *BMC Medicine* 2012; 10: 88. doi: 10.1186/1745-7015-10-88
- Cystic Fibrosis Foundation. Patient Registry 2012 Annual Data Report. Bethesda, Maryland
- Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002; 121: 64-72
- Amadori A, Antonelli A, Balteni I, Schreiber A, Bugiani M, De Rose V. Recurrent exacerbations affect FEV(1) decline in adult patients with cystic fibrosis. *Respir Med* 2009; 103: 407-413
- de Boer K, Vandemheen KL, Tullis E, Ducatelle S, Ferguson D, Freitag A, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. *Thorax* 2011; 66: 680-682
- Lieu TA, Ray GT, Farmer C, Shay GF. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics* 1999; 103: e72
- Rosenberg MA, Farrell PM. Assessing the cost of cystic fibrosis diagnosis and treatment. *J Pediatr* 2005; 147 (3 Suppl): S101-S105
- Assael BM, Pressler T, Bilton D, et al. Inhaled aztreonam lysine vs inhaled tobramycin in cystic fibrosis: a comparative efficacy trial. *J Cyst Fibros* 2013; 12: 130-40
- Botpluss database: URL available at: www.portalafarma.com
- Royal Decree-law 8/2010. URL available at: <http://www.boe.es>
- ESalud. Health costs database. URL available at: <http://www.ohlalus.com/ohlulocostes/>
- Ministerio de Sanidad, Servicios Sociales e Igualdad. Registro de Altas de los Hospitales Generales del Sistema Nacional de Salud. CMBD. Norma Estatal 2010. URL available at: <https://www.msssi.gob.es/estadEstudios/estadisticas/cmbd.htm>