



Antibiotics, Inhaled

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS^{1, 2}

Drug	Manufacturer	FDA-Approved Indications
aztreonam (Cayston®)	Gilead	<ul style="list-style-type: none"> For the improvement of respiratory symptoms in cystic fibrosis patients with <i>Pseudomonas aeruginosa</i> and a forced expiratory volume in one second (FEV₁) between 25 percent and 75 percent predicted
tobramycin (TOBI®)	Novartis	<ul style="list-style-type: none"> For the management of cystic fibrosis patients with <i>Pseudomonas aeruginosa</i>

OVERVIEW

Cystic Fibrosis (CF) is the most common lethal genetic disease among Caucasians, affecting approximately 30,000 individuals residing in the United States.^{3,4} It has been estimated that four to five percent of all Caucasians in North America are carriers of the CF gene. The incidence of CF by ethnic group has also been reported as follows: Caucasians one in 3,200; African Americans one in 15,000; and Asian Americans one in 31,000.⁵ More than 1,000 individuals are diagnosed with CF annually, with 53 percent of patients being diagnosed by six months of age and 74 percent by two years of age.⁶

CF is an autosomal recessive disorder caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome number seven.⁷ Loss of functionality of the CFTR protein causes impairment of chloride transport in epithelial cells, which results in different physiologic consequences in different organs.⁸ The typical manifestation of CF involves progressive obstructive lung disease that has been associated with impaired mucous clearance, difficulty clearing pathogens, and risk of chronic pulmonary infection and inflammation.⁹ As a result, respiratory failure is the common cause of death in patients with CF with the median expected survival age of 36 years. CF also manifests as pancreatic insufficiency that has been associated with fat and protein malabsorption and, consequently, malnutrition.¹⁰

The sweat chloride test is the gold standard of CF diagnosis since it remains to be the most discriminatory test for this disorder.¹¹ Values of chloride greater than 60 mEq/L in a sweat chloride concentration analysis are considered positive. CF can also be diagnosed by DNA analysis; however, a negative analysis result does not exclude the diagnosis of the disease.

The main objectives of CF treatment are to treat and prevent infection, promote mucus clearance, and improve nutrition.¹² Airway clearance can be achieved through different airway clearance techniques (e.g., manually assisted cough, chest physiotherapy, etc.), antibiotics, ibuprofen, inhaled hypertonic saline, inhaled beta₂ adrenergic receptor agonists, and mucolytic enzymes.^{13, 14} Since pulmonary infection is the main source of morbidity and mortality, antibiotics play an important role in CF therapy to control the progression of the disease. Chronic use of inhaled tobramycin (TOBI) is recommended in the CF Pulmonary Guidelines to reduce exacerbation for patients who are six years of age and older with persistent *Pseudomonas aeruginosa* culture in the airways.¹⁵ There were no other FDA-approved inhaled antibiotics for the treatment of CF included in this guideline published in 2007. However, chronic use of oral azithromycin for patients six years of age and older with persistent *P. aeruginosa* culture is also recommended, though the strength of recommendation is not as strong. Additionally, in patients with pulmonary exacerbations marked by chronic infection of *P. aeruginosa*, treatment with the combination of aminoglycoside and beta-lactam antibiotic is recommended.¹⁶ Typical duration of treatment is two to three weeks of intravenous antibiotics, with clinical improvement usually seen

after the first week of treatment. Inhaled aztreonam (Cayston) was not available during the formation of these guidelines.

PHARMACOLOGY

Inhaled aztreonam (Cayston) is a beta-lactamase-resistant monobactam antibiotic that only has activity against aerobic gram-negative bacteria, including *P. aeruginosa*.^{17, 18} Aztreonam exerts its effect by binding penicillin-binding protein of susceptible bacteria, forming elongated filamentous cells that eventually lyse and die.¹⁹ Aztreonam is formulated for administration by inhalation through a nebulizer so that the drug is concentrated in the airway.²⁰ A bronchodilator, and any other cystic fibrosis inhaled therapies should be taken before the administration of aztreonam.²¹

Inhaled tobramycin (TOBI) is an aminoglycoside antibiotic that binds to a protein of the 30S subunit of the microbial ribosome, interfering with the function of messenger RNA.²² As a result, abnormal, nonfunctional proteins are produced, causing a compromise of cell membrane permeability that eventually leads to cell death.²³ Tobramycin has a bactericidal effect with activity against a wide range of gram-negative bacteria including *P. aeruginosa*. Tobramycin for inhalation is formulated for administration by inhalation through a nebulizer so the drug is concentrated in the airway.

PHARMACOKINETICS^{24, 25}

Drug	Sputum Concentration After 10 Minutes of Inhalation	Sputum Concentration During Chronic Use, After 10 Minutes of Inhalation	Serum Concentration after 1 Hour	Elimination Half-life (hour)
aztreonam (Cayston)	726 mcg/g	715 mcg/g	0.59 mcg/mL	2.1
tobramycin (TOBI)	1237 mcg/g	1154 mcg/g	0.95 mcg/mL	2

Neither tobramycin nor aztreonam accumulate after chronic use; therefore, no adjustment is necessary for patients requiring long-term use of these antibiotics.^{26,27} Both tobramycin and aztreonam are renally eliminated; however, dose adjustment of aztreonam for patients with renal impairment is not required because the drug has low systemic absorption.²⁸ While tobramycin also has low systemic exposure, no specific guideline for dose adjustment is available for patients with renal impairment.²⁹ Monitoring serum concentration for tobramycin in patients with normal renal function is not required; however, it is at the discretion of the treating physician to monitor serum level in patients with renal dysfunction. Neither of these inhaled antibiotics requires dose adjustment based on weight and age of the patient.^{30, 31}

CONTRAINDICATIONS/WARNINGS^{32, 33}

Aztreonam (Cayston) is contraindicated in patients with a known allergy to aztreonam. Cross-reactivity may occur; therefore, physicians must use caution when prescribing aztreonam in patients with a known history of beta-lactam allergy. Bronchospasm with a reduction of 15 percent or more in FEV₁ may occur; therefore, healthcare providers should consider measuring a patient's baseline FEV₁ prior to initiating aztreonam for inhalation therapy.

Tobramycin (TOBI) is contraindicated in patients with a known hypersensitivity to any aminoglycoside. In patients with a known or suspected renal, auditory, vestibular, or neuromuscular dysfunction,

physicians must exercise caution when prescribing tobramycin for inhalation. Physicians should also consider performing baseline auditory and renal function screening to determine if a patient is at an increased susceptibility for the adverse effects. Patients who are pregnant or plan to become pregnant should be aware and informed of the possible harm to the fetus.

DRUG INTERACTIONS^{34, 35}

No formal drug interactions have been noted with aztreonam for inhalation (Cayston).

Concurrent use of inhaled tobramycin (TOBI) with other neurotoxic or ototoxic drugs should be avoided. Diuretics such as furosemide, ethacrynic acid, mannitol, and urea can alter tobramycin serum and tissue concentrations; therefore, concurrent use with tobramycin should also be avoided to reduce aminoglycoside toxicity.

ADVERSE EFFECTS^{36, 37, 38}

Drug	Bronchospasm	Nasal Congestion	Tinnitus	Voice Alteration	Cough
aztreonam (Cayston)	3	12 (16)	nr	nr	51 (54)
tobramycin (TOBI)	nr	nr	3	13	46 (47)

Adverse effects are reported as a percentage. Adverse effects data are reported from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Three percent of patients using inhaled aztreonam experienced bronchospasm, which can be prevented by the use of a bronchodilator before the administration of aztreonam in at-risk patients. Cough was reported with a lower rate in the inhaled aztreonam group compared to the placebo group ($p=0.047$). Arthralgia and joint swelling have also been reported with inhaled aztreonam.

More tinnitus and voice alteration were reported in patients using inhaled tobramycin. Tinnitus was transient and resolved without discontinuation of the drug. Voice alteration was mild in severity and did not cause patient withdrawal from the study.

SPECIAL POPULATIONS^{39, 40}

Pediatrics

Safety and efficacy of inhaled aztreonam (Cayston) have not been established in pediatric patients less than seven years of age. Safety and efficacy of inhaled tobramycin (TOBI) have not been established in pediatric patients less than six years of age. No dose adjustment is required in pediatric patients for either drug. Pyrexia is more commonly reported in pediatric patients than in adult patients during aztreonam treatment.

Pregnancy

Aztreonam: Category B – No well-controlled studies of inhaled aztreonam in pregnant women have been conducted so treatment should be used during pregnancy only if clearly needed.

Tobramycin: Category D – Inhaled tobramycin has not been studied in pregnant women. However, aminoglycosides can cause fetal harm (e.g., congenital deafness) when administered to pregnant

women; therefore, patients who are pregnant or plan to become pregnant should be aware of the potential hazard to the fetus.

Renal Impairment

Inhaled aztreonam requires no dose adjustment in patients with renal impairment. No recommendation has been given for inhaled tobramycin in patients with impaired renal function. However if a patient experiences nephrotoxicity while on inhaled tobramycin therapy, it should be discontinued until tobramycin serum levels fall below 2µg/mL.

DOSAGES^{41, 42}

Drug	Dose	Administration	Duration	Availability
aztreonam (Cayston)*	For adults and pediatric patients > seven years old: 75 mg three times a day	Administer drug only with Altera® Nebulizer System	28 days on treatment, followed by 28 days off	75 mg powder for inhalation (1 vial)
tobramycin (TOBI)**	For adults and pediatric patients > six years old: 300 mg twice a day	Administer drug using PARI LC PLUS™ Reusable Nebulizer with a DeVilbiss® Pulmo-Aid® compressor and as close to 12 hours apart as possible (not less than six hours between doses)	28 days on treatment, followed by 28 days off	300 mg/5 mL (1 ampule)

* aztreonam: No safety and efficacy information for patients less than seven years of age, patients with FEV₁ < 25 percent or >75 percent predicted, or patients colonized with *Burkholderia cepacia*.

** tobramycin: No safety and efficacy data for patients less than six years of age, patients with FEV₁ < 25 percent or >75 percent predicted, or patients colonized with *Burkholderia cepacia*.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

aztreonam (Cayston) versus placebo

A randomized, double-blind, placebo-controlled international trial was conducted to evaluate the safety and efficacy of inhaled aztreonam 75 mg three times daily for 28 days.⁴³ A total of 164 CF patients with *P. aeruginosa* were enrolled. Exclusion criteria included recent (within the previous 28 days) administration of antipseudomonal antibiotics, azithromycin, or aerosolized hypertonic saline

solution; current oral corticosteroid; positive culture of *Burkholderia cepacia* within the previous two years; daily oxygen supplementation; monobactam antibiotic hypersensitivity; intolerance to short-acting beta₂-agonists; lung transplantation; alanine transaminase (ALT) and aspartate aminotransferase (AST) levels more than five times the normal values; serum creatinine more than two times the normal value; pregnancy; lactation; recent change of antimicrobial, bronchodilator, anti-inflammatory, or corticosteroid medication; or new findings in the chest radiograph within the previous 90 days. The end points of the study were respiratory symptoms (determined by CF-Questionnaire-Revised Scale [CFQ-R]), pulmonary function, *P. aeruginosa* density in sputum, and non-respiratory CFQ-R scales. At the end of the 28-day treatment, patients in the treatment arm had a higher mean CFQ-R respiratory score (9.7 points difference; $p < 0.001$), improved pulmonary function (10.3 percent difference in FEV₁ predicted, $p < 0.001$), and less sputum *P. aeruginosa* density (28-day difference, - 1.453 log₁₀ CFU/g; $p < 0.001$). Inhaled aztreonam was well tolerated with similar adverse effects as the placebo group.

tobramycin (TOBI) versus placebo

Two identical multicenter, double-blind, randomized, placebo-controlled trials were conducted to evaluate the safety and efficacy of inhaled tobramycin 300 mg twice daily for a total of 24 weeks in three on-off cycles.⁴⁴ A total of 520 patients with CF and *P. aeruginosa* infection were recruited from 69 CF centers in the United States. Exclusion criteria included receipt of antibiotics within the previous two weeks, hypersensitivity to aminoglycosides, impaired renal function (serum creatinine > 2 mg/dL), or recovery of *Burkholderia cepacia* infection within the previous two years. The end points of the study were pulmonary function, density of *P. aeruginosa* in sputum, and hospitalization. At the end of the study, patients in the treatment groups had an average increase in FEV₁ of 10 percent while patients receiving placebo had a two percent decline in FEV₁ ($p < 0.001$). Density of *P. aeruginosa* was decreased by an average of 0.8 log₁₀ colony-forming units (CFU) per gram of sputum in the active treatment groups compared to 0.3 log₁₀ CFU per gram in the placebo groups ($p < 0.001$). Patients in active treatment groups were 26 percent (95% confidence interval [CI], 2 - 43) less likely to be hospitalized. Inhaled tobramycin was well tolerated with similar adverse effect rates between treatment and placebo groups. However, there were two side effects (tinnitus and voice alteration) that only occurred in the active treatment groups. These adverse effects were of mild to moderate severity and did not cause withdrawals from the study.

SUMMARY

Although there are not many pharmacological treatment options for this disease, antibiotics play a crucial role in CF therapy. Currently, there are two FDA-approved inhaled antibiotics on the market for the management of CF in patients with *P. aeruginosa*. These two medications are taken chronically to suppress the growth of *P. aeruginosa* and reduce the risk of CF exacerbation. Inhaled aztreonam (Cayston) and inhaled tobramycin (TOBI) require no dose adjustment based on weight and age and are well tolerated. Inhaled aztreonam also does not require renal dose adjustment. Nephrotoxicity has been associated with aminoglycosides as a class, however, it has not been observed in clinical studies with inhaled tobramycin. There is no published literature that directly compares the inhaled antibiotics.

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