2014

Is Aztreonam Lysine for Inhalation Effective in the Treatment of Patients With Cystic Fibrosis and Pseudomonas Aeruginosa Airway Infection?

Christine Shevchenko
Philadelphia College of Osteopathic Medicine, christineshe@pcom.edu

Is Aztreonam Lysine for Inhalation Effective in the Treatment of Patients with Cystic Fibrosis and *Pseudomonas aeruginosa* Airway Infection?

Christine Shevchenko, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In
Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not aztreonam lysine for inhalation is effective in the treatment of patients with cystic fibrosis and *Pseudomonas aeruginosa* airway infection.

STUDY DESIGN: Review of three English language primary randomized controlled trials published in 2008, 2009, and 2011.

DATA SOURCES: Three randomized, double-blind, placebo-controlled studies using Cochrane and Pubmed databases.

OUCOMES MEASURED: Patient oriented outcomes measured included change in respiratory symptoms measured by the Cystic Fibrosis Questionnaire-Revised and need for additional antipseudomonal antibiotics indicative of pulmonary exacerbation.

RESULTS: In both cystic fibrosis (CF) patients who have been treated with standard long term therapy and those who have not, 28 day therapy with aztreonam lysine for inhalation (AZLI) was shown to be effective in the treatment of chronic *Pseudomonas aeruginosa* airway infection. AZLI treatment showed statistical significance in the improvement of patient reported respiratory symptoms compared to placebo. Twice per day versus three times per day dosing did not show a significant impact on outcome. In CF patients with mild respiratory dysfunction, determined by a FEV_1 of > 75%, AZLI treatment did not significantly prevent need for additional antipseudomonal antibiotics during the course of the study.

CONCLUSION: These studies determined that AZLI is more effective at reducing respiratory symptoms in CF patients with chronic *P. aeruginosa* airway infection than placebo. AZLI therapy does not significantly decrease the number of severe pulmonary exacerbations that would require further antipseudomonal antibiotics. Twice or three times per day dosing does not significantly affect the outcomes.

KEY WORDS: aztreonam, monobactam, cystic fibrosis, *Pseudomonas aeruginosa*

INTRODUCTION

Cystic fibrosis (CF) is a chronic, autosomal recessive disease of the secretory glands.[1,2] It is characterized by increased pulmonary secretions which are especially thick and difficult to clear.[1] Common complications include superimposed airway infections and pancreatic insufficiency due to mucus blocked ducts.[1] The most common pathogen of airway infections in CF patients, and one of the most difficult to eradicate, is *Pseudomonas aeruginosa* (*P. aeruginosa*).[1] Chronic airway infections are associated with a progressive decrease in lung function and overall increased patient morbidity and mortality.[1]

Due to the recessive pattern of inheritance for CF, an affected individual must acquire one abnormal gene from each parent. Approximately 30,000 people in the United States are affected by CF, however, over 10 million Americans are carriers of the abnormal cystic fibrosis transmembrane conductance regulator (CFTR) gene.[2, 3] This condition affects all races, ethnicities and genders, but is most commonly found among Northern Europeans.[2] The precise cost of treating CF in recent years is unknown, however data from 1996 shows the direct cost per patient per year was up to $16,300 and lifetime direct costs were between $200,000 and $300,000.[4] The exact number of healthcare visits per year for CF patients has not been explicitly calculated, however the recommendation is for quarterly evaluations, not including visits or hospitalizations for worsening symptoms or pulmonary exacerbations, medication changes, social work visits or dietary evaluations.[5]

CF is caused by an inherited defect in the CFTR gene that encodes for an ion channel protein responsible for controlling salt and water movement within the cell.[2] There are a wide variety of known mutations that can affect the function of the CFTR gene, however all create a dysfunctional protein which results in thick, persistent mucus secretions.[2] Symptoms involve the

sinuses, lungs, skin, liver, pancreas, gastrointestinal tract and reproductive organs and include salty sweat, increased thick mucus production leading to chronic sinus and airway infections, dyspnea, pancreatitis, diabetes, malnutrition, and infertility.[2] Respiratory failure is the most common cause of death in CF patients, and it is due to an accumulation of tissue damage from chronic and/or recurrent pulmonary infections.[2] There is no known cure for CF at this time.[3]

Treatment of CF is multifactorial and involves a variety of body systems and treatment methods. Patients are instructed in a variety of airway clearance techniques including postural drainage, percussion, inflatable vests, pulmonary rehabilitation with exercise training, and breathing strategies.[3,6] Inhaled medications such as mucolytics, antibiotics, bronchodilators and hypertonic saline, as well as oral or IV antibiotics in severe exacerbations, have been utilized for airway infections and worsening respiratory symptomatology.[3,6] Nutrition is another focus, with supplementation implemented involving a high caloric diet, feeding tube, pancreatic enzyme supplementation and specific nutrient supplementation when medically necessary.[3,6] Surgical procedures including nasal polyp removal, endoscopy with lavage, and lung transplantation are employed as a last resort to aid in respiratory function.[3,6]

Currently, tobramycin is the most commonly used inhaled antibiotic for exacerbations of respiratory infections in CF patients, and has been shown to be effective against *P. aeruginosa*.[3,6] Since aztreonam is a monobactam antibiotic that has also been shown to have antipseudomonal properties, many studies have begun to explore inhaled aztreonam lysine as a potential effective intervention to relieve symptoms and treat *P. aeruginosa* airway infection.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not aztreonam

lysine for inhalation is effective in the treatment of patients with cystic fibrosis and *Pseudomonas aeruginosa* airway infection.

METHODS

Three randomized, double-blind, placebo-controlled studies were included in this selective EBM review. The studies involved males and females 6 years of age and older with established CF and *P. aeruginosa* airway infection. Inclusion criteria consisted of studies that were randomized, controlled, double blind and published after 1996, with patients that were 6 years of age and older with current *P. aeruginosa* airway infections. Exclusion criteria comprised of patients under the age of 6 and those that utilized repeated courses of treatment with AZLI.

The intervention was inhaled aztreonam lysine (AZLI) via nebulizer with a formulation of 75 mg of aztreonam and 52.5 mg of lysine monohydratae diluted in 1 mL of 0.17% NaCl. The comparison group received a visually matched placebo via nebulizer with a formulation of 5 mg lactose diluted in 1mL of 0.17% NaCl. Outcomes addressed included patient-reported impact on respiratory symptoms and symptom or health exacerbation requiring use of oral, IV or additional inhaled antipseudomonal antibiotics. Outcomes were measured by utilizing the CF Questionnaire-Revised where points ranged from 0-100 and increasing scores indicated improvement of symptoms, as well as explicitly counting patients who required use of added antipseudomonal antibiotics during the treatment or follow up period specified by the individual study.

Author searched articles within PubMed and The Cochrane Central Register of Controlled Trials (CENTRAL) databases between 2012 and 2013. Searches were conducted using keywords “aztreonam,” “monobactam,” “cystic fibrosis,” and “*Pseudomonas aeruginosa*.” Included articles were published in English, in 2008, 2009 and 2011, and selected based on their

relevance to CF patients with *P. aeruginosa* airway infections and because they addressed patient-oriented outcomes (POEMs). Each article was published in a peer-reviewed journal.

Table 1 – Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
McCoy (2008)[1]	Double-blind RCT	246	≥ 6 yrs old	≥ 6 yrs old, documented CF, current *P. aeruginosa* airway infection, 3+ tobramycin inhalation solution courses w/i last yr $FEV_1 \geq 25\%$ and ≤ 75% predicted, arterial oxygen saturation ≥ 90% on room air	- Current oral corticosteroid use, daily O2 supplementation or intolerance to the study's medications - Recent changes in antimicrobial, bronchodilator, anti-inflammatory, corticosteroid medications or physiotherapy technique/schedule - Acute findings on chest radiograph w/i past 90 days, high AST, ALT, or SCr levels, or airway cultures of *Burkholderia cepacia* w/i past 2 yrs - Pregnant, lactating, lung transplant, or a medical or psychiatric illness interfering with study	156	28 day course of tobramycin inhalation solution (TIS) followed by a 28 day course of 75 mg AZLI with nebulizer BID or TID
Retsch-Bogart (2009)[7]	Double-blind RCT	164	≥ 6 yrs old	≥ 6 yrs old, documented CF, *P. aeruginosa* airway infection, FEV1 ≥ 25% to ≤ 75% predicted, arterial oxygen saturation ≥ 90% on room air	- Anti-pseudomonal antibiotic or azithromycin use w/i past 28 days - Current oral corticosteroid use, daily O2 supplementation >2 L/min at night or intolerance to the study's medications - Recent changes to antimicrobial, bronchodilator, anti-inflammatory or corticosteroid medications or physiotherapy technique/schedule - Acute findings on chest radiograph w/i 90 days, high AST, ALT, or SCr levels, or airway cultures of *Burkholderia cepacia* w/i past 2 yrs - Pregnant, lactating, lung transplant, or a medical or psychiatric illness that interferes with study	40	28 day treatment course of 75 mg aztreonam lysine for inhalation administered by nebulizer TID
Wain-wright (2011)[8]	Double-blind RCT	160	≥ 6 yrs old	≥ 6 yrs, documented CF, *P. aeruginosa* airway infection, $FEV_1 \geq 75\%$ predicted; ≥ 2 chronic or intermittent CF symptoms for ≥ 28 days before baseline	- Pregnant, lactating, lung transplant, or a medical or psychiatric illness that interferes with study participation - Previous enrollment in AZLI trial, or acute findings on chest radiograph - Changes in antimicrobial, bronchodilator, or corticosteroid medications or physiotherapy technique/schedule w/i 7 days -Anti-pseudomonal antibiotic w/i past 28 days -Intolerance to the study's medications	4	28 day course of AZLI with nebulizer TID (doses separated ≥ 4 hrs)

The statistics utilized from the article or calculated by the author included relative benefit increase (RBI), absolute benefit increase (ABI), number needed to treat (NNT), relative risk increase (RRI), absolute risk increase (ARI), number needed to harm (NNH), 95% confidence intervals (CI) and p-values.

OUTCOMES MEASURED

There were a variety of outcomes addressed by each study, however the author utilized outcomes that served as POEM's to address the research question.

McCoy et al (2008) included patients with significant lung disease ($FEV_1 \geq 25\%$ to $\leq$ 75% predicted) and who had been compliant with the standard CF treatment of maintenance tobramycin inhalation solution (TIS) treatment courses in their study. All study participants were administered a 28 day course of open-label TIS (300 mg twice daily) and then randomized into a 1:1:1 grouping of AZLI (75mg of aztreonam, 52.5 mg of lysine monohydrate diluted in 1 mL of 0.17% NaCl solution) either twice or three times daily, or placebo (5 mg lactose diluted in 1 mL of 0.17% NaCl solution) via nebulizer for a treatment period of 28 days. Patients were monitored on Day 14, Day 28, and Days 42, 56, 70 and 84 during the follow up period. The outcome addressed was change in patient reported respiratory symptoms, measured by utilizing the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Minimal clinically important difference (MCID) score of 5 was used by to analyze results as it corresponds to the smallest change in symptoms noticeable by patients. Therefore, a 5 point change or more indicated improved or worsened symptoms. At Day 28 of treatment, patients were categorized as improved ($\geq$ 5 point increase from baseline CFQ-R Respiratory scores), worsened ($\geq$ 5 point decrease from baseline)

or stable/unchanged (< 5 point change). Comparisons between the experimental and the control groups were made throughout treatment and the designated follow up period.

Retsch-Bogart et al (2009) focused on patients with moderate to severe lung disease (determined by a $FEV_1 \geq 25\%$ to $\leq 75\%$ predicted) who had not been administered any inhaled, IV, or oral anti-pseudomonas antibiotics, azithromycin or aerosolized hypertonic saline solution within the past 28 days prior to the date of screening. Patients were split into groups via a 1:1 randomization, with the interventional group receiving 75 mg AZLI administered by nebulizer three times daily for 28 days and the control group receiving a visually matched placebo at the same interval for the same duration of time. The outcome addressed was change in patient reported respiratory symptoms, measured by the CFQ-R. Analysis of the questionnaire and MCID were the same as McCoy et al. Patients were followed throughout treatment and the 2 week follow up period. Comparisons between the experimental and control groups were made.

Wainwright et al (2011) selected for patients with mild lung disease ($FEV_1 \geq 75\%$ predicted). Patients were randomly assigned (1:1) to treatment with 75 mg AZLI or placebo by nebulizer three times per day, doses separated by more than 4 hrs, for 28 days. Patients were monitored at Day 14, 28, and 42 for follow-up. The outcome was symptom(s) or health exacerbation requiring use of oral, IV, or additional inhaled antipseudomonal antibiotics during the study (28 day treatment period and 14 day follow up). The outcome was measured by explicitly counting the number of patients who required use of additional antipseudomonal antibiotics in the control and experimental groups.

RESULTS

The focus of this EBM review is patient oriented outcome measures, so only those will be presented in the following section. Two of the randomized control trials, McCoy et al and

Retsch-Bogart et al, utilized the CFQ-R to determine patient reported respiratory symptoms as a means to evaluate the treatments. The third study assessed pulmonary exacerbation that required additional antipseudomonal antibiotics to determine patient outcome.

In McCoy et al, of the 246 patients enrolled and assigned groups by a 1:1:1 randomization, 211 completed the 28 day course of TIS and received at least 1 dose of AZLI or placebo, and therefore comprised the intention to treat population.[1] 173 patients (82%) completed the 28 day treatment, and 90 (43%) completed the follow-up period.[1]

Responses of twice versus three times per day dosing placebo groups were pooled for the efficacy analyses and were compared with the AZLI-pooled group. Analysis of CFQ-R used the last observation carried forward convention. At the conclusion of treatment (Day 28), adjusted mean CFQ-R respiratory scores increased 5.01 points in the AZLI-pooled group compared to placebo (95% CI, 0.81 to 9.21; P = 0.020), showing significance for AZLI in decreasing respiratory symptoms versus placebo.[1] During the treatment period, the AZLI-treated patients had more improved CFQ-R respiratory scores and less worsened respiratory scores compared with placebo-treated patients (overall categorical comparison, P = 0.029).[1] 52% of AZLI treated patients and 37% of placebo had a greater than 5 point increase in respiratory score and 28% of AZLI versus 38% of placebo had a greater than 5 point decrease in respiratory score.[1] For improved CFQ-R scores, the RBI was calculated to be 40.54%, the ABI was 15% and the NNT was seven (Table 2). Therefore, for every 7 patients treated with AZLI, one more patient showed improved respiratory symptoms compared to the control. For worsened CFQ-R scores, the calculated RRI was -26.32%, the ARI was -10% and the NNH was -10 patients (Table 3). This means that for every 10 patients treated with AZLI, one less had worsened respiratory symptoms.

Table 2. Improved Respiratory Score on CRQ-R During Treatment Period (Day 0-28)[1]

CER	EER	RBI	ABI	NNT
37%	52%	41%	15%	7 patients

Table 3. Worsened Respiratory Score on CRQ-R During Treatment Period (Day 0-28)[1]

CER	EER	RRI	ARI	NNH
38%	28%	-26%	-10%	-10 patients

The study of Retsch-Bogart, et al focused on patients without recent use of antipseudomonal antibiotics or azithromycin and had a primary efficacy endpoint of change in patient reported respiratory symptoms analyzed through the use of the CFQ-R scale. Patients were randomly assigned (1:1) a 28 day treatment of 75 mg AZLI or placebo at three times per day dosing and monitored throughout treatment and a 14 day follow up period.[7] Of the 164 patients who enrolled and began treatment, 138 completed the 28 day treatment period and 124 (76%) completed the study through the follow-up.[7] At day 28, patients were categorized as improved, worse, or stable based on their change from baseline CFQ-R respiratory scores. Five point or greater changes were determined to be the minimal clinically important difference and used to dichotomize the patient data into the categories by Retsch-Bogart, et al.[7]

The adjusted mean CFQ-R respiratory scores showed a significant improvement in the AZLI group and decline in the placebo group at Day 28, the conclusion of the treatment period (9.7 point difference, 95% CI, 4.3 to 15.1; $P < 0.001$).[7] Also established at the conclusion of treatment, the data showed AZLI was shown to be significantly better in improving CFQ-R respiratory scores, and less likely to cause worsened respiratory scores, compared to the placebo group ($P = 0.006$ for overall comparison).[7] In the AZLI group, 56% showed a greater than 5 point increase in respiratory score and 25% showed a greater than 5 point decrease in respiratory score, compared with the placebo group of 37% and 45%, respectively.[7] The calculated NNT was 6, meaning that for every 6 patients treated with AZLI, one more had improved respiratory

symptoms (Table 4). The calculated NNH was -5, meaning that for every 5 patients treated with AZLI, one less patient will have worsened respiratory symptoms (Table 5).

Table 4. Improved Respiratory Score on CRQ-R at Treatment End (Day 28)[7]

CER	EER	RBI	ABI	NNT
37%	56%	51%	19%	6 patients

Table 5. Worsened Respiratory Score on CRQ-R at Treatment End (Day 28)[7]

CER	EER	RRI	ARI	NNH
45%	25%	-44%	-20%	-5 patients

In Wainwright, et al, patients were treated with 28 days of 75 mg AZLI or placebo at three times per day dosing and followed for an additional 14 days.[8] The study enrolled and randomly assigned 160 patients, 156 (98%) of which completed the study.[8] Efficacy was assessed by comparing the number of patients that required additional oral, IV, or inhaled antibiotics during the treatment period and follow up. The need for additional antibiotics was similar amongst both the experimental and control groups from baseline through the follow up period (AZLI, 25%; placebo, 25.9%; $p > 0.999$).[8] AZLI treatment did not significantly prevent symptoms or health exacerbations requiring additional antibiotics. The calculated NNH was -112. This means that for every 112 patients treated with AZLI, one less will require additional antipseudomonal antibiotics than compared to the control (Table 6)

Table 6. Need for Additional Antipseudomonal Antibiotics During Study[8]

CER	EER	RRI	ARI	NNH
25.9%	25%	3.5%	0.9%	-112 patients

DISCUSSION

To summarize the data within the three studies analyzed, it can be concluded that 75 mg of AZLI is effective at reducing respiratory symptoms in CF patients with chronic *P. aeruginosa* airway infection and moderate to severe respiratory dysfunction (FEV_1 between 25% and 75% predicted) compared to placebo. AZLI therapy did not significantly decrease the severe

pulmonary exacerbations that would require further antipseudomonal antibiotics in patients with mild respiratory dysfunction, or a FEV1 > 75% predicted. However, in the study that evaluated need for additional antibiotics, patients had a modest symptomatic baseline, and therefore any deviation from that may have prompted patients to seek additional treatment whether they truly needed it or not.

There were several limitations and flaws in the three research studies. While this EBM review included a population of CF patients over the age of 6, all three of these studies had significantly more adults participate than children. The study performed by McCoy, et al specifically had 78% of their participants over the age of 18.[1] Retsch-Bogart, et al utilized a population where 77.4% were over the age of 18. As a general rule, along with standards of care at this point in time, more adults than children will have the moderate to severe lung impairment necessary to enter this specific study, and their disease progression may be more responsive to treatment. Therefore, these two studies may conclude a greater efficacy for children <18 years old than might be accurate. Also with Retsch-Bogart, et al, the participants were treated with TIS before AZLI or placebo. This makes it difficult to state clearly whether AZLI alone showed significant benefit to patients, or if it was the adjunctive treatment with TIS that provided significant symptom improvement.

Two of the three studies in this EBM review shared a significant patient drop out rate. While there were a wide variety of reasons as to the cause, poor patient compliance is a large issue both in research and in the medical field. In the United States, as of 2005, of the long term treatments currently available, specifically TIS or macrolide therapy, 46% of eligible CF patients over the age of 6 were not receiving maintenance treatment.[7] In addition, patient compliance rates were less than ideal, ranging from 51% in older patients to 73% in younger individuals.[7]

Researchers and medical professionals need to work together with patients to develop additional treatment options for patients with chronic *P. aeruginosa* airway infection and emphasize the importance of treatment compliance for reducing morbidity and mortality.

CONCLUSION

According to the data generated from the three research studies compiled in this systemic review, AZLI has shown to be an effective treatment for patients with CF and chronic *P. aeruginosa* airway infection, whether pretreated with TIS and received proper maintenance therapy or not.

Future research studies need to address whether inhaled antibiotic monotherapy is more efficacious in preventing pulmonary exacerbations and treating *P. aeruginosa* airway infections or if multiple products would provide greater benefit to patients. A longitudinal study to assess patient health both pre- and post-treatment periods with inhaled antibiotics, and to determine if multiple treatments would be more or less valuable to CF patients with chronic *P. aeruginosa* airway infection would be a useful undertaking. AZLI evaluated in the short term in these three studies has shown to be effective, but further investigation is necessary to determine if its' use as a long-term suppressive therapy would be beneficial.

Cystic fibrosis is a challenging condition to treat. Pulmonary involvement is debilitating for patients with regards to their ability to carry out daily activities. *P. aeruginosa* is notorious for being difficult to eradicate and responsible for increased mortality of those infected.[1] However, medical professionals have limited antibiotics that have shown to be both safe and effective in *P. aeruginosa* treatment. With continued research and patient compliance, CF patients will have improved quality of life and clinical outcomes.

REFERENCES

1. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178(9):921-928. doi: 10.1164/rccm.200712-1804OC; 10.1164/rccm.200712-1804OC.

2. Explore Cystic Fibrosis. National Heart, Lung, and Blood Institute Website. http://www.nhlbi.nih.gov/health/health-topics/topics/cf/ Accessed September 29, 2013.

3. About Cystic Fibrosis. Cystic Fibrosis Foundation Website. http://www.cff.org/AboutCF/ Accessed September 29, 2013.

4. Krauth C, Jalilvand N, Welte T, Busse R. Cystic fibrosis: cost of illness and considerations for the economic evaluation of potential therapies. *Pharmacoeconomics.* 2003;21(14):1001-24.

5. Cystic Fibrosis Outpatient Care Clinic. Nationwide Children's Website. http://www.nationwidechildrens.org/cystic-fibrosis-outpatient-clinic Accessed September 29, 2013.

6. Cystic Fibrosis. MayoClinic Website. http://www.mayoclinic.com/health/cystic-fibrosis/DS00287 Accessed September 29, 2013.

7. Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest*. 2009;135(5):1223-1232. doi: 10.1378/chest.08-1421; 10.1378/chest.08-1421.

8. Wainwright CE, Quittner AL, Geller DE, et al. Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and P. aeruginosa. *J Cyst Fibros*. 2011;10(4):234-242. doi: 10.1016/j.jcf.2011.02.007; 10.1016/j.jcf.2011.02.007.