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Abbreviated Class Review: Inhaled Antibiotics and Dornase Alfa for Cystic Fibrosis

Month/Year of Review: August 2012 **End of literature search:** May 2012
Drugs Included: Tobramycin (Tobi®), Aztreonam (Cayston®), Dornase alfa (Pulmozyme®)

Issues:

- What evidence is available for the efficacy and safety of inhaled tobramycin, aztreonam, and dornase alfa for cystic fibrosis (CF)?
- Is there comparative evidence that either inhaled tobramycin or aztreonam is superior in efficacy or safety?
- Are there specific subpopulations or clinical situations in which one inhaled antibiotic provides clear benefit over another?

Conclusions:

- There is insufficient long-term evidence available for all drugs in the class. The longest study for dornase alfa (DA) is 2 years and tobramycin inhalation solution (TIS) is 33 months. There is no evidence for aztreonam lysine for inhalation (AZLI) beyond a 28-day course.
- Efficacy and safety has not been established for use of AZLI in patients <7 years old, TIS < 6 years old, and DA <5 years old.
- There is insufficient comparative evidence for efficacy and safety of TIS and AZLI.
- There is moderate quality evidence that overall, the frequencies of pulmonary exacerbations, hospitalizations, and parenteral antipseudomonal antibiotic use are improved with chronic suppressive therapy with TIS in patients with mild to severe CF.
- There is low to moderate quality short term evidence that AZLI modestly improves lung function as measured by FEV1, improves patient-reported respiratory symptoms, and lengthens the time to use of additional antipseudomonal antibiotics compared to placebo.
- A Cochrane review showed demonstrated low quality evidence that inhaled antibiotics improved lung function in patients with CF and that TIS, specifically, significantly decreased hospitalization among patients.
- AZLI and TIS were well tolerated throughout all clinical trials, with cough being the most frequently reported adverse event. There have been post-marketing reports of hearing loss in patients using TIS.
- The Cystic Fibrosis Foundation evaluated 19 trials of DA in a total of 3140 patients. Long-term studies show a significant improvement over placebo in lung function and improvement in quality of life, while there is conflicting evidence on the effect of DA on the incidence of pulmonary exacerbations. A Cochrane review of DA, including 2469 participants, found no statistical difference in mortality compared to placebo or hypertonic saline. Spirometric lung function was improved in the treatment groups at multiple time frames up to two years.
- The only significant adverse effects found in clinical trials of DA compared to placebo were voice alteration and rash.

Recommendations:

1) Due to more published efficacy and safety data and a demonstrated continued benefit over 2 years and decrease in hospitalizations, make TIS a preferred agent on the PDL with a quantity limit of 56 vials/56 days (for cycles of 28 days on followed by 28 days off therapy)
2) Make AZLI a non-preferred agent due to a lack of comparative evidence or demonstrated clinical benefit in efficacy or safety over TIS, and limit to patients with cystic fibrosis with a quantity limit of 84 vials/56 days (for cycles of 28 days on followed by 28 days off therapy)
3) Make DA a preferred agent on the PDL with a quantity limit of 30 vials/30 days

Drug Products[1-3]	FDA approval [1-3]	FDA approved indications[1-3]	Usual Dose/Duration[1-3]	Potential Off-label Uses	Other Considerations
Tobramycin inhalation solution (Tobi)	1997	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*	300mg inhaled twice daily (as close to 12 hours apart and not less than 6 hours apart). Tobi should be administered in repeated cycles of 28 days on drug followed by 28 days off drug.	Bronchiectasis for patients without cystic fibrosis and chronic bronchial infection with *Pseudomonas aeruginosa*	Inhaled tobramycin is administered using a hand-held PAR LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aide compressor.
Aztreonam inhalation solution (Cayston)	2010	Improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*	75mg administered 3 times a day for a 28-day course, followed by 28 days off therapy	Bronchiectasis for patients without cystic fibrosis and chronic bronchial infection with *Pseudomonas aeruginosa*	Patients should use bronchodilator prior to administration of aztreonam. Aztreonam must be administered using an Altera nebulizer system.
Dornase alfa (Pulmozyme)	1993	Management of cystic fibrosis patients to reduce the frequency of respiratory infections that require parenteral antibiotics in patients with forced vital capacity (FVC) >40% of predicted; in conjunction with standard therapies, to improve pulmonary function in patients with cystic fibrosis.	2.5 mg daily using a recommended nebulizer	Non-cystic fibrosis pre-term infants suffering from atelectasis	Patients should use a recommended nebulizer/compressor system.

Methods:
A Medline literature search ending May 2012 for meta-analyses or randomized active-controlled trials (RCT's) comparing all included drugs to each other or to other drugs for the treatment of cystic fibrosis was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources. Results of this search included two RCT's for tobramycin, 3 RCT's for aztreonam, two Cochrane systematic reviews, and one evidence based treatment guideline.

Background:
CF is an inherited chronic disease that affects about 30,000 children and adults in the U.S. and about 70,000 people worldwide. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein found in exocrine tissues.[4] Transport of chloride, sodium, and bicarbonate are disrupted, which may lead to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions.[4]

Although multiple organ systems are affected in CF patients, pulmonary disease is the leading cause of morbidity and mortality in patients with CF. The thickened, viscous airway secretions obstruct the airway, resulting in endobronchial infection, and an exaggerated inflammatory response that may lead to development of bronchiectasis and progressive obstructive airways disease.[4,5] There are a number of treatment options for the maintenance of lung health in CF patients, including aerosolized antibiotics, recombinant human deoxyribonuclease (rhDNase), hypertonic saline, and anti-inflammatory agents. Although some of these treatments may be administered by multiple routes (intravenous, oral, inhaled), administration by inhalation is preferred, as this method of delivery promotes high concentrations of the drug in airways and lower concentrations in plasma, minimizing the system toxicity.[6]

Bacterial colonization of the airway secretions with *Pseudomonas aeruginosa, Haemophilus influenza, Staphylococcus aureus or Burkholderia cepacia* may occur in patients with CF. *P. aeruginosa* is the most common pathogen in CF patients, and chronic colonization may cause respiratory insufficiency and eventual respiratory failure.[7] Consequences in this patient population include increased morbidity and mortality. Therefore, therapies that may decrease or eliminate colonization in addition to treating exacerbations are essential to improving outcomes. The CF foundation defines clinically meaningful endpoints as time to need for additional antipseudomonal antibiotics and hospitalization. The Cystic Fibrosis Questionnaire-Revised (CFQR) has been validated as a subjective measure to assess multiple domains of patient quality of life and is approved by the FDA as a patient reported outcome measure. The clinical importance is uncertain due to no known correlation to other clinically meaningful endpoints.

There are two inhaled antibiotic agents approved for the management of patients with CF that is complicated by *Pseudomonas aeruginosa,* TIS and AZLI. AZLI is a monobactam antibiotic that was FDA approved in 2010. It is administered via nebulizer at a dose of 75mg three times daily for 28 days, followed by 28 days off therapy. TIS is an aminoglycoside antibiotic that was FDA approved in 1997 and is administered at a dose of 300mg twice daily for 28 days, followed by 28 days off therapy.[1,2] Inhaled antibiotics help reduce exacerbations and improve lung function by reducing *P.aeruginosa* concentrations. Guidelines published by the Cystic Fibrosis Foundation in 2007 (prior to approval AZLI) recommend the routine use of TIS in patients with chronic *P. aeruginosa* infections for asymptomatic and symptomatic CF patients ≥ 6 years old cultures to improve lung function and/or reduce exacerbations. Data from their registry suggests that almost 70% of eligible patients use inhaled tobramycin.[5] AZLI is the only other inhaled antibiotic approved for use in CF patients.[2]

DA is a purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme that assists in the breakdown of DNA which accumulates in cystic fibrosis patients. It treats the thickened secretions in the lungs that facilitate bacterial infection and airway obstruction in CF patients. It works by degrading the excess DNA that accumulates with CF mucus, and promoting airway clearance. DA was approved in 1993 for the management of cystic fibrosis patients to reduce the frequency of respiratory infections that require parenteral antibiotics in patients with forced vital capacity (FVC) >40% of predicted; in conjunction with standard therapies, to improve pulmonary function in patients with CF.[3] The Cystic Fibrosis Guidelines recommend use of DA in patients with asymptomatic, mild, moderate, or severe lung disease to improve lung function and reduce exacerbation.[5]

Hypertonic saline (HS) inhalation increases hydration of airways surface liquid in patients with CF, which helps improve mucociliary clearance. For patients 6 years of age and older with C , the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations (fair level of evidence, grade of recommendation B).[5]

Systematic Reviews:

CF GUIDELINES

The Cystic Fibrosis Foundation published treatment guidelines on chronic medications for maintenance of lung health in 2007, prior to the FDA approval of AZLI. The guidelines strongly recommend TIS to improve lung function and reduce exacerbations in patients ≥6 years old, who have moderate to severe lung disease and with *P. aeruginosa* persistently present in cultures of the airways. The guidelines also recommend chronic use of TIS to reduce exacerbations in patients ≥6 years old that are asymptomatic or with mild lung disease, and with *P. aeruginosa* persistently present in cultures of the airways.[5]

The recommendations are based on results from a systematic review of 6 trials, with a total of 679 participants. Three of the studies showed that patients taking TIS had a significantly improved forced expiratory volume at one second (FEV_1), with a net benefit in lung function of 7.8 to 12%. The largest study (n=520), reported a 26% reduction in hospitalizations and a 36% reduction in the use of IV anti-pseudomonal antibiotics for those using tobramycin compared to placebo.[5]

The Cystic Fibrosis Foundation recommends the use of DA for CF patients with mild lung disease, and they strongly recommend its use for CF patients with moderate to severe lung disease. DA was studied in 19 trials (n=3140) of varying lengths. Most short-term studies showed a significant improvement in FEV_1 by 11.2-15.4%, and long-term studies uniformly demonstrated improvement in lung function. One study (n=968) found that FEV_1 increased by 5.8% compared to placebo after 24 weeks of treatment with dornase alfa, and another study (n=320), saw a similar improvement in FEV_1 (net benefit 7.3%) in patients with severe CF lung disease who were treated for 12 weeks. DA was well tolerated as there were few adverse events that were increased by DA compared to placebo. The most common adverse event was voice alteration.[5]

INHALED ANTIBIOTIC COCHRANE REVIEW

A 2009 Cochrane review found 19 trials, including 1724 patients from a literature search ending January 2011, which evaluated the effect of any inhaled antibiotic treatment as long-term therapy in people with CF, compared to placebo or usual treatment. Investigators found that inhaled antibiotics improved lung function and reduced the frequency of exacerbations during the study and that the best evidence is for inhaled tobramycin. Further research is necessary to show maintenance of benefits, and to establish a preferred antibiotic therapy and dosage regimen. There was significant heterogeneity among the trials, in terms of design, drug type, dose and delivery, duration of treatment and outcome measures, which complicated interpretation of the results and reduces the validity of pooling the data. [14]

Eight trials, including 1152 patients, compared TIS to usual treatment from 1 to 33 months, with the majority of participants (45%) included in one high quality trial. Three trials reported the mean change in % predicted FEV_1, which was greater for inhaled antibiotics compared to placebo [mean difference: 9.48 (95% CI 5.92, 13.04)]. Two of these trials (81.9% of the evaluable population) studied the effectiveness of TIS. Three trials reported the change in % predicted FVC, which was greater for inhaled antibiotics compared to placebo [mean difference 8.04 (95% CI 4.24, 11.85)]. Two of these trials (81.9% of the evaluable population) studied the effectiveness of TIS. The largest trial included in the Cochrane review, with 520 participants, reported a mean increase in FEV_1 of 10% in the TIS treated group, compared to a 2% decrease in mean FEV_1 in the control group after 20 weeks ($P<0.001$). The same trial reported a mean increase in FVC of 8% in the TIS treated group, compared to a mean of a 1% decrease in the mean FVC in the control group.[14]

Two trials with a duration of three to 12 months had outcomes for hospital admissions available for analysis. There was a significant risk reduction for one or more hospital admissions [RR 0.72 (95% CI 0.60, 0.86)]. One trial of more than 12 months had a nonsignificant risk reduction for at least

one hospital admission [RR 0.59 (95% CI 0.34, 1.05)]. The longest trial was 32 months and found no significant difference for hospital admissions [RR 0.80 (95% CI 0.39, 1.65)]. All four of these trials were conducted using TIS as the study drug.[14]

Two trials included AZLI. In one trial, Participants were treated with aztreonam lysine for 28 days and followed after this period to measure the time to a pulmonary exacerbation treatment; estimated as 92 days in the aztreonam lysine group and 71 days in the control group (P = 0.007). This study did not utilize intent to treat analysis, had a moderate rate of patient discontinuation, and was of short duration. The second study evaluated CFQR as the primary endpoint but was not included in the analysis because it was classified as "awaiting classification" until more information available.[14]

There was no evidence of clinically important adverse effects during the trials. Overall, patients who used inhaled antibiotics experienced more resistance to antibiotics, tinnitus and change in voice than those in placebo groups. Five trials measured renal function and found no significant evidence of renal impairment. However, one trial found that nine people in the TIS group and the placebo group saw transient increases of 50% or more in the creatinine level. Five trials measured audiometry and found that four stated that no abnormality was found.[14]

DORNASE ALFA COCHRANE REVIEW

A 2010 Cochrane review on DA in CF set out to determine whether DA improved mortality and morbidity compared to placebo or other mucolytics (hypertonic saline, acetylcysteine, and mesna) and to identify adverse effects. The last data search occurred on July 17, 2009. A total of 43 trials were identified, but only trials that were randomized or quasi-randomized which compared DA to placebo, standard therapy, or another mucolytic were included in the analysis. Fifteen trials remained after exclusion criteria were applied, which contained 2469 participants. Of these studies, 12 compared DA to placebo or no DA treatment; one compared daily DA with hypertonic saline and alternate day DA; and two compared daily DA to hypertonic saline. The timeframe of these studies ranged from six days to two years and included patients of all ages.[13]

Outcomes of the review were grouped into the following timeframes: one, three, six, and twelve months and annually thereafter. The primary outcomes were changes in lung function (FEV_1 and FVC) from baseline, change from baseline in quality of life, mean number of exacerbations, and number of deaths. Secondary outcomes were number of days treatment with IV antibiotics, number of days treatment with oral antibiotics, number of days in hospital due to respiratory exacerbations, change in weight from baseline, number of adverse events such as alteration in voice, hemoptysis, bronchospasm, and cost.[13]

Dornase alfa versus placebo or no dornase alfa treatment.
Overall there was no statistical difference in mortality between treatment groups at any time period. For the mean percentage change of FVC in DA treated group versus placebo there was improvement at one month [mean difference 7.52 (95% CI 1.34, 13.69)], three months [mean difference 5.10 (95% CI 1.23, 8.97)], six months [mean difference 3.80 (95% CI 2.62, 4.98)], but not at two years [mean difference 0.70 (95% CI -1.24, 2.64)]. The only identified increased adverse effect was voice alteration and rash. No differences were seen in mean number of days of IV antibiotics at three months [mean difference 2.96 (95% CI -7.29, 1.37), or mean number of inpatient treatment at 3 months [mean difference 0.92 (95% CI -2.19, 4.05)]. For safety outcomes there was no difference in hemoptysis, dyspnea, or pneumothrax. There was an increase in voice alteration at one month in the treatment group [mean difference 4.03 (95% CI 1.29, 12.62), three months [RR 2.87 (95% CI 1.44, 5.71), but not at six months [RR 1.73 (95% CI 0.69, 4.34). There was increase in the incidence of rash at two years [RR 4.63 (95% CI 1.35, 15.89)].[13]

Dornase alfa versus mucolytic
There was a reported 8% (95% CI 2, 14%) increase in FEV1 from baseline in the DA group compared to hypertonic saline. There were no deaths reported in any of the trials. There was no difference in number of inpatient days of treatment when DA was compared to hypertonic saline [mean difference -0.4 (95% CI -2.32, 1.52). The most frequently reported adverse events were increased cough, coryza, throat infection, allergic reaction to antibiotic, wheeze, breathlessness, hemoptysis, chest pain, and oral thrush.[13,15]

Randomized Controlled Trials (Evidence table in Appendix 1).
There are no published head to head trials comparing TIS to AZLI. An open-label, randomized, phase 3 trial, sponsored by Gilead Sciences, has been conducted comparing AZLI to TIS. Preliminary results have been published only in abstract form. 268 patients received 28-day, intermittent, repeating courses of either treatment over 24 weeks. The co-primary endpoints were non-inferiority of AZLI for mean percent change in FEV1 percent predicted at Day 28 compared to baseline and superiority of AZLI for mean actual change in FEV1 percent predicted across three treatment cycles (six months).

<u>TOBRAMYCIN</u>
Pivotal studies evaluating the use of tobramycin have been included in the Cystic Fibrosis Foundation Pulmonary Guidelines published in 2007, as well as a 2009 Cochrane Review of inhaled antibiotics. Since the publication of these reviews, one additional study has been published evaluating the safety and efficacy of TIS.[8]

In the Early Inhaled Tobramycin for Eradication (ELITE) trial, the short and long term efficacy of tobramycin inhalation solution (TIS) 300mg/5ml twice daily was evaluated in CF patients with early onset *P. aeruginosa* infection (n=88). All patients received TIS twice daily for 28 days, at which

point they were randomized to either discontinue TIS (28-day group) or receive an additional 28 days of therapy (56-day group). Patients were excluded from the efficacy analysis if there was no eradication at 1 month after their last dose of TIS, protocol deviation or use of prohibited medications. This trial was rated of poor quality because it was not blinded which may have increased the risk of bias and included a high attrition rate.[8] Of the 88 patients randomized, only 65 were included in the efficacy analysis (74%). [8]

AZTREONAM

The efficacy and safety of AZLI, dosed 75mg two or three times daily, has been studied in two phase III, randomized, placebo-controlled trials (AIR-CF1 and AIR-CF2), and a phase IIIb published study (AIR-CF4). Efficacy endpoints and inclusion/exclusion criteria varied across studies.[6,18]

AIR-CF1 was a fair quality, randomized, double-blind, placebo-controlled, international study (n=164) which evaluated the short-term efficacy and safety of AZLI in patients with cystic fibrosis, *P. aeruginosa* infection, and moderate-to-severe lung function [FEV_1 25%-75% predicted].[9] Patients ≥6 years old with no recent use of anti-pseudomonal antibiotics or azithromycin were treated with 75mg AZLI three times a day for 28 days or placebo and monitored for 14 days after study completion.[9] The primary endpoint was the change in patient-reported respiratory symptoms using the CF-Questionnaire-Revised (CFQ-R) Respiratory Scale. The CFQ-R scale is a validated, disease-specific, health related quality-of-life instrument that meets most of the US FDA guidelines on patient reported outcomes.[6] After 28 days, patients treated with AZLI saw an improved mean CFQ-R respiratory score compared to placebo [9.7 points (95%CI 4.3, 15.1), p<0.001]. Although the scores of both groups declined after treatment, at day 42, the treatment difference was still significant [6.3 points (95% CI 1.2, 11.4), p=0.15). The minimum clinically important difference for clinically stable patients is 5 points for the CFQR. The increase in disease scores was independent of disease severity, although patients treated with AZLI also saw a significant improvement in all secondary endpoints of FEV_1 (10.3% predicted, p<0.001), sputum *P. aeruginosa* density (-1.453 log 10 cfu/g, p<0.001), and non-respiratory CFQ-R scales (e.g. eating, emotional functioning, health perceptions), compared to placebo.[9]

AIR-CF2 was a fair quality, randomized, double-blind, placebo-controlled, multicenter study (n=211) which evaluated maintenance treatment for a *P. aeruginosa* infection in patients with CF. This study included patients ≥6 years old who had a pulmonary *P. aeruginosa* infection requiring ≥3 courses of TIS within the previous year.[6,10] Patients were randomized into one of three treatment groups (placebo, AZLI twice daily or AZLI three times daily) and treated for 28 days and followed up with for an additional 56 days (day 84). The primary efficacy endpoint was the time to need for inhaled or intravenous anti-pseudomonal antibacterials to treat symptoms of pulmonary exacerbations. The median time to need additional inhaled antibiotics in patients treated with AZLI was 21 days longer compared to the placebo group (92 vs 71 days, measured from baseline; p=0.007). Pulmonary function was also improved in AZLI patients compared to placebo. Pooled data for AZLI showed a mean change in FEV_1 of 6.3% [95% CI 2.5, 10.1); p=0.001], and a significant improvement in mean change in CFQ-R score [5.01 points (95% CI 0.81, 9.21); p=0.02].[10] The prespecified statistical plan compared subjects in each treatment regimen to the corresponding placebo regimen, however there was not sufficient power to compare dosage regimens and the data was pooled.[6]

AIR-CF4 is a fair quality phase IIIb trial with a similar study design to AIR-CF1, but extends the efficacy and safety evaluation of AZLI to include patients with CF, *P. aeruginosa* airway infection, and milder impairment of lung function (FEV_1 >75% predicted).[11] Patients were randomized to a 28-day course of AZLI or placebo, administered three times daily. The primary endpoint was the change from baseline at day 28 on the CFQ-R Respiratory Scale. Patients treated with AZLI saw a non-statistically significant improvement in CFQ-R score of 1.80 versus placebo [(95% CI: -2.83, 6.44); p=0.443)]. Statistically significant treatment effects were seen in AZLI-treated patients for several secondary endpoints: change from baseline at day 28 for adjusted mean log 10 PA CFUs in sputum (AZLI -1.4, placebo -0.14; p=0.016), and relative change in FEV_1% predicted (AZLI 0.29%, Placebo -2.5%; p=0.21). This study did not meet its primary endpoint, and authors suggest that the sensitivity of the CFQ-R is not sufficient for patients with modest symptoms at baseline, or the study may not have been adequately powered to detect a change.[11]

Safety/tolerability:

AZTREONAM:

Overall, in clinical trials, AZLI was well tolerated. Most adverse events were mild to moderate in severity, and the most commonly reported adverse events were associated with respiratory symptoms, such as cough, productive cough, nasal congestion, respiratory tract congestion, wheezing and pharyngolaryngeal pain.[6,11] The observed respiratory symptoms are consistent with those generally seen in patients with cystic fibrosis lung disease, and there were no statistically significant differences between treatment groups in drug-related adverse events or serious adverse events.[6]

In AIR-CF1, the only adverse event with a statistically significant difference in incidence between treatment groups was productive cough (12% in AZLI-treated patients vs. 25% in placebo-treated patients; p=0.047).[9] During the study, 5% of AZLI-treated patients were hospitalized, compared to 14% of placebo-treated patients; the difference was not statistically significant (p=0.064).[6] Six AZLI-treated patients and 13 placebo-treated patients discontinued the study due to an adverse event. Sixteen of these patients required treatment with non-study anti-pseudomonal antibiotics and had symptoms indicative of pulmonary exacerbation. There were no deaths or reports of anaphylaxis reported in this study.[9] In AIR-CF2, there were no statistically significant differences between treatment groups in the type and incidence of adverse events. Overall, seven patients were hospitalized during the treatment period for pulmonary exacerbations (AZLI-BID:2, AZLI-TID:4, placebo-1). No deaths were reported during this study period.[10]

The safety profile of AZLI was similar in AIR-CF4. The most common adverse events seen in both treatment groups were cough, productive cough, respiratory tract congestion, fatigue, pulmonary function test decreased, and abdominal pain. Abdominal pain is the only adverse effect that occurred at a higher rate in one group than the other (12.3% placebo, 1.3% AZLI, p=0.01). Serious adverse events occurred in 11.8% of AZLI-treated patients and 3.7% of placebo-treated patients (p=0.073), and all of these adverse events resulted in hospitalizations, but none were considered to be treatment related. There were no deaths in this study.[11]

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Appendix 1:

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	Efficacy Results[2] (CI, p-values)	ARR / NNT	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating[4]; Comments
1. Ratjen et al. 2010[8]. RCT, OL, MC	1. TIS 300mg/5ml x 28 days n=45 2. TIS 300mg/5ml x 56 days n=43	• ≥ 6 months old • Confirmed CF • First/early PA infection (new detection of PA after negative cultures for ≥ 1 yr and ≥ 4 negative cultures available or up to 2 yrs with 4 negative cultures in the absence of anti-pseudomonal treatment	Median time to recurrence of any strain of PA: 28 day group: 26.12 months 56 day group: 25.82 months HR 0.81; 95% CI 0.37 to 1.75 Difference: 0.3 months 95% CI (0.37,2.75) P=0.593	N/A	Treatment emergent adverse events: 28 day group: 73% 56 day group: 58% Serious adverse events: 28 day group: 14% 56 day group: 12% P-values not reported	N/A	Quality Rating: Poor **Internal Validity: RoB** Selection: The number of subjects analyzed was lower than investigators initially planned. Unclear on generation of randomization sequence. Performance: This was an open-label study, increasing the risk of bias. Good adherence in both groups. The comparato used of TIS for 56 days is not standard treatment or an indicated length of therapy in CF. Detection: Patient's selected in routine clinic visits with positive P. aeruginosa diagnostic test causing possible increased diagnostic interventions. Attrition: Patients who received at least one dose of the study medication were included in the analysis, however, if there was no PA eradication at 1 month after their last dose of TIS, protocol deviation or use of prohibited medications, patients were excluded from analysis. Although 88 patients were randomized, only 65 were included in the efficacy analysis. **External Validity:** Recruitment: Only included patients who regularly attended outpatient clinic appointments. Patient Characteristics: Appropriate Setting: Clinic Setting Outcomes: Microbiological outcome and not clinical outcome used as primary endpoint

2. Retsch-Bogart et al.[9] 2009 (AIR-CF1) Phase 3, RCT, DB, MC	1. AZLI 75mg TID x 28 days n=80 2. Placebo (PBO) n=84	• ≥6 yrs old • Cystic fibrosis • Positive for PA on throat swab or sputum culture • FEV_1 ≥25% to ≤75% of predicted • No antipseudomonals within 4 weeks	Δ in CFQ-R score: Day 28 treatment difference: 9.7 points 95% CI (4.3, 5.1) P<0.001 Day 28 mean FEV_1 (% change from baseline) AZLI: 7.9% PBO: -2.4% Diff: 10.3%; 95% CI (6.3-14.3) P<0.001 Hospitalizations AZLI: 5% PBO: 14% P=0.064	N/A N/A N/A	Productive cough: AZLI: 10 (12.5%) PBO: 21 (25%) P=0.047 Incidence of all other adverse events was similar between treatment groups.	ARR: 12.5% NNT: 8	Quality Rating: Fair **Internal Validity: RoB** Selection: Computer generation central randomization schedule, unclear concealment of allocation. Slightly older mean age in placebo group. Performance: Short term efficacy measured (1 cycle of treatment), double-blinded Detection: Unclear blinding of evaluators. Attrition: Efficacy and safety analyses included all randomly assigned patients receiving one or more doses of AZLI/placebo. FEV1 and CFQ-R analyses used the last-observation-carried-forward convention. 84% of patients completed treatment and only 75% of patients completed follow-up **External Validity:** Recruitment: N/A Patient Characteristics: Patients included in this trial were receiving lower doses of maintenance therapy than recommended in clinical guidelines. They had received fewer courses of TIS during the previous year (mean 1.8 compared to 5.3 in previous clinical trials), and fewer patients were using dornase alfa (65% vs 85% in other trials), and none had received azithromycin. This may have impacted patient intolerance to available therapies, lack of clinical response to specific therapies, clinician and patient preferences, or difficulty of obtaining drugs. Setting: International sites; 63% in the US and Canada Outcomes: Treatment difference was larger than the 5 point minimal clinically important difference previously determined, but used primary endpoint that is subjective based on patient ratings.

McCoy et al.[10] 2008 (AIR-CF2) Phase 3, RCT, DB, MC	1. AZLI 75mg BID x 28 days n=69 2. AZLI 75mg TID x 28 days n=66 3. Matching PBO n=76	• ≥6 yrs old • Cystic fibrosis • PA infection requiring ≥3 courses of TIS within the previous year	Median time to need antipseudomonal antibacterials: AZLI: 92 days PBO: 71 days Diff: 21 days P=0.007	NA	Treatment-emergent adverse events were comparable; differences were not statistically significant.	NA	Quality rating: Fair **Internal Validity: RoB** Selection: The proportion of patients younger than 18 years in the placebo group (15.8%) was smaller than that in the AZLI-pooled group (25.2%), adding potential bias as a higher percentage of patients >18 y/o are pseudomonas positive.. Unclear information regarding randomization sequence generation and allocation concealment. Performance: High dosing compliance, double blinded Detection: Unclear blinding of evaluators. Attrition: Efficacy and safety analyses included all randomly assigned patients receiving one or more 1 doses of AZLI/placebo. CFQ-R and FEV1 efficacy analyses used the last observation carried forward convention. **External Validity:** Recruitment: N/A Patient Characteristics: Only patients who had 3 or more courses of tobramycin inhalation solution within the previous year Setting: All study patients completed a course of tobramycin inhalation prior to starting aztreonam inhalation Outcomes: Primary endpoint depended on clinician judgment/patient report of symptoms. The prespecified statistical plan compared subjects who received AZLI with those who didn't, but there was not sufficient power to compare dosage regimens. (DRUGS) Results from treatment and placebo groups were pooled.

4.Wainwright et al.[11] 2011 (AIR-CF4) RCT, DB, MC	1. AZLI 75mg TID n=76 2. PBO n=81 x28 days	• ≥6 yrs old • Cystic fibrosis • Positive for PA on throat swab or sputum culture • FEV_1 ≥75% of predicted • No symptoms of pulmonary exacerbation w/in 7 days of baseline	Δ in CFQ-R score: AZLI: 3.22 PBO: 1.41 Diff: 1.8 points, 95% CI(-2.83,6.44) P=0.443	NA	Serious adverse events: AZLI: 11.8% PBO: 3.7% Difference: 8.1% P=0.073 None were considered treatment-related	NA	Quality rating: Fair **Internal Validity: RoB** Selection: Unclear information regarding randomization sequence generation and allocation concealment. Performance: Double-blinded Detection: Unclear blinding of evaluators. Attrition: low attrition rate, ITT analysis using all patients receiving at least 1 dose of drug **External Validity:** Recruitment: N/A Patient Characteristics: Included patients with milder impairment of lung function than previous trials (FEV1 > 75%). Setting: Appropriate Outcomes: This study did not meet its primary endpoint. Authors suggest that the sensitivity of the CFQ-RSS is not sufficient for patients with modest symptoms at baseline, or the study may not have been adequately powered to detect a change.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, MC=mulitcentre, OL=open label.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid), RoB=risk of bias

Appendix 2: Drug Information

Pharmacology:

Tobramycin[1]	Aztreonam[2]	Dornase alfa[3]
An aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelop, and eventual cell death.	A beta-lactam antibiotic that exhibits activity *in vitro* against Gram-negative pathogens including *P. aeruginosa*. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis and death of the cell.	A deoxyribonuclease (DNA) enzyme genetically engineered from Chinese Hamster Ovary cells which selectively cleaves DNA of the viscous mucous in cystic fibrosis patients. This reduces viscosity and improves airflow, potentially decreasing the risk of bacterial infection.

Pharmacokinetics:

Table 1. Pharmacokinetic comparison

Parameters	Tobramycin[1]	Aztreonam[2]	Dornase alpha[3,16]
Protein Binding		56%	
Half-life (h)	2 hrs (for IV administration)	2.1 hrs	Unknown
Metabolism		Hepatic (IM administration, minor)	Unknown
Elimination	Renal/expectorated sputum	Renal (10%)	Unknown
Renal Dose Adjustment	None listed	None	None listed
Hepatic Dose Adjustment	None listed	None	None listed
Food effect on pharmacokinetics	None listed	None	None listed
Mean Sputum Concentration	1237 mcg/g 10 minutes after dose	726mcg/g 10 minutes after dose	3 µg/mL
Mean Plasma Concentration	0.95mcg/mL 1 hour after dose	0.59 mcg/mL 1 hour after dose	
Mean sputum concentration 2 hours following inhalation			0.6 µg/mL
Concentration following bronchoalveolar lavage fluid obtained within 90 minutes of first dose in patient 3 months to 10 years			0.007 to 1.8 µg/mL
Over an average of 14 days of doses, serum DNase concentrations (mean $\pm$ SD) increase			Patients 3 months to <5 years: 1.3 $\pm$ 1.3 ng/mL Patients 5 to $\leq$ 10 years 0.8 $\pm$

			1.2 ng/mL

Contraindications/warnings

Tobramycin[1]

- **Contraindication:** Patients with a known hypersensitivity to any aminoglycoside.
- **Warnings:**
  - **General:** Caution should be exercised when prescribing tobramycin to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate.
  - **Ototoxicity:** Ototoxicity, as measured by complaints of hearing loss or by audimetric evaluations, did not occur with tobramycin therapy during clinical studies. However, transient tinnitus occurred in eight tobramycin-treated patients versus no placebo patients in the clinical studies. Onset of tinnitus warrants caution. In post-marketing experience, patients receiving tobramycin have reported hearing loss.
  - **Nephrotoxicity:** Nephrotoxicity was not seen in clinical trials with tobramycin but has been associated with aminoglycosides as a class. If nephrotoxicity occurs, tobramycin should be discontinued until serum concentrations fall below 2 mcg/mL.
  - **Muscular Disorders:** Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.
  - **Bronchospasm:** Bronchospasm can occur with inhalation of tobramycin. In clinical studies, changes in FEV_1 measured after the inhaled dose were similar in the tobramycin and placebo groups.

Aztreonam[2]

- **Contraindication:** Patients with a known allergy to aztreonam.
- **Warnings:**
  - **Allergic reactions:** Severe allergic reactions have been reported following administration of aztreonam for injection in patients with no known history of exposure to aztreonam. If an allergic reaction occurs, stop administration and initiate treatment as appropriate. Caution is advised when administering aztreonam to patients if they have a history of beta-lactam allergy, although patients with a known beta-lactam allergy have received aztreonam in clinical trials and no severe allergic reactions were reported.
  - **Bronchospasm:** Bronchospasm is a complication associated with nebulized therapies. Reduction of 15% or more in FEV_1 immediately following administration of study medication after pretreatment with a bronchodilator was observed in 3% of patients treated with aztreonam.
  - **Decreases in FEV_1 after 28-day treatment cycle:** In clinical trials, patients with increases in FEV_1 during a 28-day course of aztreonam were sometimes treated for pulmonary exacerbations when FEV_1 declined after the treatment period. Consider a patient's baseline FEV_1 measured prior to aztreonam therapy and the presence of other symptoms when evaluating whether post-treatment changes in FEV_1 are caused by a pulmonary exacerbation.

- **Development of drug-resistant bacteria:** Prescribing aztreonam in the absence of known *Pseudomonas aeruginosa* infection in patients with CF is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.

Dornase alpha[3]

- **Contraindication:** Patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product.
- **Warnings:**
  - **Decreased pulmonary function** of less than 40% of normal. It does not significantly reduce the risk of respiratory infections that require intravenous antibiotics. Safety and efficacy studies have not been conducted for daily administration for greater than 1 year.

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