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Class Update: Inhaled products for Cystic Fibrosis

Month/Year of Review: March 2014
PDL Classes: Inhaled Antibiotics

Date of Last Review: August 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: DORNASE ALFA, SODIUM CHLORIDE FOR INHALATION, TOBRAMYCIN IN 0.225% NACL
- Non-Preferred Agents: AZTREONAM (CAYSTON®)

PA Criteria: A quantity limit of 56 vials/56 days and 84 vials/56 days (for cycles of 28 days on followed by 28 days off therapy) is in place for inhaled tobramycin solution (TIS) and aztreonam lysine for inhalation (AZLI), respectively.

Previous Conclusions:

- There is insufficient long-term evidence available for all drugs in the class. The longest study for 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 or TIS < 6 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 Cystic Fibrosis (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.
- There is moderate quality evidence that treatment with hypertonic saline for patients six years of age and older improves short term lung function, decreases pulmonary exacerbations, and has a small effect on improvement in quality of life. There is insufficient evidence to determine the long term effects of hypertonic saline on mortality in patients with CF.

Conclusions:

- There is moderate quality evidence that both inhaled tobramycin and inhaled aztreonam improve lung function and quality of life in moderate to severe disease for individuals with CF and *Pseudomonas (P.) aeruginosa* persistently present in cultures of the airways. However, there is evidence that inhaled tobramycin reduces exacerbations in patients with CF, while the trials of inhaled aztreonam are short term with limited follow up.
- There remains insufficient evidence to recommend for or against the chronic use of other inhaled antibiotics (ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations in patients with CF.
- There is insufficient evidence to recommend oral anti-psuedomonal antibiotics for pulmonary exacerbations or long-term treatment of chronic infection.
- There is low quality evidence that Tobi Podhaler is noninferior to tobramycin inhalation nebulizer solution in improving lung function.
- There is low quality evidence that Tobi Podhaler results in a higher incidence of discontinuations due to adverse events (14% vs. 8%) and total discontinuations (26.9% vs. 18.2%) than tobramycin nebulizer, respectively.

Recommendations:

- There is no new clinical evidence of effectiveness or safety resulting in recommended changes to current PDL agents. Maintain tobramycin inhalation solution as preferred and evaluate costs in executive session.
- Make tobramycin inhalation powder (Tobi Podhaler) non-preferred and consider requiring step therapy with tobramycin inhalation solution before approval.

Methods:

A Medline OVID search was conducted with the following search terms: inhaled antibiotics, tobramycin, aztreonam, cystic fibrosis, respiratory tract infections, pneumonia, Pseudomonas aeruginosa, pneumonia, bacterial infections. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to December week three 2013. The Cochrane Collection, Agency for Healthcare Research and Quality (AHRQ) National Institute for Health and Care Excellence (NICE), Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

Background:

CF is an inherited chronic disease that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein found in exocrine tissues. 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 an increased slat content in sweat gland secretions. Pulmonary disease is the leading cause of morbidity and mortality in patients with CF.

Bacterial colonization of the airway secretions may occur in patients, with *P. aeruginosa* as the most common pathogen in CF patients. Chronic colonization may cause respiratory insufficiency and eventual respiratory failure. Therapies that may decrease or eliminate colonization in addition to treating exacerbations are essential to improving outcomes. The CF foundation defined clinically meaningful endpoints as time to need 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.

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There are two inhaled antibiotic agents approved for the management of patients with CF that is complicated by *P. aeruginosa*, TIS and AZLI. Both are administered for 28 days, followed by 28 days off therapy. Dornase alfa (DA) is a purified solution of recombinant human deoxyribonuclease (rhDNase), an enzyme that assists in the breakdown of DNA which accumulated in CF patients. The CF guidelines recommend the use of DA in patients with asymptomatic, mild, moderate, or severe lung disease to improve lung function and reduce exacerbation. 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).

New Systematic Reviews:

A Cochrane Collaboration systematic review evaluated the benefit or harm of oral anti-psuedomonal antibiotic therapy for people with CF, colonized with *P. aeruginosa*, in the treatment of pulmonary exacerbation and long-term treatment of chronic infection.[1] Five randomized, open-label trials were identified in the literature search, all of them comparing oral to IV interventions. Three evaluated pulmonary exacerbations and two examined long-term therapy. There was no statistically significant difference between oral antibiotics and other treatments for quality of life or lung function for either pulmonary exacerbations or long-term treatment. One trial resulted in significantly better lung function when treating an exacerbation with oral ciprofloxacin compared to IV treatment. None of the trials were blinded, increasing the risk of bias. The authors concluded that there was no conclusive evidence that an oral anti-psuedomonal antibiotic regimen is more or less effective than an alternative treatment for either pulmonary exacerbations or long-term treatment of chronic infection.

Another Cochrane systematic review attempted to determine if treatment of pulmonary exacerbations with inhaled antibiotics improves their quality of life, reduces time off school or work and improves their long-term survival.[5] Randomized controlled trials comparing inhaled antibiotics to placebo or another inhaled antibiotic were included. Six trials (n=208) were included in the analysis. However, risk of bias was difficult to assess as results were not fully reported and only limited data was available. The lack of evidence made it difficult to demonstrate whether one treatment was superior to the other or not. The authors concluded that further research is needed to establish whether inhaled tobramycin may be used as an alterative to intravenous tobramycin for some pulmonary exacerbations.

Littlewood et al performed a network meta-analysis on inhaled antibiotics used in cystic fibrosis patients to treat *P. aeruginosa* lung infections. Seven trials (n=1798) were included that used at least one of the following medications: tobramycin, colistimethate, or aztreonam. The primary outcome studied was percent change in forced expiratory volume in one second (FEV_1) from baseline after four weeks. Tobramycin inhalation powder showed improvement in percent of FEV_1 from baseline compared with aztreonam (3.64%; 95% CI -1.04 to 8.26) and colistimethate (5.77%; 95% CI -1.20 to 12.75), although the difference was not statistically significant. There was no difference in percent of FEV_1 between tobramycin powder and tobramycin nebulizer formulations (-0.55%; 95% CI -3.50 to 2.4). Tobramycin nebulizer solution patients had significantly improved percent of FEV_1 compared with aztreonam (Az vs. Tobi -4.19%; 95% CI -8.14 to -0.21) and colistimethate (Co vs. Tobi -6.32%; 95% CI -12.61 to -0.02). Conclusions should be made with caution, as outcomes discussed as endpoints were not reported in the final publication. Individual studies were not evaluated for quality.[6]

Guidelines:

1) The Cystic fibrosis (CF) Foundation's Pulmonary Clinical Practice Guidelines Committee updated their guideline for Chronic Medications for Maintenance of Lung Health in 2012. Recommendations were graded on the overall strength of the evidence and measured on the certainty of the magnitude of benefit minus

harm. All recommendations were given the grade of A, B, C, D, or I. Recommendations were also rated on the quality of the evidence used for the recommendation. High quality recommendations were based on consistent results from well-designed, well-conducted studies; conclusions were unlikely to be affected by the results of future studies. Moderate quality recommendations were considered sufficient to predict the effects of an outcome but confidence in the estimate was constrained by quality of individual studies. Low quality recommendations were based on limited, inconsistent, or flawed studies; the available evidence was considered insufficient to predict or assess a therapy outcome.[7]

- For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations. (Recommendation grade A, evidence level high)
- For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations. (Recommendation grade B, evidence level moderate)
- For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations. (Recommendation grade I, evidence level low)
- For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life. (Recommendation grade A, evidence level high)
- For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life. (Recommendation grade B, evidence level moderate)

2) In March, 2013, the National Institute for Health and Care Excellence (NICE) issued guidance for the use of colistimethate and tobramycin dry powders for inhalation for treating pseudomonas lung infection in CF.[8] The following were recommended:

- Tobramycin dry powder for inhalation is recommended as an option for treating chronic pulmonary infection caused by *P. aeruginosa* in people with CF only if:
    - Nebulized tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated, is not tolerated or has not produced an adequate clinical response
- Colistimethate sodium is recommended as an option only if:
    - They would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulized form and thus tobramycin therapy would other be considered

New drugs:
None

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New Formulations/Indications:
Tobramycin inhalation powder (Tobi Podhaler) was approved by the FDA in March of 2013 for management of Cystic fibrosis with *P. aeruginosa* infections. It is formulated into capsules for inhalation using the Podhaler device. This is different than tobramycin inhalation solution, which is formulated into an ampule for inhalation using a nebulizer.

Approval was based on two placebo randomized controlled trials and one active-comparator open-label randomized trial.[9] The placebo-controlled trials included patients between 6 and 21 years old with an FEV_1 of 25% to 80% of predicted normal values. The first placebo-controlled trial was stopped early for demonstrated benefit, with a relative change in FEV_1 to end of cycle 1 dosing of 12.54% in the tobramycin group compared to 0.09% in the placebo group (p=0.002). Respiratory-related hospitalizations occurred in 4.4% of patients in the tobramycin group compared to 12.2% in the placebo group. The second placebo-controlled trial did not show a significant difference in change in FEV_1 between tobramycin inhalation powder and placebo (8.19% vs. 2.27%; p=0.157). The authors noted that this study was underpowered due to barriers in recruiting patients.

Konstan et al was a randomized, poor-quality, open-label trial, comparing two formulations of inhaled tobramycin for treating *P. aeruginosa* infections in CF patients over six years old.[10] This was the primary safety analysis. Subjects (n=517) were randomized in a 3:2 ratio to tobramycin inhalation powder or tobramycin nebulizer solution. The study duration was three treatment cycles of 28 days on tobramycin and 28 days off. Subjects on the tobramycin powder were more likely to experience adverse events than the nebulizer patients (90.3% vs. 84.2%; p< 0.05) and experienced more discontinuations due to adverse events (14% vs. 8%, respectively). Serious adverse events were similar between groups (27.4% vs. 29.2%); three deaths occurred during the study, all in the powder group, although no deaths were related to the study medication. Change in percent of FEV_1 was similar with 1.1% relative change between groups, which was within the predefined 6% margin for noninferiority for the powder compared with the nebulizer solution. Eradication of *P. aeruginosa* at the end of treatment was similar between groups: 11.6% of the powder and 9.9% of the nebulizer subjects were *P. aeruginosa* free after treatment. Patients' requiring an additional antibiotic during treatment for *P. aeruginosa* infection was significantly higher for the powder group than the nebulizer subjects (64.9% vs. 54.5%; p=0.0148); although the number of patients hospitalized for respiratory events was not significantly different between treatment groups (24.4% vs. 22.0%). Outcome reporting could be difficult to follow as endpoints were not always identified or described prior to reporting. [10]

New FDA safety alerts:
None

New Trials (Appendix 1):
A total of 46 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, three relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Schuster et al conducted an open label controlled trial comparing nebulized tobramycin and inhaled colistimethate. CF patients (n=380) aged 6 years and older with a confirmed chronic *P. aeruginosa* infection were randomized to twice daily tobramycin given in alternating 28-day cycles or twice daily colistimethate given every day through the study duration of 24 weeks. The primary endpoint was change in percent of FEV_1 at study end; 261 subjects finished the study per protocol. There was no significant difference between treatment groups in change in percent of FEV_1 (-0.56%; 95% CI -2.71 to 1.70%). A secondary study

measurement was an evaluation of colistin resistant microorganisms present in subjects' sputum. The minimum inhibitory concentration to inhibit 50% of bacterial isolates (MIC_{50}) was similar for both treatment groups throughout the study. No statistical analysis was provided. The rate of adverse events was much higher in the colistimethate group than in the tobramycin subjects (82.2% vs. 46.6%). This was also true for percent of patients discontinuing due to adverse events (9.7% vs. 1.6%). This was a low quality study. Clinically relevant outcomes such as *P. aeruginosa* eradication or decreased hospitalizations were not studied. No details were provided for randomization protocol or other study methodology, and the study was open label.[11]

Proesmans et al compared a 28 day regimen of tobramycin inhalation solution with three months of inhaled Na colistimethate plus oral ciprofloxacin. Children (n=58) under 18 years old with CF and a new *P. aeruginosa* infection were randomized to one of the two treatment groups and followed for two years. The primary outcome was *P. aeruginosa* eradication at the end of treatment. Secondary outcomes were time to relapse, change in FEV_1, body mass index (BMI) and *P. aeruginosa* status at two years. There was no difference in the rate of *P. aeruginosa* elimination between treatment groups at the end of therapy (89.7% vs. 79.3%; RR 0.88, 95% CI 0.71 to 1.11). The median time to relapse of *P. aeruginosa* infection was nine months for colistimethate (95% CI 0.0 to 19.0 months) and five months for tobramycin (95% CI 1.7 to 8.3 months) although this was not a significant difference (p=0.608). After two years, 19 colistimethate and 13 tobramycin patients remained *P. aeruginosa* free (p=0.78). No difference was seen in change in FEV_1 or BMI between treatment groups. This was a fair quality open-label study that had well described methodology for randomization, outcome procedures, and follow-up.[12]

Taccetti et al evaluated inhaled tobramycin versus inhaled colistin in Cystic fibrosis patients with a new *P. aeruginosa* infection. Subjects (n=223) were randomized to treatment for a duration of 28 days in this open label study. Both treatment arms were given oral ciprofloxacin. The primary outcome was eradication of *P. aeruginosa* after six months. This occurred in 62.8% of colistin and 65.2% of tobramycin patients (OR 0.90; 95% CI 0.52 to 1.55). There was a noted increase in Stenotrophomonas maltophilia infection (OR 3.97; 95% CI 2.27 to 6.94) although there was no difference between occurrence in treatment groups (p =0.88). This was a low quality study.[13]

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Appendix 1: Abstracts of Randomized Control Trials

Schuster A, Haliburn C, Doring G, Goldman MH, for the Freedom Study Group. Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study. *Thorax*. 2012;68(4):344–350. doi:10.1136/thoraxjnl-2012-202059.

Purpose To assess efficacy and safety of a new dry powder formulation of inhaled colistimethate sodium in patients with cystic fibrosis (CF) aged ≥6 years with chronic Pseudomonas aeruginosa lung infection. Study design and methods A prospective, centrally randomised, phase III, open-label study in patients with stable CF aged ≥6 years with chronic P aeruginosa lung infection. Patients were randomised to Colobreathe dry powder for inhalation (CDPI, one capsule containing colistimethate sodium 1 662 500 IU, twice daily) or three 28-day cycles with twice-daily 300 mg/5 ml tobramycin inhaler solution (TIS). Study duration was 24 weeks.

Results 380 patients were randomised. After logarithmic transformation of data due to a non-normal distribution, adjusted mean difference between treatment groups (CDPI vs TIS) in change in forced expiratory volume in 1 s (FEV1% predicted) at week 24 was −0.98% (95% CI −2.74% to 0.86%) in the intention-to-treat population (n=373) and −0.56% (95% CI −2.71% to 1.70%) in the per protocol population (n=261). The proportion of colistin-resistant isolates in both groups was ≤1.1%. The number of adverse events was similar in both groups. Significantly more patients receiving CDPI rated their device as 'very easy or easy to
use' (90.7% vs 53.9% respectively; p<0.001).

Conclusion CDPI demonstrated efficacy by virtue of non-inferiority to TIS in lung function after 24 weeks of treatment. There was no emergence of resistance of P aeruginosa to colistin. Overall, CDPI was well tolerated.

Proesmans M, Vermeulen F, Boulanger L, Verhaegen J, De Boeck K. Comparison of two treatment regimens for eradication of Pseudomonas aeruginosa infection in children with cystic fibrosis. *Journal of Cystic fibrosis*. 2013;12(1):29–34. doi:10.1016/j.jcf.2012.06.001.

In patients with cystic fibrosis (CF), treatment of new Pseudomonas aeruginosa (Pa) infection postpones the occurrence of chronic infection, but the best eradication regimen is unknown .

Aim of the study: Compare 2 Pa eradication regimens in children with new Pa infection.

Methods: Children with CF (0–18 years) and a new isolation of Pa from sputum, cough swab or BAL were randomized to treatment with tobramycin inhalation solution for 28 days (TIS) or inhaled sodium colistimethate (2×2 mill U/day) plus oral ciprofloxacin (30 mg/kg/day) for 3 months (CC). Airway cultures were taken for 6 consecutive months, then every 3 months. The primary outcome was Pa eradication at the end of treatment. Secondary outcome parameters were: time to Pa relapse from end of treatment, total and Pa specific IgG, FEV1, BMI and Pa status at 2 year follow-up.

Results: 58 patients with new Pa isolation were randomized. Their median age was 9 years (IQR 4.7–13.1) and their median FEV1 98% predicted (IQR 87–107). Eighteen treatments concerned the first Pa isolation 'ever' (TIS: 8; CC: 10). For the remaining, median time since previous Pa was 19 months (IQR 9–41). Eradication at end of treatment was similar for both treatments: 26/29 CC and 23/29 in TOBI treated patients (p=0.47). Median time to recurrence of Pa was 9 months (95% CI 0.0–19.0) for CC and 5 months (95% CI 1.7–8.3) for TIS (p=0.608). After 1 year, the 2 groups did not differ in change in total and Pa specific IgG, FEV1 and BMI. After 2 years, 10% of patients had chronic Pa infection.

Conclusion: In children with CF and new Pa infection, inhalation of TIS (28 days) or CC (3 months) resulted in similar eradication success at the end of treatment (80 and 90% respectively) and similar clinical evolution during the first 2 years of follow-up.

Taccetti G, Bianchini E, Cariani L, et al. Early antibiotic treatment for Pseudomonas aeruginosa eradication in patients with cystic fibrosis: a randomised multicentre study comparing two different protocols. *Thorax*. 2012;67(10):853–859. doi:10.1136/thoraxjnl-2011-200832.

Background Pseudomonas aeruginosa chronic pulmonary infection is an unfavourable event in cystic fibrosis. Bacterial clearance is possible with an early antibiotic treatment upon pathogen isolation. Currently, no best practice exists for early treatment. The efficacy of two different regimens against initial P aeruginosa infection was assessed.

Methods In a randomised, open-label, parallel-group study involving 13 centres, the superiority of inhaled tobramycin/oral ciprofloxacin compared with inhaled colistin/oral ciprofloxacin (reference treatment) over 28 days was evaluated. Patients were eligible if they were older than 1 year with first or new P aeruginosa isolation. Treatments were assigned equally by centralised balanced randomisation, stratified by age and forced expiratory volume in 1 s values. The participants and those giving the intervention were not masked to arm assignments. The primary endpoint was P aeruginosa eradication, defined as three successive negative cultures in 6 months. Analysis was by intention to treat.

Results 105 patients were assigned to inhaled colistin/ oral ciprofloxacin (arm A) and 118 to inhaled tobramycin/ oral ciprofloxacin (arm B). All patients were analysed. P aeruginosa was eradicated in 66 (62.8%) patients in arm A and in 77 (65.2%) in arm B (OR 0.90, 95% CI 0.52 to 1.55, p¼0.81). Following treatment, an increase in Stenotrophomonas maltophilia was noted (OR 3.97, 95% CI 2.27 to 6.94, p¼0.001) with no differences between the two arms (OR 0.89, 95% CI 0.44 to 1.78, p¼0.88).

Conclusions No superiority of treatment under study was demonstrated in comparison to the reference treatment. Early eradication treatment was associated with an increase in S maltophilia.

Konstan MW, Flume PA, Kappler M, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *Journal of Cystic fibrosis*. 2011;10(1):54–61. doi:10.1016/j.jcf.2010.10.003.

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Background: A light-porous-particle, dry-powder formulation of tobramycin was developed, using PulmoSphere® technology, to improve airway delivery efficiency, substantially reduce delivery time, and improve patient convenience and satisfaction. We evaluated the safety, efficacy and convenience of tobramycin inhalation powder (TIP™) versus tobramycin inhalation solution (TIS, TOBI®) for treating Pseudomonas aeruginosa infection in cystic fibrosis (CF) patients aged ≥6 years.
Methods: In this open-label study, 553 patients were randomized 3:2 to TIP (total 112 mg tobramycin) via the Novartis T-326 Inhaler or TIS 300 mg/5 mL via PARI LC® PLUS nebulizer twice daily for three treatment cycles (28 days on-drug, 28 days off-drug). Safety, efficacy, and treatment satisfaction outcomes were evaluated.
Results: TIP was generally well-tolerated; adverse events were similar in both groups. The rate of cough suspected to be study drug related was higher in TIP-treated patients (TIP: 25.3%; TIS: 4.3%), as was the overall discontinuation rate (TIP: 26.9%; TIS: 18.2%). Increases in FEV1% predicted from baseline to Day 28 of Cycle 3 were similar between groups; the mean reduction in sputum P. aeruginosa density (log10 CFU/g) on Day 28 of Cycle 3 was also comparable between groups. Administration time was significantly less for TIP (mean: 5.6 versus 19.7 min, p 0.0001). Treatment satisfaction was significantly higher for TIP for effectiveness, convenience, and global satisfaction.
Conclusions: TIP has a safety and efficacy profile comparable with TIS, and offers a far more convenient treatment option for pseudomonas lung infection in CF.

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