Resource Use Evaluation of Tobramycin Formulations in a State Medicaid Program

Shellie L. Keast, PharmD, PhD

OBJECTIVE Patients with cystic fibrosis (CF) often suffer from chronic infection with *Pseudomonas aeruginosa*. For patients with CF, 6 years of age and older, with *P aeruginosa* persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations. To ease treatment burden, a new dry powder formulation was developed. The objective of this research was to compare resource utilization between tobramycin inhaled solution (TIS) and a new tobramycin dry powder (TIP) formulation in a state Medicaid program.

METHODS Members that switched from TIS to TIP were matched to TIS-only beneficiaries via propensity score based on age, sex, race, and residence location. The outcomes (tobramycin reimbursement, inpatient hospital reimbursement, additional antibiotic therapy reimbursement, length of inpatient stays, odds of adherence, odds of inpatient hospital stay, and additional mean days of antibiotic therapy) were assessed by using multivariable regression and included baseline clinical surrogates.

RESULTS No difference was found between 54 matched members for tobramycin reimbursement, length of inpatient stays, odds of adherence, or odds of hospital stay. Cost of additional antibiotic therapy was higher for TIP (+\$518, $p < 0.001$) and inpatient reimbursement was higher for TIS (+\$503, $p = 0.031$). Additional mean days of antibiotic therapy were lower for TIP (8.6 vs. 10.1, $p = 0.374$), but was not statistically significant.

CONCLUSIONS In patients that switched from TIS to TIP, an increase in cost of additional antibiotic therapy was observed, while inpatient costs were lower. Research should be considered in larger populations to fully determine the impact of the new dry powder formulation on overall resource use and outcomes.

ABBREVIATIONS AOR, adjusted odds ratio; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DRG, diagnosis-related group; FEV₁, forced expiratory volume; GLM, generalized linear model; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; OHCA, Oklahoma Health Care Authority; PDC, proportion of days covered; PMPM, per member per (eligible) month; TIP, tobramycin inhaled powder; TIS, tobramycin inhaled solution

KEYWORDS health services research; Medicaid; policy; tobramycin; utilization

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Introduction

Cystic fibrosis (CF) is a life-threatening, autosomal recessive disease. The primary genetic cause of CF is an abnormality in the CF transmembrane conductance regulator (CFTR) gene.¹ Common symptoms (based on phenotype) include cough and sputum production, airway obstruction, nasal polyps, digital clubbing, abnormalities of the gastrointestinal tract, excessive salt loss, and genital abnormalities. Advances to date have raised life expectancy from 34.0 years in the early 1990s to 45.2 years.² A common sequela of CF is infection with *Pseudomonas aeruginosa* (*P aeruginosa*), and it is considered to be the most common pathogen for airway infection in patients with CF.³ Chronic infection leads to chronic inflammation, and *P aeruginosa* infection is a major predictor of morbidity and mortality in CF.⁴ Chronic infection with *P aeruginosa* leads to increased

risk of death, decreased weight, lower forced expiratory flow rates (FEV₁), increased risk of acute respiratory infections, and hospitalizations.⁴

Tobramycin is the antibiotic of choice for treating chronic *P aeruginosa* infection in patients with CF.⁵ Tobramycin is an aminoglycoside antibiotic that has been shown to produce lower rates of antibiotic resistance when treating chronic infection.⁶ If used early in the infection, it may be possible to eradicate *P aeruginosa* completely.⁶ However, if used cyclically, it can be used to reduce chronic infection and thus chronic inflammation.⁶ Inhaled tobramycin is frequently used on a cyclic basis with 28 days on therapy followed by 28 days off therapy to avoid aminoglycoside resistance.⁶

Daily therapeutic regimens for CF are time-consuming and burdensome to the patient. Sawicki et al⁷ found the burden of CF to the patient is dependent on

various factors including number of therapies and complexities involved in their administration. In general, the total number of inhaled therapies increases treatment burden. The average number of medications taken by an adult with CF was 7 (with a range of 0 to 20), and total time required to complete therapies was 108 ± 58 minutes per day.⁷ Therefore, it is not only a life-shortening disease by total lifespan, but also results in decreased quality of life for both patient and caregivers. Pharmaceutical manufacturers have been encouraged to develop alternate formulations that reduce administration time and burden for CF patients.⁶

The US Food and Drug Administration approved a new formulation of tobramycin in 2013.⁸ The new dry powder inhaled formulation of tobramycin (TIP) was found to be both safe and well tolerated, with a generally similar adverse event profile when compared to the inhaled tobramycin solution (TIS), although the study authors noted that TIP was associated with increased cough and dysphonia.⁹ Higher discontinuation rates with TIP versus TIS were also observed.⁹ While TIP was not found to be inferior to TIS, it was noted that there was higher use of antipseudomonal antibiotics with TIP despite events appearing to be of milder clinical significance.⁹ The average day supply of additional antibiotics, however, was found to be lower for TIP than TIS (30.9 vs. 33.4, $p = 0.2039$). Additionally, the number of respiratory-related hospitalizations was similar between the 2 groups. A time saving of 28 minutes per day occurred with TIP, and patient satisfaction was also higher.⁹

TIS became available as a generic product in November 2013, making the TIP formulation a more expensive option in terms of medication acquisition cost. Despite this, given higher discontinuation rate, higher adverse event rate, and increased use of antipseudomonal antibiotics with the TIP formulation, the overall cost-effectiveness of the new TIP formulation involves broader considerations. Additionally, with diseases of lower prevalence such as CF, it may be difficult to determine minimal clinically important differences owing to small sample sizes. Thus it is important to consider all research performed in this patient population in order to provide effective disease management. As such, the objective of this research was to compare resource utilization between TIS and TIP formulations in a state Medicaid program.

Methods

Study Design Overview. This was a longitudinal, historical cohort study designed to assess Medicaid members who switched inhaled tobramycin formulations from solution to dry powder between May 1, 2013, through April 30, 2014, and for 12 months post switch date. The total study period extended from May 1, 2012, through April 30, 2015. Paid Medicaid prescription claims were reviewed to locate patients

who started on TIP during the switch period. The date of initiation on TIP was the start date of follow-up for each member of the TIP cohort. Patients who continued on TIS were matched by using a propensity score¹⁰ to each TIP cohort member. The unique identification numbers of cohort members were used to link all medical and prescription claims and enrollment data for each member of the cohort prior to de-identification. This research was approved by both the University of Oklahoma Health Sciences Center Institutional Review Board and the Oklahoma Health Care Authority (OHCA). OHCA is the administrator of the Medicaid program for Oklahoma.

Data Source. The data for this research were from an administrative paid claims database maintained by Pharmacy Management Consultants, a department of the University of Oklahoma College of Pharmacy. Claims include comprehensive prescription, physician, and hospital claims reimbursed to providers through the Oklahoma Medicaid program. A pharmacy claim contains information related to the medication dispensed to the patient, reimbursement amount to the pharmacy, quantity supplied, number of days of therapy as supplied by the pharmacy, date filled by the pharmacy, and prescriber of record. Medical claims included outpatient physician claims with similar information related to the specific service provided, inpatient and outpatient hospital-based claims, and any other non-pharmacy services. Each medical claim contained codes related to diagnosis or procedures, dates of service, and reimbursement amounts to providers. While all pharmacy and medical claims data can be linked via an OHCA member identification number, all personally identifiable elements were removed prior to final data analysis.

Data Inclusion and Exclusion Criteria. To be included in the study, a Medicaid member must have had at least 2 instances of an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for CF (277.0x) on a physician or hospital claim during the study period. Members were excluded if they became eligible for Medicare at any time during the study period. For the TIP cohort, the date of the first paid claim for the TIP product was the index date. Members who did not switch (and remained on TIS) were matched on a ratio of 1:1 to the TIP members by assigned index date and through the use of a propensity score incorporating age at study entry, sex, race, and metropolitan area designation.¹⁰ Members who were not matched were dropped from the study (Figures 1 and 2).

Study Variables. Outcomes (Dependent Variables). The dependent outcomes involving health care resource utilization were related to costs and frequency of occurrence. All cost outcomes were calculated as per member per eligible month (PMPM) (the denominator is each month a patient is eligible to receive benefits from the plan during the specific time period, specifically in this study, this measure only includes patients included

Figure 1. Inclusion/exclusion flow diagram.

CF, cystic fibrosis; TIP, tobramycin dry powder; TIS, tobramycin inhalation solution

in the study and not the entire plan population) and measured direct medical costs from the perspective of payer reimbursement to providers and not net costs (copays and coinsurance paid by the patient or manufacturer rebates were not included), as the perspective of the study is that of the payer. The cost outcomes included tobramycin prescription cost; non-tobramycin antipseudomonal antibiotic costs; and cost of stay for respiratory-related hospitalizations. The frequency of occurrence outcomes included adherence to tobramycin therapy (based on a proportion of days covered [PDC] value of 0.8 indicating the patients had medication available to them for 80% of the days indicated on the prescription in the review period),^{11,12} day supply for non-tobramycin antipseudomonal antibiotic PMPM (any antibiotic for *P. aeruginosa* used during the EAGER⁹ trial such as ciprofloxacin, cefepime, ceftazidime, and aztreonam; but not including any alternate form of tobramycin), occurrence of at least 1 respiratory-related hospitalization (based on a respiratory diagnosis-related group [DRG] code on an inpatient claim), and length of stay for respiratory-related hospitalizations (average per stay).

Covariates and Independent Variables. Age, sex, race, and urban designation were included as predisposing and enabling characteristics.¹³ However, owing to the small population size, these characteristics were limited to descriptive demographics and propensity score matching.¹⁰ To control for clinical status of the members, the average PMPM length of inpatient stay and average PMPM days of additional antipseudomonal antibiotic therapy for the 12 months pre index date were calculated and included in the models. Additionally, baseline PMPM was included in both the additional antipseudomonal PMPM and inpatient PMPM models to

control for baseline differences in these models. Baseline costs for tobramycin therapy were not included in the model for tobramycin PMPM, as patients were switching to a more expensive product. Following propensity score matching based on age, sex, race, rural or urban location, and index date, the key independent variable analyzed was the TIP versus TIS cohort.

Statistical Analysis. Descriptive statistics were used to summarize dependent variables and covariates. The average PMPM costs, utilization, and member demographics were determined for those members categorized as TIP or TIS for the post switch period. Logistic regression was used to calculate the propensity score for each member, based on their age at study entry, race, sex, and metropolitan designation (based on county of residency). This resultant score and index date was used to match TIS patients to TIP patients at a rate of 1:1. Because the index date for the TIS could not be determined until the match was made, these were the only variables available for matching and no baseline clinical characteristics could be used. For frequency tables, chi square tests were used unless low cell counts required a Fisher exact test. For non-binary dependent variables, goodness-of-fit tests were used to evaluate normal distribution; however, none were found to fit, as expected with health care data. Thus, tobramycin cost PMPM and non-*Pseudomonas* antibiotic cost PMPM and days of therapy PMPM were log-transformed (as no zero values were present) and modeled by using a generalized linear model (GLM) and Huber-White robust estimates.¹⁴ Results are also presented in both transformed and untransformed values (raw numbers) to assist with interpretation. Inpatient hospitalization cost PMPM was found to fit a gamma distribution, while average length of stay was found

Figure 2. Study period diagram.

TIP, tobramycin dry powder.

to fit a negative binomial distribution and both were assessed via GLMs, maximum likelihood estimation.¹⁴ Hospitalization occurrence and tobramycin therapy adherence were modeled by using logistic regression. All data were analyzed with SAS 9.2 for Windows (SAS Institute Inc, Cary, NC).

Results

From May 1, 2013, through April 30, 2014, there were 135 Oklahoma Medicaid members who received a prescription claim for an inhaled tobramycin product with 35 patients switching from the TIS to the TIP formulation. A total of 80 patients met criteria for inclusion (Figure 1). After matching TIP patients to the TIS patients, 27 matched sets remained. The remaining 54 patients were reviewed for the 12-month period after their index date.

The mean age was 14.3 ± 5.3 years for the TIP cohort and 13.9 ± 8.7 years for the TIS group and was not found to be different ($p = 0.925$) (Table 1). There was no difference between percentage of males across cohorts (TIP = 59.3%, TIS = 63.0%; $p = 0.770$), those who were white versus all other races (TIP = 70.4%, TIS = 66.7%; $p = 0.769$), or for those living in rural areas (TIP = 11.1%, TIS = 14.8%; $p = 0.685$) (Table 1). Baseline utilization for each cohort is also displayed in Table 1. There was a difference in baseline antipseudomonal antibiotic PMPM between the 2 groups with TIP patients having a higher mean PMPM (TIP = \$926, TIS = \$248; $p = 0.002$). Other baseline utilization was not found to be statistically different, although inpatient PMPM and corresponding length of stay for TIP (\$57 and 0.08,

respectively) were lower than for TIS (\$114 and 0.2, respectively). Additional antipseudomonal antibiotic days of therapy PMPM were not different at baseline (TIP = 8.2, TIS = 5.2; $p = 0.079$) (Table 1).

Tobramycin reimbursement to pharmacies PMPM did not statistically differ and is therefore considered equivalent, with the untransformed PMPM for TIP being \$3394 versus \$2387 for TIS (0.296, $p = 0.114$) (Table 2). Antipseudomonal antibiotic reimbursement PMPM was significantly different with higher reimbursement for the TIP group (\$1095 untransformed) compared to TIS (\$577 untransformed) ($p < 0.001$) and an untransformed difference of \$518 (Table 2). Inpatient hospitalization reimbursement PMPM for the TIP group was lower than for the TIS group (–\$503 untransformed; $p = 0.031$) (Table 2). The average days of additional antipseudomonal antibiotic therapy PMPM did not differ between the TIP group and TIS group (TIP = 8.6, TIS = 10.1; $p = 0.374$) (Table 2).

The odds of having a hospital stay was not different between groups (adjusted odds ratio [AOR] 0.735; 95% CI 0.214, 2.53; $p = 0.625$) (Table 3). The average length in days of inpatient hospital stays was also comparable (TIP = 3.48, TIS = 5.95) ($p = 0.532$) (Table 2). Finally, the proportion of members considered adherent to tobramycin therapy was equal for the TIP group (55.6) and the TIS group (44.4) ($p = 0.457$) (Table 1), with no difference in odds of being adherent between groups (AOR 1.661; 95% CI 0.553, 4.986; $p = 0.366$) (Table 3).

Discussion

This research evaluated the resource use of mem-

Table 1. Patient Characteristics

	Dry Powder (n = 27)	Solution (n = 27)	p value
Age, yr, mean $\pm$ SD	14.26 $\pm$ 5.3	13.89 $\pm$ 8.7	0.925
Male, %	59.26	62.96	0.780
White, %	70.37	66.67	0.770
Rural, %	11.11	14.81	0.685
Tobramycin adherence, n (%)	15 (55.6)	12 (44.4)	-
Inpatient hospitalization occurrence, n (%)	8 (29.6)	11 (40.7)	-
Baseline utilization			
Antipseudomonal antibiotic PMPM, mean $\pm$ SD	\$926 $\pm$ 1015	\$248 $\pm$ 438	0.002
Antipseudomonal antibiotic therapy days PMPM, mean $\pm$ SD	8.2 $\pm$ 5.5	5.2 $\pm$ 6.8	0.079
Inpatient PMPM, mean $\pm$ SD	\$57 $\pm$ 296.4	\$114 $\pm$ 293.4	0.481
Length of stay, days, mean $\pm$ SD	0.08 $\pm$ 0.4	0.2 $\pm$ 0.6	0.495

PMPM, per member per (eligible) month

bers who switched to TIP, compared to members who continued with TIS, in a state Medicaid program and builds upon the current available knowledge regarding the new formulation. Although the size of the population for this research was limited, this work contributes additional information regarding use of additional antibiotics and hospitalizations for payers and providers to consider when managing this complicated disease. The members in this study were predominately white males living in urban areas, and the minimum age for a member was 1 year and the maximum age was 31 years.

While it is not known if this variation in age range had an effect on the outcomes, morbidity and mortality are often a function of factors such as forced expiratory volume (FEV) and arterial oxygen and carbon dioxide as well as age and sex.¹⁵ Previous studies have demonstrated that females younger than 18 years have worse prognosis when lung function impairment is present.¹⁵ The proportion of patients with respiratory-related inpatient hospitalization occurrence was higher

for this research than that seen in other studies and may indicate differences in the health status for the studied population.^{9,16} Additionally, baseline utilization indicates that some of the trends found in the study, such as increased cost of antipseudomonal antibiotics, were present prior to switching (although every attempt was made to account for these differences). This may indicate a difference in clinician decisions to begin TIP therapy or that differences found were not related to TIP therapy but to other uncollected factors.

The PMPM reimbursements in the TIP cohort were higher than in the TIS cohort, except for inpatient hospitalizations (which was lower for TIP). Intuitively, it was expected that the medication acquisition costs for the TIP product itself would be higher than the generic TIS product.¹⁷ While length of stays and occurrence of stays were not statistically significant, from a payer's perspective, these differences could result in decreased overall PMPM for patients. Further research should be done in a larger population to determine if

Table 2. Resource Utilization Outcomes

Variable	Dry Powder (TIP) (n = 27)		Solution (TIS) (n = 27)		p value	Difference*
	Mean $\pm$ SD*	Median*	Mean $\pm$ SD*	Median*		
Tobramycin PMPM	\$3394 $\pm$ 3272	\$2940	\$2387 $\pm$ 1550	\$2106	0.114 [†]	\$1007
Antipseudomonal antibiotic PMPM	\$1095 $\pm$ 1099	\$836	\$577 $\pm$ 1322	\$7	<0.001 [†]	\$518
Antipseudomonal antibiotic therapy days PMPM	8.6 $\pm$ 6.81	7.0	10.1 $\pm$ 14.14	3.5	0.374 [†]	1.5
Inpatient PMPM	\$212 $\pm$ 477	\$0	\$714 $\pm$ 1559	\$0	0.031 [†]	\$503
Length of stay, days	3.48 $\pm$ 5.81	0.00	5.95 $\pm$ 9.40	0.00	0.532 [§]	2.46

PMPM, per member per eligible month; TIP, tobramycin dry powder; TIS, tobramycin inhalation solution

* Untransformed values.

[†] Log-transformed with Huber-White robust estimates.

[‡] Gamma distribution with log link.

[§] Negative binomial with log link.

Table 3. Logistic Regression for Tobramycin Adherence and Hospital Occurrence

	Estimate	p value	Odds Ratio	95% CI
Tobramycin adherence				
TIP (TIS reference)	0.254	0.366	1.661	0.553, 4.986
Inpatient hospitalization occurrence				
TIP (TIS reference)	-0.154	0.625	0.735	0.214, 2.53

TIP, tobramycin dry powder; TIS, tobramycin inhalation solution

reductions in inpatient service costs are greater than increases in medication costs for this population, and to determine if lower costs are related to the use of TIP or other clinical factors not captured here.

The increase in antibiotic PMPM cost is consistent with clinical trial data, which indicated that patients using the TIP formulations had higher usage of antibiotics, but it was not determined if use is inconsistent with the report that the episodes were milder.⁹ The higher overall cost after the switch to TIP could indicate treatment of more complicated occurrences, or simply clinician choice. Konstan et al⁹ reported that a higher proportion of patients required additional antibiotics, but mean days of additional antibiotic therapy for TIP users remained lower than for TIS users (30.9 vs. 33.4, respectively; $p = 0.2039$).⁹ The current study found that the average number of additional antibiotic therapy days for TIP users remained similar after switching as compared to baseline (8.2 vs. 8.6), although there was an increase for TIS (5.2 vs. 10.1). Because additional tobramycin was excluded from this study, it may account for the differences in antibiotic days of therapy seen here as compared to the clinical trial. The type of antibiotic used was not part of this current research and may be an important factor. Further research in a larger population should be performed to determine if there are true differences in additional antibiotic use and whether those differences are clinically significant. Other medical costs such as equipment and physician office visits were not part of this research and could account for additional offsets in costs.

Both TIP and TIS formulations were evaluated for adherence to prophylactic tobramycin therapy, with no difference indicated between groups ($p = 0.446$). Additionally, no difference in inpatient length of stays was observed ($p = 0.505$). It is not possible to ascertain from claims data alone that members were on prophylactic rather than episodic treatment. Use of TIP may be associated with better adherence and fewer occurrences of hospitalizations; however, rates of discontinuation were not evaluated. Additionally, since prophylactic tobramycin therapy is given in a cyclic rather than continuous fashion,¹⁸ adherence in itself can be difficult to determine. Further research with larger populations is required to determine if there are differences in length of stay as well as use of additional antibiotic therapy.

Limitations. As with all research performed on ad-

ministrative claims data, limitations exist regarding the nature of the data itself. Errors in billing and diagnostic coding could create errors in patient identification. Of particular note for these data is the use of a cyclic prescription product rather than a daily medication. While the small population of CF patients in this program was evaluated in the current study, the use of propensity score matching and inclusion of baseline values sought to statistically control for unbalanced patient characteristics. Importantly, exogenous factors that relate to overall health status and medication therapy could not necessarily be captured and may affect resource use. The use of pharmaceutical rebates by Medicaid agencies may also limit the generalizability of the current findings, as rebates tend to be greater for a brand product than for a generic product. Given that the amount of these rebates was not available to the researchers and could have an effect on the final cost to the health care plan, caution should be exercised in extrapolating findings to other plans or other programs. As all insurers currently have unique pricing strategies, each entity should seek to compare findings with plan-specific data. Finally, quality of life is an important consideration for CF patients; however, improvement in quality was not a part of this research.

Conclusions

The real-world results of this research of CF patients within a state Medicaid program supported the findings from clinical trial results that reported differences in resource use in patients on TIP. Extending beyond clinical trials, medication therapy costs were higher for TIP, but use of TIP was associated with lower inpatient costs. Further work should be considered in larger populations to fully determine the impact of the new dry powder formulation on overall resource use, and to further clarify differences in additional antibiotic requirements. Additionally, important patient clinical characteristics should be included if available to fully account for the role of patient overall health status on these outcomes.

ARTICLE INFORMATION

Affiliation University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma

Correspondence Shellie L. Keast, PharmD, PhD;
shellie-keast@ouhsc.edu

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