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Resource Use, Costs, and Utility Estimates for Patients with Cystic Fibrosis with Mild Impairment in Lung Function: Analysis of Data Collected Alongside a 48-Week Multicenter Clinical Trial

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A B S T R A C T

Objectives: Transport of ions to generate epithelial rehydration (TIGER)-1 was a randomized trial conducted to evaluate the safety and efficacy of denufosol versus placebo in patients with cystic fibrosis with mild impairment in lung function. The trial met its primary end point at 24 weeks, but a subsequent trial did not show a sustained effect of denufosol at 48 weeks. By using the 48-week data, we characterized resource use, direct medical costs, indirect costs, and utility estimates. **Methods:** Data on medications, outpatient and emergency visits, hospital admissions, tests, procedures, and home nursing were captured on study case report forms. Sources for unit costs included the Medicare Physician Fee Schedule, the Nationwide Inpatient Sample, and the Red Book. Health utilities were derived from the Health Utilities Index Mark 2/3. We used multivariable regression to evaluate the impact of baseline covariates on costs. **Results:** Characteristics of the 352 participants at enrollment included mean age of 14.6 years, history of *Pseudomonas aeruginosa* colonization in 45.2%, use of dornase alfa in 77.0%, and long-term use of inhaled antibiotics in 37.2%. Over 48 weeks, 22.4% of participants were hospitalized and, on average, participants missed 7.4 days of school or work. Mean total costs (excluding denufosol) were $39,673 (SD $26,842), of which 85% were attributable to medications. Female sex and *P. aeruginosa* colonization were independently associated with higher costs. **Conclusions:** Prospective economic data collection alongside a clinical trial allows for robust estimates of cost of illness. The mean annual cost of care for patients with cystic fibrosis with mild impairment in lung function exceeds $43,000 and is driven by medication costs.

Keywords: costs and cost analysis, cystic fibrosis, denufosol.

Introduction

Cystic fibrosis (CF) is the most common autosomal genetic disease among white persons. It affects 1 in 2500 newborns and is progressive and incurable. Advances in treatment have dramatically increased life expectancy from less than 1 year in the 1930s to a median of 37 years today [1–3]. Despite treatment advances, there is a lack of therapies that address the underlying pathophysiology of disease rather than complications of the disease. This underscores the importance of regimens to maintain health and the development of practice guidelines by the Cystic Fibrosis Foundation on appropriate long-term use of medications to preserve lung function [2,4–6].

Denufosol is a novel ion-channel regulator designed to target small airways and correct the ion-transport defect early in disease progression to delay the onset and reduce the rate of lung function loss [7]. A phase 3, multicenter, randomized, double-blind, placebo-controlled trial (Transport of ions to generate epithelial rehydration [TIGER]-1, Study 08-108) was recently conducted to evaluate the safety and efficacy of denufosol in patients aged 5 years and older with near normal to mildly impaired lung function, defined as baseline forced expiratory volume in the first second of expiration (FEV_1) of 75% or more of the predicted level, when added to the patient's current therapeutic regimen. Decline in FEV_1 reflects progression of disease [8]. The clinical results of TIGER-1 demonstrated a statistically significant benefit of denufosol on FEV_1 at 24 weeks in a patient population with extensive background therapy [9]. In a subsequent 48-week randomized trial of denufosol (TIGER-2), however, there were no sustained clinical benefits [10].

Clinical trial designs that incorporate routine clinical care afford an efficient means of rigorously determining the total cost of medical care when economic data are collected prospectively as part of the trial [11]. A prospective economic evaluation was integrated into TIGER-1 to allow for estimation of the cost of illness over a 48-week period in persons with CF with normal to mildly impaired lung function. Data on medical resource use, health utilities, and CF disease–related time lost from school and work were collected during the trial.

Trial Registration: clinicaltrials.gov Identifier: NCT00357279.

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Methods

Study design

The clinical trial was conducted at 61 sites in the United States and 1 site in Canada. Eligible participants were aged 5 years or older, had a confirmed diagnosis of CF, had mild impairment in lung function with an FEV_1 of 75% or more of the predicted level, and were clinically stable for 4 weeks before screening. Medications used to treat CF were allowed, and participants were instructed to continue taking their medications consistently throughout the study. The main exclusion criteria included abnormal renal or liver function, history of liver or lung transplant, *Burkholderia cepacia* colonization, change in medications within 28 days of screening, use of inhaled hypertonic saline within 2 weeks of screening, and use of oral corticosteroids exceeding 10 mg once daily or 20 mg every other day.

Participants were randomly assigned to active treatment with denufosol or placebo. The double-blind treatment period continued for 24 weeks and was followed by a 24-week open-label safety extension period. Contact with participants occurred every 4 weeks during the 48-week trial and consisted of eight scheduled clinic visits (in addition to screening and post-trial visits) and six telephone contacts to verify interval resource use, medication use, and adverse events. Additional details of the clinical trial protocol have been described elsewhere [9]. The institutional review board of the Duke University Health System approved this study.

Health utilities

Patient-reported health preferences were measured at the randomization visit and every 12 weeks during the trial with a Health Utilities Index Mark 2/3 (HUI2/3) questionnaire and a visual analogue scale ("feeling thermometer") [12,13]. The HUI2/3 is a 15-item questionnaire designed to measure multiattribute health utility scores representing the desirability of a given health state and has been tested in adolescents with CF [13]. The questionnaire was self-administered by trial participants 14 years and older. Parents or caregivers of participants 13 years and younger completed the instrument as proxies [14]. The HUI2/3 multiattribute utility scale ranges from −0.36 to 1.00, where 0 represents death and 1.00 represents perfect health. Scores less than 0 represent health states considered worse than death. The feeling thermometer rates health states from the patient's perspective on a vertical visual analogue scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state.

Medical resource use and missed school days/workdays

Data on medical resource use were recorded in the trial case report form during each study visit or phone call through patient report and supplemented with medical information available at the study site. Resource use data included information on concomitant medications, planned and unscheduled clinic visits to the study site and primary care physician, inpatient and outpatient tests and procedures, hospitalizations, emergency department visits, and home nursing care. The number of days missed from work or school by the participant because of CF-related illness was also ascertained during each study visit and phone call.

Cost assignment

We valued costs from a societal perspective and included direct medical costs and indirect costs attributable to missed school days and workdays. If 2008 cost estimates were unavailable, we updated the values by using the consumer price index for medical care [15].

We used average wholesale prices reported in the 2008 Red Book [16] to assign medication costs. We assigned a daily cost to each drug on the basis of dose, route, and frequency of administration recorded in the case report form. We then multiplied the daily cost by the estimated number of days of use from the date of randomization through 48 weeks. If a dosage was not provided, we assigned the most commonly used dose. We assumed that pancreatic enzymes reported taken "as needed" were taken four times daily. We did not assign costs to the other 7.7% of drug records with "as-needed" dosing.

Costs for outpatient visits, tests, and procedures were based on 2008 Current Procedural Terminology codes and average reimbursement rates from the 2008 Medicare Physician Fee Schedule [17]. Costs for emergency department visits and procedures were also based on the Medicare Physician Fee Schedule. If the emergency department visit did not result in hospitalization, the marginal cost of an emergency department visit was also included to represent facility costs [18]. Home nursing visits were estimated from the standardized, service-specific, per-visit payment rates published by the US Centers for Medicare & Medicaid Services for home health care in 2008 [19].

Hospitalization costs included physician fees for physician rounds, physician fees for procedures, and hospital costs. Physician fees for rounding and inpatient procedures were assigned corresponding Current Procedural Terminology codes and valued by using the 2008 Medicare Physician Fee Schedule [17]. For the hospital component, we developed a costing methodology to ensure that inpatient costs would better represent costs incurred by patients with CF [20]. First, we assigned primary, secondary, and tertiary *International Classification of Diseases, Ninth Revision, Clinical Modification,* codes based on the reasons for hospitalization and inpatient procedures recorded in the trial. We then identified hospitalizations of patients with CF in the 2001-2005 Nationwide Inpatient Sample databases available from the Agency for Healthcare Research and Quality [21]. We matched hospitalizations in the trial to multiple Nationwide Inpatient Sample records based on *International Classification of Diseases, Ninth Revision, Clinical Modification,* diagnostic and surgical procedure codes. We estimated hospitalization costs in the trial by multiplying the median daily cost based on matched Nationwide Inpatient Sample discharges with each participant's length of stay in TIGER-1.

Indirect costs due to days lost from work were valued by using the average hourly wage ($19.85) in the United States [22]. For pediatric participants who missed a day of school, we assumed that a parent missed a day of work.

Statistical analysis

We estimated costs across several participant subgroups prespecified in an economic analysis plan, including subgroups defined by age, long-term use of inhaled antibiotics, use of recombinant human deoxyribonuclease (dornase alfa or rhDNase), and *Pseudomonas aeruginosa* infection. The use of pancreatic enzymes was not considered as a subgroup because of near ubiquitous use. In a post hoc analysis, we compared costs between treatment groups after stratifying participants by body mass index (BMI) below and above a threshold indicating malnutrition (<18.5 vs. ≥ 18.5 kg/m^2) [23].

In multivariable analysis, we evaluated baseline determinants of costs at 48 weeks by using a generalized linear model with a gamma error distribution and log link [24], which has been shown to fit medical cost data reasonably well when extreme cost outliers are not present. Among the independent variables, we treated age as categorical (i.e., 5–7, 8–12, 13–17, ≥18 years). Treatment group assignment and the presence of two or more positive cultures for *P. aeruginosa* within 2 years of randomization were dichotomous variables. Baseline FEV_1 and BMI were modeled as continuous variables. We developed two separate models. One model applied