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Original Article

Rationalizing endpoints for prospective studies of pulmonary exacerbation treatment response in cystic fibrosis

D.R. VanDevanter [a,*], S.L. Heltshe [b,c], J. Spahr [d], V.V. Beckett [c], C.L. Daines [e], E.C. Dasenbrook [a], R.L. Gibson [c], R. Jain [f], D.B. Sanders [g], C.H. Goss [b,c], P.A. Flume [h] on behalf of the STOP Study Group [1]

[a] Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA
[b] University of Washington, Seattle, WA 98121, USA
[c] CFF Therapeutics Development Network Coordinating Center, Seattle Children's Research Institute, Seattle, WA 98105, USA
[d] Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA 15224, USA
[e] University of Arizona, Tucson, AZ 85724, USA
[f] University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
[g] University of Wisconsin, Madison, WI 53792, USA
[h] Medical University of South Carolina, Charleston, SC 29425, USA

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Abstract

Background: Given the variability in pulmonary exacerbation (PEx) management within and between Cystic Fibrosis (CF) Care Centers, it is possible that some approaches may be superior to others. A challenge with comparing different PEx management approaches is lack of a community consensus with respect to treatment-response metrics. In this analysis, we assess the feasibility of using different response metrics in prospective randomized studies comparing PEx treatment protocols.

Methods: Response parameters were compiled from the recent STOP (Standardized Treatment of PEx) feasibility study. Pulmonary function responses (recovery of best prior 6-month and 12-month FEV_1% predicted and absolute and relative FEV_1% predicted improvement from treatment initiation) and sign and symptom recovery from treatment initiation (measured by the Chronic Respiratory Infection Symptom Score [CRISS]) were studied as categorical and continuous variables. The proportion of patients retreated within 30 days after the end of initial treatment was studied as a categorical variable. Sample sizes required to adequately power prospective 1:1 randomized superiority and non-inferiority studies employing candidate endpoints were explored.

Results: The most sensitive endpoint was mean change in CRISS from treatment initiation, followed by mean absolute FEV_1% predicted change from initiation, with the two responses only modestly correlated (R^2 = .157; P < 0.0001). Recovery of previous best FEV_1 was a problematic endpoint due to missing data and a substantial proportion of patients beginning PEx treatment with FEV_1 exceeding their previous best measures (12.1% > 12-month best, 19.6% > 6-month best). Although mean outcome measures deteriorated approximately 2-weeks post-treatment follow-up, the effect was non-uniform: 62.7% of patients experienced an FEV_1 worsening versus 49.0% who experienced a CRISS worsening.

Conclusions: Results from randomized prospective superiority and non-inferiority studies employing mean CRISS and FEV_1 change from treatment initiation should prove compelling to the community. They will need to be large, but appear feasible.

Keywords: Exacerbation; Endpoints; Clinical trial; Sample size

1. Introduction

People with cystic fibrosis (CF) are prone to acute intervals of exaggerated signs and symptoms of airway infection that are

* Corresponding author at: 12520 33rd Street Ct E, Edgewood, WA 98372, USA.
E-mail address: drv15@case.edu (D.R. VanDevanter).

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frequently coupled with lung function decline, weight loss, and malaise that we collectively identify as 'pulmonary exacerbations' (PEx) [1]. PEx management commonly includes chest physiotherapy and treatment with antibiotics targeted at bacterial opportunists previously detected in the patient's airway, as well as nutritional and psychosocial support [2]. It has proven difficult to reach consensus on a prospective objective definition of CF PEx for clinical research purposes [1], but associations between poor health outcomes and PEx as defined by a clinician's decision to treat PEx signs and symptoms with antibiotics are indisputable. In 2014, 17,882 PEx were treated with intravenous (IV) antibiotics among 9318 individuals followed in the US CF Foundation Patient Registry (CFFPR) [3]; more than twice as many were likely diagnosed and treated with outpatient antibiotics during the same year [4]. IV antibiotic-treated PEx have been associated with decreased quality of life [5], increased resource utilization [6,7], accelerated lung function decline [8], overall loss of lung function [9], and increased mortality risk [10–13].

Unfortunately, objective evidence supporting current PEx management practices is both scant and inconclusive [1]. The few relatively small prospective studies comparing PEx treatments that have been reported have mainly failed to provide actionable clinical guidance with respect to antibiotic choice(s), routes of delivery, or treatment duration [1]. Observations of poor overall PEx outcomes [9] and substantial variability in PEx management both within and between CF care programs [14–16] have precipitated a discussion of PEx management practices [17], and specifically whether current practices are optimal or whether objective clinical trials might be able to distinguish 'better' PEx treatment regimens from those that are either less effective or are similarly effective but with greater associated burden, expense, or toxicities.

The US CF Foundation has sponsored multicenter studies to determine if standardized PEx treatment protocols can be introduced and tested in CF Care Centers, with an aspirational goal of bringing evidence-based medicine to PEx treatment in order to optimize outcomes. A recent multi-center US study of IV antibiotic treatment of PEx (Standardized Treatment of PEx; STOP) probed feasibility of patient/clinician participation in future prospective protocol-driven PEx treatment studies, and systematically collected treatment response data in order to identify/characterize efficacy endpoints to be employed in prospective PEx treatment studies [18,19]. In this communication, we describe endpoint properties derived from STOP study data for assessing PEx treatment protocol efficacy, and evaluate the strengths and weaknesses of potential exacerbation study efficacy endpoints, including change in forced expiratory volume in 1 s (FEV_1), change in signs and symptoms of exacerbation, and retreatment with IV antibiotics within 30 days.

2. Methods

Data were obtained from the STOP study (NCT02109822), which has been previously described [18,19]. Lung function changes were evaluated using spirometry, and specifically the percentage predicted of FEV_1 (FEV_1% predicted) based on a subject's sex, age, height, and race using the GLI normative equations [20]. Signs and symptoms of pulmonary exacerbation were collected using the Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Infection Symptom Score (CRISS) [21,22]. FEV_1% predicted and CRISS data were collected at hospital admission for IV antibiotic treatment (Visit 1), at Day 7 (±3 days) of treatment, at IV antibiotic treatment termination (Visit 2), and at Day 28 (Visit 3). When available, a patient's best FEV_1% predicted measures recorded in the prior 6 months and the prior 12 months were collected from the CFFPR. Finally, time to next PEx treated with IV antibiotics (or censor) following treatment was collected for each subject from the CFFPR.

Descriptive statistics (mean, standard deviation [SD], median, range, etc.) were calculated for FEV_1% predicted score and CRISS change from Visit 1 (admission) to Day 7, Visit 2 and Visit 3. In addition, statistics associated with the proportion of a subject's recovery of their historic best FEV_1% predicted (in the prior 6 months and 1 year as recorded in the CFFPR) were calculated for STOP study visits. Individuals with missing data were excluded from these calculations. As sensitivity analyses, missing Visit 3 data were imputed using the last observation carried forward (LOCF) method to estimate effects of missing data on change from admission outcomes. Time-to-next IV antibiotic treatment for PEx from end of treatment was studied using Kaplan–Meier survival methods to account for censoring (subjects who experienced no subsequent event at the time of analysis) and the proportion of subjects receiving retreatment with IV antibiotics for PEx within 30 days of Visit 2 was studied as a categorical variable.

To characterize endpoint utility for future prospective, randomized, comparative superiority and non-inferiority trials, sample size estimates were generated. PEx protocol-based superiority studies employing continuous variable endpoints were generated for FEV_1% predicted and CRISS as changes from Visit 1 to Visit 3 as two-sided t-tests assuming 1:1 randomized allocation, 80% or 90% power, and alpha = 0.05. Sample sizes for 1:1 randomized non-inferiority (NI) studies of clinically identical treatments with 80% or 90% power and alpha = 0.025 were determined based on observed standard deviations for FEV_1 and CRISS responses as a function of varying NI margins. Sample sizes for NI study designs were determined where NI margins preserved ≥50% of the lower 95% confidence bound [23] of observed STOP means assuming 1:1 randomization, 80% or 90% power, and one-sided alpha = 0.025.

Variables were also categorized as proportions of treated subjects achieving a) ≥100% of their best prior 12-month and 6-month CFFPR FEV_1% predicted, b) ≥9% predicted improvement from admission in FEV_1, c) ≥17% relative improvement from admission in FEV_1% predicted, and d) ≥11-point decrease from admission in CRISS [24]. Absolute and relative FEV_1 improvement thresholds were derived from the previous observation that a 15% relative FEV_1 drop is strongly associated with antibiotic treatment for exacerbation:[25]: a 9% predicted absolute FEV_1 improvement is roughly equal to recovery of a 15% loss of the average best FEV_1% predicted in the prior 6 months for STOP subjects (0.15 × 60.6% predicted = 9.1% predicted; N = 200); a 17% relative FEV_1 improvement represents recovery of a 15%