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Innovating cystic fibrosis clinical trial designs in an era of successful standard of care therapies

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Abstract

Purpose of review—Evolving cystic fibrosis (CF) ‘standards of care’ have influenced recent CF clinical trial designs for new therapies; care additions/improvements will require innovative trial designs to maximize feasibility and efficacy detection.

Recent findings—Three CF therapeutic areas (pulmonary exacerbations, *Pseudomonas aeruginosa* airway infections, and reduced CF Transmembrane Conductance Regulator [CFTR] protein function) differ with respect to the duration for which recognized ‘standards of care’ have been available. However, developers of new therapies in all three areas are affected by similar challenge: standards of care have become so strongly entrenched that traditional placebo-controlled studies in CF populations likely to benefit from newer therapies have become less and less feasible. Today, patients/clinicians are more likely to entertain participation in active comparator trial designs, which have substantial challenges of their own. Foremost among these are the selection of ‘valid’ active comparator(s), estimation of a comparator’s *current* clinical efficacy (required for testing non-inferiority hypotheses), and effective blinding of commercially available comparators.

Summary—Recent and future CF clinical trial designs will have to creatively address this collateral result of successful past development of effective CF therapies: patients and clinicians are much less likely to accept simple, placebo-controlled studies to evaluate future therapies.

Keywords

cystic fibrosis; active comparators; non-inferiority; controlled trials

Introduction

As the formulary of therapies approved for cystic fibrosis (CF) has expanded since the approval of the first therapy in 1993 [1], these treatments have become standards of care and have contributed towards substantial improvements in morbidity and mortality for individuals with CF across the decades [2]. Clinical investigators exploring newer or alternative versions of these established therapies have been forced away from traditional

additive study designs, in which study subjects are randomly allocated to receive either a novel active treatment or a placebo, towards studies which employ active comparators consisting of these current ‘standards of care’. The presence of effective versions of these newer agents creates an ethical challenge: how (and for how long) can we ask patients to stop taking effective therapies so that we may more easily test the efficacy of new ones? Demonstrating clinical efficacy using active comparators can be logistically challenging, particularly where non-inferiority of a new therapy is hypothesized. Extreme diversity of care or rapidly evolving standards of care can complicate the identification/choice of broadly acceptable comparators, and there are situations where it can be difficult or impossible to blind subjects and investigators to treatments when active comparators are employed.

In this article, we will consider challenges with active comparator trial designs in three areas of CF treatment that are relevant today: acute antibiotic treatment of pulmonary exacerbations, chronic inhaled antibiotic management, and chronic treatment with agents targeting mutant Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein activity (termed CFTR modulators). Each area has challenges unique to the nature of the therapy, measurement of clinical efficacy, state of current practices, and the degree to which there are recognized ‘standards’ of care from which to draw valid active comparators for study.

1. Comparisons of acute treatments for pulmonary exacerbations

Pulmonary exacerbations, periodic increases in respiratory signs and symptoms frequently accompanied by acute reductions in lung function and weight loss, are commonly treated with systemic antibiotics, chest physiotherapy, and nutritional and psychosocial support [3]. CF exacerbation treatment with antibiotics is as old as antibiotics themselves, predating the era of chronic respiratory therapies. Today, exacerbation treatment guidelines encourage clinicians to treat patients until, in their clinical judgement, (an undefined) response has been achieved [4–6], a guidance which results in an extremely broad distribution of antibiotic treatment times [7]. Unfortunately, there are surprisingly few objective data on which current treatment guidelines are based [5,6].

Historical studies

Recognition that pulmonary exacerbations are associated with poor health outcomes, including reduced quality of life, loss of lung function, and increased mortality risk explains why there has been no room for truly placebo-controlled studies of exacerbation treatments for decades [3]. Nearly all previous studies have employed active comparator designs in which a treatment is added to a background of ‘routine’ exacerbation care. A recent Cochrane review of 40 randomized controlled studies of IV antibiotic treatment of pulmonary exacerbation involving 1717 subjects noted that “with a few exceptions, these [were] comprised of mainly small, inadequately reported studies” [8]. Beyond problems with the sizes of these (primarily single-center) studies, their interpretation is hampered by uncertainty as to what constitutes routine/standard antibiotic choices (e.g., numbers and types, routes of administration, and dosages) as well as treatment durations. Finally, there has been no real discussion, let alone consensus, on what variables are most appropriate for

measuring exacerbation treatment response, when these measures are best made, and what differences in response should be considered clinically meaningful.

Although seemingly innocuous, the issues of treatment duration and when to measure response create substantial complexity for comparative exacerbation treatment studies. If an investigator wants to test an adjuvant to improve response, should the adjuvant be administered for a fixed duration (ideal) or given throughout antibiotic treatment? Should the investigator demand a specific antibiotic treatment duration for both study arms, risking poor enrollment, increased protocol violations, and limited applicability of findings to the broader population? Traditionally, comparisons have been made between exacerbation treatment groups at the cessation of antibiotic administration, regardless of duration, which makes sense given that guidelines suggest 'treat until better'. However, there is evidence that such an approach may be misleading: exacerbating patients treated with intravenous (IV) antibiotics for less than 9 days (presumably because of an observation of rapid response) are at about double the risk of being retreated within 30 days as their peers treated longer with IV antibiotics, irrespective of other risk factors [7]. Further, it has been demonstrated that some patients continue to recover pulmonary function and experience reduced signs and symptoms of exacerbations for weeks after treatment stops (and unfortunately, the health of others degrades shortly after treatment cessation) [7,9,10]. Thus, clinical presentation immediately at the end of treatment may not accurately reflect clinical status even weeks after treatment.

The STOP Studies

Recently, a multicenter program (Standardized Treatment of Pulmonary exacerbations; STOP) sponsored by the US CF Foundation has been organized to systematically address pulmonary exacerbation treatment variability. STOP commenced with an initial observational study in which >200 adolescents and adult patients were admitted to hospital for IV antibiotic treatment of an exacerbation. Treated patients were followed from admission through Day 28 by spirometry and a sign and symptom questionnaire. This initial study was completed in 2016 [11,12]. Surveys of clinician and patient treatment goals were also collected and, in combination with treatment responses, sample size requirements and relative strengths and weaknesses of different possible efficacy endpoints for prospective randomized comparative trials of exacerbation treatments were delineated [10]. Currently, a larger, innovative multicenter study (STOP2; NCT02781610), in which IV antibiotic treatments of 10, 14, and 21 days in adults with CF will be compared is in active enrollment [13]. The primary STOP2 efficacy comparisons will be lung function change from IV treatment initiation to 2 weeks after treatment end. An important innovation in the STOP2 design is the recognition from the initial observational study that patient responses could generally be divided into 2 categories, those who had an early robust response (ERR) by both lung function increase and sign and symptom reduction within 7 to 10 days of treatment initiation, and those who were non-ERR (NERR) [13]. The STOP2 protocol incorporates an ERR/NERR assessment between days 7 and 10 of treatment, with ERR patients then allocated 1:1 to receive either 10 days or 14 days of IV antibiotic treatment (with a lung function response comparison at 24 and 28 days, respectively). In contrast, STOP2 patients identified as NERR are allocated 1:1 to receive either 14 days or 21 days of

antibiotic treatment (with lung function response comparisons at days 28 and 35, respectively). This bifurcated design allows investigators to test whether a) 10 days of treatment is not inferior to 14 days of treatment among ERR patients and b) whether 21 days of treatment is superior to 14 days of treatment among NERR patients [13].

The STOP2 ‘study within a study’ design appears to have addressed major (apparently contradictory) patient and clinician concerns: patients who routinely receive about 2 weeks of treatment raised concerns about the quality of life, associated risks, and additional costs associated with substantially longer treatments, while those accustomed to longer treatments raised concerns about abbreviation of treatments before full responses had been realized. To date, strong subject enrollment and infrequent study withdrawals suggest that this innovative study design can address the fundamental question in exacerbation management of how long to treat.

If STOP2 results can support rationalization/standardization of exacerbation antibiotic treatment durations, subsequent studies comparing different exacerbation treatments can presumably employ fixed treatment durations, with a potential to improve interpretation.

2. Efficacy of chronic inhaled antibiotic treatments

Guidelines for the management of patients with CF and chronic *Pseudomonas aeruginosa* include chronic bacterial suppression with inhaled antipseudomonal antibiotics [6,14]. Although extemporaneous use of inhaled antibiotics had occurred for decades (particularly inhaled colistimethate in Europe [6]) use was sufficiently inconsistent in the 1990’s that a large 6-month placebo-controlled study of intermittent twice daily treatment with 300 mg inhaled tobramycin was successfully completed in the mid-1990’s [15]. This 28-day on/off regimen, which was selected in an attempt to reduce emergence of tobramycin resistance [16], became the approved indication for inhaled tobramycin and eventually a standard of care in North America. Subsequent inhaled aztreonam [17,18] and inhaled levofloxacin [19,20] development programs have reinforced the “on/off” inhaled antipseudomonal antibiotic treatment paradigm. Initially, this “on/off” period treatment paradigm facilitated creative study designs utilizing placebo controls: patients could be randomized to a new inhaled antibiotic or placebo in the off period following a standard 28-day “on” treatment (in essence a randomized treatment withdrawal design). By extending follow up to 90 days, a time to “need for antibiotic” efficacy endpoint could be studied [17]. Although this approach satisfied the need for a placebo-controlled pivotal trial for regulatory approval of inhaled aztreonam in the US, it was not adequate to meet European Medical Agency (EMA) development guidelines for a non-inferiority active comparator trial versus inhaled tobramycin [21]. This active comparator requirement introduces substantial design challenges, including an inability to blind treatments that employ different formulation platforms, delivery devices, and regimens as well as the challenge of subjective choice of a non-inferiority margin for clinical efficacy. This latter problem is perhaps of greater concern, in that it is not trivial to estimate the efficacy of inhaled tobramycin in a contemporary study population with substantial prior inhaled tobramycin experience, and where there may be substantial risk of “biocreep”, in which noninferiority to an active comparator with reduced efficacy leads to approval of a significantly less effective therapy.

Unfortunately, while randomized controlled CF inhaled antibiotic study designs were balkanizing the 28-day off-drug period, North American standards of CF care for patients with more advanced disease were evolving to be much closer to the older European model of continuous treatment originated with inhaled colistimethate [16,22,23]. Today, most US CF patients with measurable lung disease who receive inhaled antibiotics are treated continuously, with either monotherapy or regular rotation of multiple inhaled antibiotic classes [23]. This shift in North American practice has now made both placebo-controlled studies and 28-day on/off studies of inhaled antibiotics less feasible in those patients with the greatest potential to benefit from new classes of inhaled antibiotics. Importantly, these observations suggest that the EMA guidance for new inhaled antibiotic products to be compared to the labeled inhaled tobramycin regimen [21] is becoming less and less realistic. This situation was clearly demonstrated recently by an inability to fully enroll a randomized controlled study comparing 6 months of alternating 28-day cycles of inhaled tobramycin and inhaled aztreonam (i.e., with no off antibiotic periods) to 6 months of the approved inhaled tobramycin regimen (3 cycles of 28 days on/off drug) [24]. Investigators reported that eligible/targeted patients were likely to be receiving continuous inhaled antibiotics and were unwilling to take a chance on being randomized to receive the labeled inhaled tobramycin regimen including 28-day off periods.

Further complicating the study of new chronic inhaled antibiotics is an apparently increasing preference by US regulators for reduction in risk/rate of pulmonary exacerbation over sustained lung function improvement as a measure of inhaled antibiotic clinical efficacy. In contrast to estimation of lung function benefit, which can be readily demonstrated within weeks, demonstration of a reduced exacerbation incidence or risk requires substantially longer studies [22]. Given that patients with the greatest medical need are apparently receiving (extemporaneous) continuous inhaled antibiotic therapy [23], it is not clear how to choose a valid/acceptable active inhaled antibiotic comparator for extended studies.

The recent inability to compare what appears to be a current standard of care (continuous treatment) to an approved inhaled antibiotic regimen [24] highlights the challenges faced by inhaled antibiotic developers. Going forward, placebo-controlled studies of new inhaled antibiotics appear to be infeasible in those patients most likely to benefit, as will studies of >28 days if labeled indications for inhaled tobramycin or aztreonam are employed as active comparators. Given that CF patients are expected to live for decades with chronic airway *P. aeruginosa* infections and that benefits from the limited formulary of approved inhaled antibiotics will likely attenuate over time for these patients, investigators and regulators will need to think creatively about demonstrating efficacy for new agents in this population.

3. Efficacy of new modulators targeting genotypes for which modulators have been approved

In contrast to the acute treatment of pulmonary exacerbations or the chronic suppression of *P. aeruginosa* airway infection, chronic treatment with CFTR modulators is a very recent CF treatment advancement. Demonstration of the clinical efficacies of ivacaftor (Kalydeco®, Vertex Pharmaceuticals) in patients with gating mutations and lumacaftor/ivacaftor

(Orkambi®, Vertex Pharmaceuticals) in patients with two F508del mutant alleles included traditional extended, randomized, placebo-controlled studies [25,26]. However, a recent survey of both CF clinicians and patients with genotypes for which ivacaftor and lumacaftor/ivacaftor have been approved reveals a striking unwillingness of patients to participate in future placebo-controlled studies of newer modulators targeting these genotypes [27]. Survey respondents with access to approved modulators consistently reported only modest interest in new placebo-controlled studies of 2 to 4 weeks in duration, and substantially greater disinterest in enrolling in longer placebo-controlled studies [27]. Thus, developers and regulators may be quick to consider active-comparator studies for newer modulators targeting these genotypes.

There are multiple reasons why this observation should be of concern to CF clinical investigators and regulators, and why an alternative of shorter, placebo-controlled efficacy studies combined with extended, open-label safety studies may be a preferred alternative for registration of newer versions of existing modulators. Perhaps most importantly, where a placebo-controlled study might require 100 patients to demonstrate the efficacy of new modulator, demonstration of non-inferiority of the same therapy to a current, effective modulator might require the study of 1000 patients. For less common CFTR genotypes, these sample size requirements may exceed the available number of individuals with these genotypes. Practical problems beyond sample size requirements exist: acquisition costs for active CFTR modulator comparators (currently retailing for hundreds of thousands of dollars per patient-year) for extended studies will likely be prohibitive. Further, blinding of commercial comparators, if possible, may introduce uncertainty. For instance, blinding overpackaging may change the bioavailability of an active commercial comparator. Implementation of an active comparator trial in an open label fashion which enrolls patients already on the standard of care modulator, although logistically reasonable, presents several issues with respect to interpretation and selection bias.

These observations suggest that development of additional CFTR modulators, which have a real potential to introduce market competition and reduce acquisition costs, will require creativity on the part of investigators and regulators to overcome reluctance of patients to stop taking their current modulator therapies for extended periods.

Conclusions

We have reviewed three CF therapeutic areas where active comparator designs for study of future treatments appear unavoidable, each with unique challenges. Recent and current experiences suggest that how active comparators are identified and justified will affect both study feasibility and interpretability of study results. It will be incumbent on the CF community (the affected, their families, clinical investigators, and regulators) to recognize and address the challenges posed by this new era of active comparator study design. Development of methodologies that can reduce known biases and utilize patient registries or external controls from completed clinical trials as alternative comparators would be welcome advances supporting future novel study designs.

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Key points

- Increasing effectiveness of CF therapies has led to a reduced feasibility of placebo-controlled study designs for development of newer CF therapies.
- Studies employing active comparators may appear to be ethically feasible alternatives to placebo-controlled designs.
- Active-comparator study designs are complicated by a need to a) establish ‘valid’ active comparator(s), b) estimate a comparator’s *current* clinical efficacy (required for testing non-inferiority hypotheses), and c) acquire and effectively blind commercially-available comparators.
- Study designs of shorter duration with features such as rescue therapy may enable ethical and feasible use of a placebo comparator to promote streamlined development of new therapies in the presence of existing standard of care.