Developing Inhaled Antibiotics in Cystic Fibrosis: Current Challenges and Opportunities

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Cystic fibrosis (CF) is a genetic disease affecting multiple organ systems (1). The respiratory system is affected by complications resulting from impaired mucociliary clearance in the airways, and is the primary cause of morbidity in the current era (2). This impaired host defense against inhaled debris and microbes results in persistent lower airway bacterial infections, the most common of which are *Staphylococcus aureus* and *Pseudomonas aeruginosa* (3). *P. aeruginosa*, in particular, is linked to greater airway inflammation and overall decline in health (4, 5). Because of this, strategies to administer anti-pseudomonal antibiotics to the airways have been a cornerstone of CF clinical care for many years.

People with CF inhale antibiotics regularly as a chronic, suppressive therapy against persistent bacterial infection. This achieves high drug concentration at the site of infection (i.e., in the airway) without the high systemic exposure and associated risks of systemic side effects when administered enterally or intravenously (6). Prospective clinical trials and long-term observational studies have demonstrated relatively low risks of serious side effects from even years of intermittent inhaled antibiotic therapy, which is now the standard of care in the United States (7). Not all antibiotics are equally suited to inhalation, and desirable qualities include stability and tolerability when aerosolized, suitable pH, retained activity in the airway environment, and limited systemic absorption.

There are currently two anti-pseudomonal inhaled antibiotics approved for CF in the United States by the U.S. Food and Drug Administration (FDA). The first was tobramycin, initially approved in 1997 as a solution for inhalation, and more recently as a dry powder inhaler in 2013. Both formulations were proven safe and effective in clinical trials (8, 9). The other is aztreonam, approved in 2010 as a solution for inhalation delivered via a high-efficiency nebulizer device, as tested in clinical trials (10–12). Both antibiotics are approved for use for 28-day periods, and are typically administered chronically every other month. This cyclic approach to treatment was based on the hypothesis that it would reduce the selective pressure for antibiotic resistance compared with continuous treatment with one antibiotic (13). Studies suggest that *in vitro* drug sensitivity is modestly decreased with longstanding use of these medications, but high-level drug resistance is rare (14). Furthermore, data indicate that people with CF who are chronically infected with bacterial strains categorized as antibiotic resistant by *in vitro* minimal inhibitory concentration criteria often continue to benefit clinically from inhaled antibiotic therapy (14–16). Because of this, strict reliance on current measures of *in vitro* antibiotic resistance when considering the clinical benefits and risks of inhaled antibiotics as a therapeutic option is largely unfruitful.

With the development of inhaled aztreonam as a second commercial product, many people with CF eliminated the 4-week "off" periods when they did not receive inhaled anti-pseudomonal drug therapy (17, 18). Some were already doing so by nebulizing intravenous preparations of antibiotics off label, but many more began cycling between tobramycin and aztreonam in a pattern that is termed "continuous alternating therapy" (CAT). This approach has become increasingly popular—especially among patients with greater impairment in lung function or greater frequency of acute pulmonary exacerbations (17). The U.S. CF National Patient Registry (CFNPR) collects

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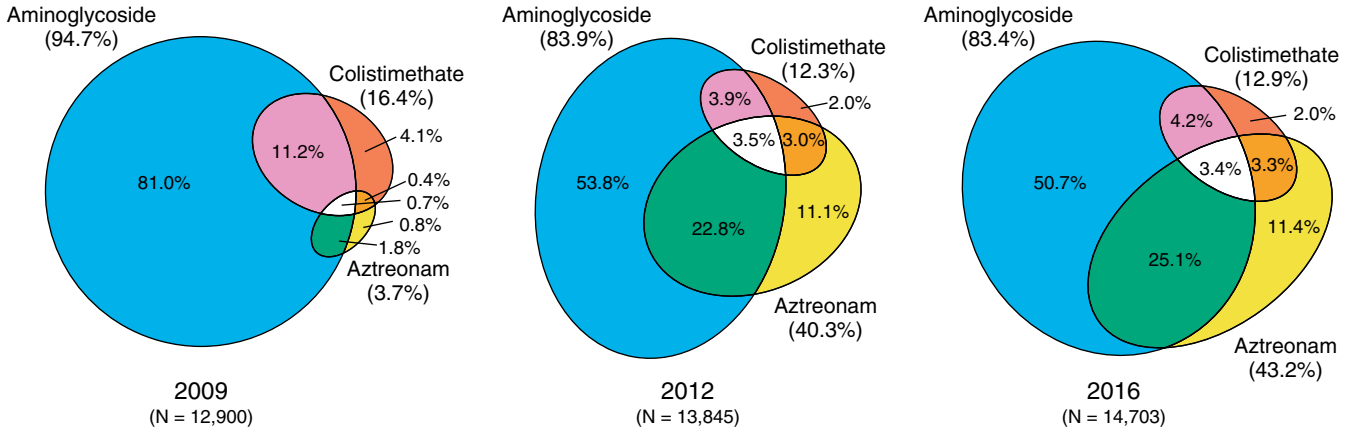

Figure 1. Shifting patterns of inhaled antibiotic use in the United States. Area-proportional diagrams of proportions of patients in the Cystic Fibrosis National Patient Registry receiving inhaled antibiotics during 2009, 2012, and 2016 by antibiotic classes recorded. Adapted by permission from Reference 18.

clinical data and therapy use on approximately 90% of those with CF in this country, and is a valuable tool for understanding patterns of clinical care (19). Recent data demonstrate the increasing popularity of CAT (Figure 1) (17). Indeed, it appears that a majority of people with CF who fit key inclusion criteria used in prior clinical trials of inhaled anti-pseudomonal antibiotics are now prescribed more than one inhaled antibiotic as part of clinical care (Figure 2). This is important, because it will fundamentally affect the ways in which additional inhaled antibiotics can be developed in future studies.

In preparation for an FDA-sponsored workshop held on June 27, 2018 to consider the clinical development of new inhaled antibiotics for people with CF and non-CF bronchiectasis, a group of CF investigators met to outline key considerations for CF inhaled antibiotic development. Herein are the central points of discussion and the consensus opinion of the authors, which were subsequently presented in this workshop. It is not meant to reflect opinions of the FDA or other regulatory agencies, but rather to serve as a perspective on current challenges for inhaled antibiotic development in CF and potential ways to address them. Summaries and recorded materials of the FDA workshop are available at www.fda.gov/drugs/newsevents/ucm602331.htm.

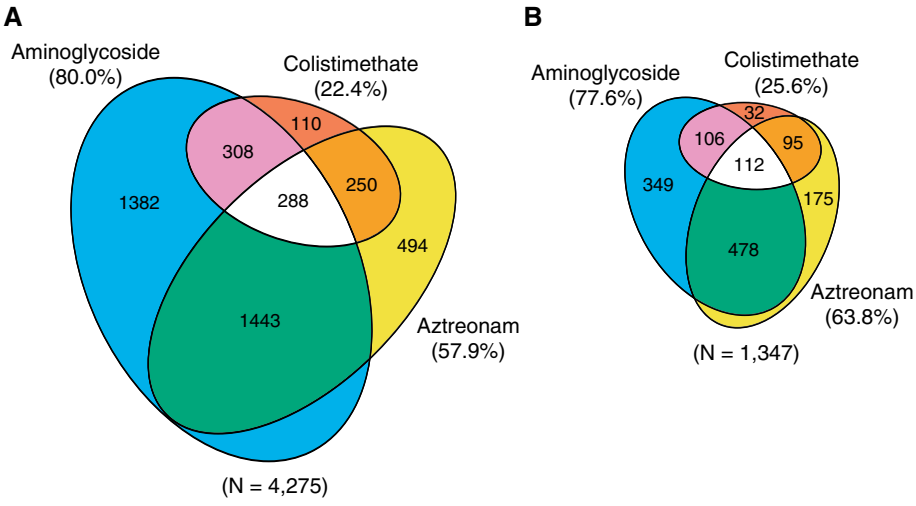

Figure 2. Inhaled antibiotic choices among patients in the 2016 Cystic Fibrosis National Patient Registry (CFNPR) subgroups. (*A*) Patients with demographics comparable to those studied in prior inhaled antibiotic clinical trials (≥12 yr old with forced expiratory volume in 1 second between 25% and 75% predicted, with at least one intravenous-treated pulmonary exacerbation in the prior year). (*B*) Patients in the CFNPR shown in *A* that had participated in at least one CF clinical trial since 2010.

Additional Inhaled Antibiotic Therapies for People with CF Are Needed

Inhaled antibiotics have a long history in the treatment of people with CF, historically by using intravenous formulations or compounding drugs for inhaled use. Tobramycin and aztreonam were developed and FDA approved for management of CF (tobramycin) and to improve respiratory symptoms in patients with CF with *P. aeruginosa* (aztreonam) nearly 20 and 10 years ago, respectively. Clinical prescriptions of both drugs rapidly increased once commercial products became available. These commercial products are now prescribed in the United States far more than the next-most-common inhaled antibiotic, colistimethate intravenous preparation inhaled off label (Figure 1) (17). Despite the availability and the common use of both tobramycin and aztreonam through CAT, large numbers of patients continue to experience acute pulmonary exacerbations and declining lung function. Few oral antibiotics are active against *P. aeruginosa*; thus, treatment for acute exacerbation events often requires intravenous drug administration with associated health risks, such as hearing loss, renal impairment, and socioeconomic costs. The clinical decline that many patients continue to experience highlights a need to develop new therapies, which includes additional effective inhaled antibiotics.

Understanding the Greatest Unmet Need for Additional Inhaled Antibiotics

Available drug regimens have proven effective and are largely meeting the needs of several important aspects of CF clinical care. Specifically, both inhaled tobramycin and aztreonam are highly effective at eradicating first or very early infection with *P. aeruginosa* (20, 21). Success rates are greater than 75%, and this is seen as important progress in treating CF. The prevalence of chronic *P. aeruginosa* infection in the U.S. CF population has steadily decreased over the last several years, with the greatest reductions observed in younger populations where successful eradication strategies may have played a pivotal role (22).

People with CF who develop chronic airway infection after failure of early eradication attempts are another important group to target with inhaled antibiotic therapy, but may not have the greatest unmet need for new medications. Results from the EPIC (Early Pseudomonas Infection Control) study suggest that those who do not clear *P. aeruginosa* when first identified in airway cultures may experience only modest clinical decline as compared with those who are able to eradicate the infection (23). Eradication remains an important goal, but patients unable to clear *P. aeruginosa* infection can often be adequately treated for many years with cycled or continuous alternating use of existing antibiotic options (24). Most patients will find a suitable and well-tolerated therapy among existing commercial products.

However, some patients will not be able to tolerate current approved inhaled antibiotics, or they may continue to experience clinical worsening despite use of available drug products. Clinical worsening may present as ongoing loss of lung function, persistent or increasing symptoms, and acute pulmonary exacerbations. Why some people develop a diminished clinical treatment response to these drugs is poorly understood and is not explained solely by *in vitro* resistance testing. CF is a generally progressive illness, and clinical worsening over time does not necessarily indicate diminishing response to any particular ongoing drug therapy. Nonetheless, new antibiotic options are likely to benefit people experiencing health decline, despite fully availing themselves of current commercial options. Recognizing this group most in need of new therapies will help to formulate the study population and trial designs that may be more attractive to potential participants and their care providers. In addition, little is known about the effects of alternative treatment strategies through combining more than one inhaled antibiotic or using continuous rather than cycled inhaled antibiotics. A greater number of proven drug options may facilitate comparative effectiveness studies to test these or other alternative treatment regimens.

Airway Pathogens Other Than *P. aeruginosa* Deserve Attention and Face Some Unique Challenges

P. aeruginosa remains a dominant therapeutic target for inhaled antimicrobial treatments because of an extensive body of epidemiologic data suggesting that acquisition of chronic *P. aeruginosa* infection is associated with disease acceleration and increased mortality risk. However, other bacterial airway opportunists also warrant consideration in CF inhaled drug development, including bacteria for which the direct effects on pulmonary health are more difficult to understand. *S. aureus* is the most common bacterium cultured from the airways of people with CF (17). This organism can be found in similar healthy populations as well, particularly when depending on swab sampling from the posterior pharynx (25). This complicates the interpretation of prevalence data, but does not negate a role for *S. aureus* in CF lung disease progression. Results from clinical trials of antibiotic therapy targeting *S. aureus* have been mixed. Methicillin-resistant *S. aureus* (MRSA) has received additional consideration, and relevant inhaled antibiotics are being developed—namely, vancomycin (26). Experts debate whether MRSA infection is an independent driver of clinical decline or, instead, evidence of a generally more severe disease phenotype that associates with greater antibiotic exposure (27–29). Clearly, both positions may be true, and results from ongoing or expected studies testing inhaled vancomycin may be informative when considering the value of targeting MRSA.

People with CF also develop airway infections with other, most commonly, gram-negative, organisms. Examples include *Burkholderia*, *Achromobacter*, and *Stenotrophomonas* species. U.S. CFNPR data indicate prevalence rates of nearly 10% for some of these bacteria, which are often intrinsically resistant to many antimicrobials (17). The prevalence of nontuberculous mycobacteria has also increased, and drug regimens for nontuberculous mycobacteria airway infections often include an inhaled antibiotic (30, 31), despite no FDA-approved option for people with CF. Similarly, fungal species can be cultured from respiratory samples in a significant minority of people with CF. Determining the pathogenicity of fungal airway infection, with or without an associated host allergic response, can be challenging, but inhaled antimicrobial therapy may have a role in treating this infection as well. A key challenge in drug development targeting infection with these "other" species is frequent coinfection with *P. aeruginosa* (and other species). It can be difficult to delineate the effects of treating copathogens in a population receiving chronic *P. aeruginosa* suppression (i.e., standard of care). The complexity of these types of investigations is compounded by relatively low population prevalence, creating logistic challenges in study enrollment. For all of these reasons, progress in drug development for lower-prevalence bacterial species has been relatively slow; however, there are antimicrobial agents in early development that may be better positioned to address some of these challenges (32). These candidate drugs work through distinct mechanisms that are largely agnostic to bacterial genus or species. Drugs with broad antimicrobial effects may be one way to develop new therapies for populations with low-prevalence pathogens and/or polymicrobial infection with both common and less common species.

Clinical Trial Designs to Test New Inhaled Anti-Pseudomonal Antibiotics in the United States or Similar Populations Will Differ from Prior Studies

Nearly all trials of inhaled tobramycin and aztreonam have been conducted in people with CF treated with, at most, a single inhaled antibiotic that is cycled on/off. These trials have included repeated or

prolonged periods (from 3 to 6 mo) during which some participants received either placebo or no active inhaled antibiotic. Measuring the effects of an inhaled antibiotic versus a placebo after an antibiotic-free period provides a more direct assessment of a single antibiotic therapy (8, 10, 11). As routine care has changed toward much greater use of CAT in patients with chronic *P. aeruginosa* airway infection, the feasibility of these prior trial designs must be revisited. Analyses of the 2016 U.S. CFNPR data, when limited to people likely to meet eligibility criteria for a trial of a new inhaled anti-pseudomonal antibiotic, find that nearly all are using chronic inhaled antibiotics, and most are prescribed two or more antibiotics for what is assuredly a CAT regimen (Figure 2). These patients experience at most 1-month periods without inhaled antibiotics, and many are avoiding the time off of inhaled antibiotics altogether. This will make it difficult to enroll subjects in randomized trials that require any prolonged periods without active inhaled antibiotic exposure (i.e., use of placebo). The time without active antibiotic use includes not only the direct observational period within a trial but also any required run-in or follow-up periods during which antibiotics are restricted.

Some more recent trials of inhaled antibiotics have included populations of patients with CF who receive a different standard of care than those treated in regions such as North America, Australia, or Western Europe (9, 33). Baseline demographic data indicate that many of these study participants have relatively more advanced lung disease for age and less frequent use of several concomitant medications. Although such differences in standard of care may allow for more traditional trials of new medications in some countries, the results produced from trials enrolling dissimilar subject populations are harder to generalize, and may not accurately predict the clinical response in the U.S. population. There are also important ethical considerations when using a patient population for clinical research purposes that is unlikely to benefit from subsequent access if the product is approved. Many CF research leaders and patient advocates call both for the conduct of pivotal clinical trials in study subjects similar to the intended patient population and broader availability of such medications to people with CF in all countries.

Advancing New Inhaled Antibiotics Will Require Alternative, More-Creative Designs for Pivotal Trials

Developing new therapies in the context of existing standard of care requires several key considerations: will participants be willing to risk randomization to placebo? How long can one be asked to forego active antibiotic therapy during a trial? What can be learned from open-label studies, and do active comparator trials need to be designed to show superiority to existing therapy? Finally, what are the relevant clinical endpoints that can be feasibly measured?

The first decision in the trial design process is whether to compare a new therapy to placebo or an existing active medication. Given the growing population of patients with CF receiving CAT, it is tempting to conclude that an active comparator study would be the most feasible and informative study design. However, this choice includes several major limitations, the first being that the study would likely need to be open label to avoid the significant challenges of purchasing and blinding another sponsor's drug. Open-label studies are more susceptible to bias, and the interpretation of such studies, particularly for effort-dependent or subjective efficacy measures, can be difficult. If a sponsor intends to blind a study, aerosol appearance, smell, taste, and irritability are much harder to mask than those of oral or intravenous agents. Furthermore, because approved inhaled antibiotics call for specific aerosol generators and formulations, maintaining the blinded nature of the study would require a double-dummy design, wherein each subject would be required to administer both active and placebo products throughout the trial. Such a design places a significant burden on participants that could lessen enthusiasm and adherence to protocol.

A second major limitation to active-comparator studies arises if developers want to demonstrate noninferiority (NI), as opposed to superiority, to an existing therapy. This approach will require the establishment of an NI margin to measure the primary endpoint. In proposing an NI margin, developers must be able to *a priori* justify the expected efficacy of the comparator, which is dependent on the availability of robust clinical efficacy data, ideally taken from multiple completed trials, for the proposed comparator. Unfortunately, in the case of proposing CAT as an active comparator, the only randomized, controlled CAT study was halted prematurely due to lack of enrollment (30). There are no data from which to estimate the efficacy of CAT in a contemporary cohort and thus rationalize an NI design. Even using data from inhaled tobramycin or aztreonam registration studies to propose NI margins for either approved therapy as an active comparator would be problematic, as both were developed and tested in relatively treatment-naive populations that would not be available today for randomized studies.

The alternative is, of course, a placebo-controlled design, which, for reasons of ease of interpretation, may have greater appeal to regulators. However, a requirement for sizable numbers of volunteers with disease to forgo active antimicrobial treatments for prolonged periods is a hurdle that may not be justified or easily overcome. That said, experience indicates that inhaled antibiotics targeting *P. aeruginosa* improve a key clinical efficacy measure, forced expiratory volume in 1 second (FEV_1), within 2–4 weeks. This allows greater opportunity for shorter-duration placebo-controlled assessments of candidate drugs that would be more feasible to recruit in the context of CAT as standard of care. In this scenario, durability of effect would still need to be demonstrated, presumably from longer-term open-label studies.

Consider the scenario in which a new inhaled antibiotic has demonstrated robust *in vitro* and nonhuman *in vivo* antimicrobial activity, produces a clinically meaningful and significant improvement in FEV_1 over 4 weeks as compared with placebo, and is safe, as demonstrated by a longer-duration safety database over several months. It could be argued that this represents an acceptable data "package" that would suffice to meet the needs of the CF community for establishing clinical efficacy and safety of a new therapy. Success of this approach is predicated on the assumption that significant FEV_1 improvement over 4 weeks as compared with placebo is an acceptable demonstration of clinical efficacy.

Important limitations to shorter placebo-controlled trials include: *1*) inability to evaluate effect durability; *2*) limited opportunity to assess other outcome measures (e.g., risk of pulmonary

exacerbation) versus placebo; and *3*) lack of long-term safety data. The shorter duration studies outlined here would typically only be appropriate in the setting of a new therapy for which a clinically meaningful FEV_1 response is expected. A definition of a clinically meaningful FEV_1 improvement in the current CF era is debatable, and may be smaller than the effect size observed with inhaled tobramycin or even aztreonam (discussed subsequently here). Rapid improvement in other efficacy measures (e.g., validated symptom or quality-of-life assessment tools) would provide added value, but may not be adequate alone in this context.

Operationally, a 4-week trial with an FEV_1 primary endpoint and an expected effect size of 5% change in absolute FEV_1 % predicted could require as few as 100 patients for adequate statistical power—a huge feasibility advantage in the current landscape of CF trials. This duration and subject number would be insufficient to establish safety; thus, an expanded enrollment strategy in a longer open-label study may be necessary. In addition, enrolling a parallel observational standard-of-care control group would afford long-term comparisons and generate important supportive data, in particular with respect to safety endpoints, but also with other efficacy measures, such as pulmonary exacerbation risk.

An emphasis on shorter placebo-controlled efficacy trials coupled with longer open-label studies of safety and durability is a pragmatic, but not radical, design adaptation to enable new drugs to become available for those in need. Such trials may not necessarily be easier for sponsors to conduct than past studies, and effect sizes may be smaller overall due to increasing benefits observed from the adoption of highly effective CF modulators into standard of care and likely study population demographics. However, it is important to propose feasible, informative designs that can be conducted in the population for whom the drug is likely to be used.

Effect Sizes in Key Outcome Measures Are Expected To Be Smaller than Has Been Seen in the Past

Efficacy of inhaled antibiotics has been demonstrated by change in lung function measured by spirometry (e.g., FEV_1), improved quality of life based on self-reported symptoms, reduction in the concentration of bacteria cultured from sputum samples, and risk of acute pulmonary exacerbation (8–11). It is important to recognize that baseline lung function has improved and symptom burden has lessened in recent years as people with CF increasingly benefit from a growing armamentarium of treatment options, including CF transmembrane conductance regulator modulators. Furthermore, CF populations in greatest need of alternative inhaled antibiotic classes consist mainly of adults, a group that has always experienced more modest lung function benefits from inhaled antibiotics (8, 10). In addition, as already noted, study designs may need to limit, or avoid entirely, periods without inhaled antibiotics (34). For all of these reasons, developers would be well advised to anticipate smaller treatment effect sizes in future inhaled antimicrobial studies. Early-phase clinical testing often focuses on safety, dose determination, and pharmacokinetics, but developers should also consider how early-efficacy measures can help predict the effect size in a population likely to enroll in later pivotal trials.

In summary, the clinical care of people with CF is rapidly improving. This progress is to be celebrated, but does not negate the need for inhaled antibiotic therapies. Currently available FDA-approved treatment options are meeting the needs of certain important aspects of clinical care, but these drugs have been used now for up to 20 years. New antibiotic options are needed both for those with longstanding infections with *P. aeruginosa* and for those with other, often less common, but highly resistant, airway pathogens. Years of successful drug development and standardized clinical care guidelines have provided better overall health and led to more common chronic use of one or more inhaled antibiotics. This significantly alters how future trials with new drug candidates can occur. Despite these challenges, feasible, informative developmental pathways exist. Clinical trial leaders and prospective sponsors are encouraged to consider the key points provided here when developing study designs and in discussions with regulatory agencies. It is hoped that this will lead to successful design and completion of trials that will make available new inhaled antibiotics for people with CF. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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