Potential for Therapeutic Benefit among Cystic Fibrosis Populations Excluded from Clinical Trials or Labeling of Marketed Therapies

Donald R. VanDevanter¹, Sonya L. Heltshe², and John J. LiPuma³

¹Case Western Reserve University School of Medicine, Cleveland, Ohio; ²Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, Seattle Children's Research Institute and Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington; and ³University of Michigan Medical School, Ann Arbor, Michigan

ORCID ID: 0000-0002-5727-8164 (D.R.V.).

Abstract

Remarkable advances in the management of individuals born with cystic fibrosis (CF) would not have been realized without empiric trial and error by CF clinicians with treatments developed and available for other purposes. As the testing and registration of CF-specific treatments have increased, so too have associated health care costs, particularly those of chronic medications. The transition of CF from a lethal pediatric disease to a life-shortening one with an adult majority, concurrent with sharp increases in chronic medication costs, has placed many CF treatments under increased scrutiny by third-party payers, particularly when prescribed to individuals from CF subpopulations that may not

have been included in registration trials. Despite overall health improvements in the CF cohort and the increasing availability of CF-specific therapies, many physicians remain tasked with managing the health of patients from subpopulations that may be too young, too sick, or too complicated to have been included in clinical trials. An understanding of why particular CF subpopulations may have been excluded from registration trials, as well as consideration of a treatment's described mechanism of action, can support assessment for the potential for benefit (and risk) in these populations and help physicians advocate for patient access to treatments.

Keywords: cystic fibrosis; excluded subjects; off-label; risk and benefit

(Received in original form June 14, 2016; accepted in final form August 7, 2016)

Disclaimers: The views expressed in this article do not communicate an official position of Case Western Reserve University School of Medicine, the Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, the University of Washington School of Medicine, or the University of Michigan Medical School.

Correspondence and requests for reprints should be addressed to Donald R. VanDevanter, Ph.D., 12520 33rd Street Ct E, Edgewood, WA 98372. E-mail: Drv15@case.edu

Ann Am Thorac Soc Vol 13, No 11, pp 1890–1893, Nov 2016

Copyright © 2016 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201606-462PS

Internet address: www.atsjournals.org

Pricing associated with cystic fibrosis (CF) modulator therapies ivacaftor (Kalydeco; Vertex Pharmaceuticals, Boston, MA) (1) and lumacaftor-ivacaftor (Orkambi; Vertex Pharmaceuticals) (2) has gained the attention of both the CF clinical community (3) and third-party payers (4). In a situation not unique to CF, the high costs of these latest CF treatments have elevated the profile of negotiations among patients, families, physicians, and third-party payers with respect to treatment access. What may be less obvious is that this is only the most recent chapter in a continuing struggle to gain patient access

to approved and established CF treatments.

The ability and right of physicians to accept responsibility for the administration of available medical treatments to their patients, irrespective of whether these treatments have been studied or approved for the intended use or patient type, is an essential component of our medical delivery system. It is a system that allows for flexibility, innovation, and access to treatments for patients with rare diseases, but which places tremendous accountability on physicians, who are responsible for weighing the risk and benefit potentials of

treatments in individuals from populations not included in previous clinical trials, all the while striving to “do no harm” (5). In addition, physicians are expected to fully inform patients and families of the extent to which objective safety and efficacy evidence supporting proposed treatments are available (5, 6).

Demonstration of the safety and efficacy of a treatment, a requirement for marketing authorization, is most commonly achieved via blinded, randomized, controlled trials in defined patient populations (7). Results from these registration trials are summarized in

prescribing information (i.e., the treatment “label”) that accompanies marketed therapies. However, for the half-century following the initial description of CF, when there were no treatments specifically indicated for the disease, median predicted survival among children diagnosed with CF steadily increased from months, to years, to decades (8). At present, more than one-half of persons in the United States with CF are adults (9), a remarkable milestone and improbable were it not for aggressive “off-label” treatment of disease-associated gastrointestinal and airway complications over the preceding decades. In the past two decades, several chronic CF therapies have been extensively studied in and approved for specific CF subpopulations, leaving CF clinicians faced with risk/benefit assessment of their potential for effectiveness in subpopulations who were not included in clinical trials.

Reasons for Inclusion versus Exclusion of Subpopulations in Clinical Trials

When considering objective clinical trial evidence that supports a CF treatment label, it is important to distinguish between patient subpopulations that have been excluded from a label indication because the target of that therapy is not present (e.g., lack of an infecting bacterial species for antibiotic therapies [10, 11] or lack of a specific gene mutation for mutation-specific CF therapies [12, 13]), or because of a demonstrated contraindication (i.e., where risks associated with treatment have been demonstrated to outweigh benefit potential in clinical trials; these subpopulations are included in labeling), and those subpopulations for which there is little/no safety or efficacy information because they were not included in clinical trials.

Participants are screened and enrolled in prospective clinical trials on the basis of specific demographic, physical, and clinical criteria that confer trial “eligibility.” Although objective demonstration of safety and efficacy is dependent on inclusion in controlled trials, there is no basis for an *a priori* conclusion of increased treatment risk or treatment ineffectiveness in excluded patient populations. Rather, treatment safety and

efficacy remain undemonstrated. For patient subpopulations without a known contraindication but who nonetheless have been excluded from clinical trials, estimation of the potential for a marketed CF therapy to provide benefit can be aided by an appreciation of likely reason(s) for their trial exclusion and the mechanism of action of the treatment in question.

Importantly, exclusion of specific CF populations from clinical trials is as likely to occur for pragmatic reasons related to efficacy end points or subject safety as to a hypothesis of a lack of potential for clinical benefit. Indeed, many CF efficacy end points are considered reliable and sensitive only in specific CF subpopulations. Measurement of treatment-associated CF lung function benefit is illustrative. About 80% of persons with CF in the United States die directly or indirectly as a result of lung function loss (9), with initiation of progressive lung disease evident in newborns with CF (14). For this reason, preservation of lung function has been identified as a clinically meaningful measure of treatment efficacy by CF investigators (15).

The most commonly used and perhaps best-described measure of CF lung function, FEV₁, a spirometric measure that has supported the registration of several chronic CF therapies (1, 2, 10–13, 16), cannot be reliably measured in children less than 6 years of age. Further, treatment-associated improvements in FEV₁ are most likely to be observed in individuals with CF who have experienced some prior loss of FEV₁ (17). For these reasons, CF trials using FEV₁ as a measure of treatment-associated clinical efficacy have routinely excluded children less than 6 years of age and older subjects with FEV₁ measures that approximate those of unaffected peers of the same age, height, sex, and race.

However, substantial and progressive lung damage can be demonstrated in children with CF before a measurable effect on FEV₁ (14). Because the etiology of progressive lung disease is related to the primary CF defect and is evident early in life (14), it is reasonable to conclude that FEV₁-preserving interventions may also have the potential to provide lung function-sparing benefit outside of “FEV₁ end point-appropriate” trial populations. By analogy, if investigators were using work

absenteeism as a measure of health and well-being and for this reason only studied gainfully employed individuals, it would be reasonable to conclude that a therapy that significantly reduced absenteeism in working populations would also be effective in the unemployed.

In fact, use of FEV₁ as an efficacy end point for registration of chronic CF therapies has had serious implications for patient access to approved treatments. For example, several state Medicaid programs currently restrict access to lumacaftor-ivacaftor to only those individuals with CF who have between 40% and 90% of their predicted lung function (18–21) (i.e., the subpopulation included in registration studies [1, 2]). Unfortunately, individuals with CF and lower socioeconomic status, including those reliant on state Medicaid programs, have been repeatedly shown to have overall poorer health outcomes (22–24) and presumably have great potential for respiratory benefit regardless of their FEV₁.

The sensitivity and applicability of particular end points are not the only pragmatic justifications for excluding CF populations with a potential for clinical benefit from randomized, controlled trials. Subpopulations that may add variance to an end-point measure are often excluded to increase the probability of demonstrating statistical significance. Perhaps most common is the exclusion of individuals with airways infected with particular bacterial species. A prominent example has been the exclusion of persons with CF and airway infection with *Burkholderia cepacia* complex from trials of chronic inhaled antibiotics among subjects with *Pseudomonas aeruginosa* infection (10, 11), as well as their exclusion from trials of other chronic CF therapies (1, 2).

This unfortunate practice is a vestigial remnant of especially poor outcomes among persons with CF in North America and the United Kingdom who were infected with “*B. cepacia*” in the 1980s (25, 26). Early reports described rapid deterioration, necrotizing pneumonia, bacteremia, and sepsis among infected persons; this “cepacia syndrome” was observed in as many as 20% of infected patients (27). We now appreciate, however, that these initial reports were impacted by the dominance of a particularly virulent strain of *B. cepacia* complex (since identified as *B. cenocepacia* strain ET-12). Subsequent trials have made it clear that not all individuals with CF and

chronic *B. cepacia* complex infections are at the same risk for cepacia syndrome as individuals infected with the ET-12 strain (27), yet typically they have been excluded from registration trials. These individuals have every right (and perhaps a greater need) to receive benefit offered by therapies shown to be safe and effective in other CF subpopulations; they must be provided access if their clinician has determined they may safely benefit.

Finally, there may be pragmatic safety reasons for exclusion of subpopulations from trials. A common example is the exclusion of subjects with renal insufficiency from trials of CF therapies with a potential for nephrotoxicity (1, 2, 10, 11). Investigators and regulators are understandably inclined to collect evidence of potential for nephrotoxicity in “healthy” trial subjects rather than compromised volunteers at elevated risk for renal failure. However, such exclusions need not necessarily influence subsequent patient access, as patients with poor renal function should still have access to (safely and carefully administered) therapies.

Consider that although trials of inhaled treatments with the potentially nephrotoxic antipseudomonal antibiotics tobramycin and aztreonam excluded subjects with poor renal function (10, 11), both treatments are associated with substantially lower systemic drug exposures than their intravenous counterparts, and thus might be considered attractive alternatives to systemic treatment for the very population in question: individuals with poor renal function. Similarly, exclusion of pregnant or lactating females from clinical trials is almost uniform, with justifications ranging from serious concerns identified in preclinical animal trials to a simple lack of adequate knowledge of safety to the fetus or newborn.

Although these are extremely important risk considerations, they should not be interpreted as an indication that pregnant or lactating women have no potential for clinical benefit from a treatment, or that pregnant or lactating women should not receive care. Rather, these decisions reflect the potential for harm to a fetus or newborn for a therapy for which overall benefit has yet to be demonstrated. Postmarketing case reports in the peer-reviewed literature (which typically do not result in label amendments) can provide important additional information for safety

assessment associated with pregnancy and/or breastfeeding (28, 29). Importantly, not all safety-based exclusions are merely pragmatic. Exclusion of individuals with known hypersensitivities to treatments is, in essence, recognition of previously identified contraindications.

Anticipating Effectiveness Potential in Patients from Excluded Populations

The points above have highlighted subpopulation exclusions that are not necessarily related to benefit potential. However, exclusion of subpopulations from registration trials for reasons other than benefit potential does not mean that excluded subpopulations should be automatically predicted to experience clinical benefit. An important source of information on benefit potential for subpopulations not included in registration studies is the peer-reviewed literature.

For instance, large randomized controlled postmarketing studies have suggested dornase alfa (30) and inhaled tobramycin (31) treatment benefits outside of registration subpopulations. However, neither product label was amended to reflect these postmarketing findings. In the absence of informative postmarketing studies, it is useful to consider the mechanism of action of a treatment as well as what we can infer about the results of the treatment in unstudied compared with studied populations. Specifically, when treatments have a “target” or “receptor,” then at a minimum the presence of these in the untreated population would seem necessary to anticipate clinical benefit. For example, treatment with dornase alfa, an inhaled therapy that cleaves high molecular weight DNA released from dead neutrophils in CF airway mucus, would not be predicted to be as effective in patient populations with little or no local inflammation as it would be in individuals with excessive neutrophil infiltrates. Similarly, inhaled antipseudomonal antibiotics might be predicted to be less beneficial in individuals without evidence of pseudomonal airway infection.

With respect to the results of a treatment in unstudied populations, pharmacokinetics and pharmacodynamics related to dosing and bioavailability may be important considerations. For instance, it

may be difficult to predict a safe, efficacious, or palatable dose of a treatment studied and registered in adolescents and adults in very young children with CF, even if the treatment “target” is present. In addition, it may be difficult to physically deliver a therapeutic dose because of physiological or developmental differences. Consider, for instance, that dry powder formulations of inhaled antibiotics require a degree of active inhalation by patients for lung deposition that is not feasible in infants, where passive inhalation of wet aerosols using a face mask is common.

Finally, there may be reports of adverse events in studied populations that could pose serious risks during treatment of patients from unstudied subpopulations and that must be carefully evaluated by physicians and fully discussed with patients. For instance, associations between dyspnea and abnormal respiration and lumacaftor-ivacaftor treatment (2) may be viewed as unacceptably risky in patients with FEV₁ less than 40% predicted. Greater physician experience in studied patients and/or publication of postmarketing studies in other populations will likely improve the risk/benefit assessment of off-label treatment of these patients. Evaluating these important factors is one of the many responsibilities our system affords treating physicians, not third-party payers, when off-label treatments are a viable option.

Conclusions

The remarkable advances in the overall health of persons with CF is a testament to the potential for off-label, empiric use of therapies to modify a rare, life-shortening disease. Despite overall improvement in the health of the CF cohort and the increasing availability of CF-specific therapies, many physicians remain tasked with managing the health of patients from subpopulations whose members are too young, too sick, or too complicated to have been included in clinical trials. The potential for these patients to benefit from treatments is not necessarily defined by their past trial eligibility, and they are certainly no less entitled to beneficial treatments than others.

As more and more CF therapies gain registration, it will be important for CF clinicians and caregivers to advocate for access to these life-changing therapies for all patients with a potential for benefit,

including those from subpopulations whose members may have been excluded from clinical trials. As emphasis on personalized treatment of disease increases throughout medicine,

opportunities for improved patient outcomes accompanied by greater physician accountability will expand. With careful deduction, it will be possible for physicians to advocate for their

patients by articulating a rationale for anticipation of clinical efficacy. ■

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

References

- Vertex Pharmaceuticals. Kalydeco prescribing information. 2015 [accessed 2016 June 14]. Available from: http://pi.vrtx.com/files/uspi_ivacaftor.pdf
- Vertex Pharmaceuticals. ORKAMBI prescribing information. 2016 [accessed 2016 June 14]. Available from: http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf
- Orenstein DM, O'Sullivan BP, Quinton PM. Cystic fibrosis: breakthrough drugs at break-the-bank prices. *Glob Adv Health Med* 2015;4:8–57.
- Silverman E. Orkambi's slick unveiling puts insurers in a bind. *Managed Care Magazine* 2015 [accessed 2016 June 14]. Available from: <http://www.managedcaremag.com/archives/2015/8/orkambis-slick-unveiling-puts-insurers-bind>
- American Academy of Pediatrics, Committee on Drugs. Uses of drugs not described in the package insert (off-label uses). *Pediatrics* 2002; 110:181–183.
- Dresser R, Frader J. Off-label prescribing: a call for heightened professional and government oversight. *J Law Med Ethics* 2009;37: 476–486, 396.
- Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Food and Drug Administration, U.S. Department of Health and Human Services. Guidance for industry: providing clinical evidence of effectiveness for human drug and biological products. 1998 May [accessed 2016 June 14]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf> + Providing + clinical + evidence + of + effectiveness + for + human + and + bioclient = FDAgovsite = FDAgovlr = proxystylesheet = FDAgovoutput = xml_no_dtdie = UTF-8access = poe = UTF-8
- Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947–2003. *Eur Respir J* 2007;29:522–526.
- Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry, 2014: annual data report to the center directors. Bethesda, MD: Cystic Fibrosis Foundation; 2015.
- Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasiljev-K M, Borowitz D, Bowman CM, Marshall BC, et al.; Cystic Fibrosis Inhaled Tobramycin Study Group. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med* 1999;340:23–30.
- Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, Cooper PJ. Efficacy and safety of inhaled aztreonam lysine for airway *Pseudomonas* in cystic fibrosis. *Chest* 2009;135:1223–1232.
- Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, Giese M, McKone EF, Wainwright CE, Konstan MW, et al.; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365: 1663–1672.
- Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, De Boeck K, Flume PA, et al.; TRAFFIC Study Group; TRANSPORT Study Group. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015;373:220–231.
- VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: a review of disease manifestation, progression, and response to early treatment. *J Cyst Fibros* 2016;15: 147–157.
- Ramsey BW, Boat TF. Outcome measures for clinical trials in cystic fibrosis: summary of a Cystic Fibrosis Foundation consensus conference. *J Pediatr* 1994;124:177–192.
- Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, Rosenstein BJ, Smith AL, Wohl ME; Pulmozyme Study Group. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;331:637–642.
- VanDevanter D, Konstan MW. CF drug developers: victims of our own success. *Respir Drug Deliv* 2008;1:11–18.
- State of California—Health and Human Services Agency, Department of Health Care Services. Lumacaftor/ivacaftor (Orkambi). N.L. 06-0915. 2015 Sept 4 [accessed 2016 Sept 10]. Available from: <http://www.dhcs.ca.gov/services/ccs/Documents/ccsnl060915.pdf>
- Illinois Department of Healthcare and Family Services. Orkambi (lumacaftor–ivacaftor tablet): prior authorization criteria. 2015 September [accessed 2016 Sept 10]. Available from: <http://www.illinois.gov/hfs/SiteCollectionDocuments/OrkambiCriteria.pdf>
- Division of Medical Assistance Programs, Oregon Health Authority. Oregon Medicaid Pharmaceutical Services prior authorization criteria. 2016 Jan 1 [accessed 2016 Sept 10]. Available from: <https://www.oregon.gov/oha/healthplan/tools/Oregon%20Medicaid%20PA%20Criteria,%20January%202016.pdf>
- Magellan Health Services. Clinical criteria, step therapy, and quantity limits for TennCare preferred drug list (PDL). 2016 July 20 [accessed 2016 Sept 10]. Available from: https://tenncare.magellanhealth.com/static/docs/Preferred_Drug_List_and_Drug_Criteria/Criteria_PDL.pdf#nameddest=cystic_fibrosis_agents
- Quittner AL, Schechter MS, Rasouliyan L, Haselkorn T, Pasta DJ, Wagener JS. Impact of socioeconomic status, race, and ethnicity on quality of life in patients with cystic fibrosis in the United States. *Chest* 2010;137:642–650.
- Schechter MS, McColley SA, Silva S, Haselkorn T, Konstan MW, Wagener JS; Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis; North American Scientific Advisory Group for ESCF. Association of socioeconomic status with the use of chronic therapies and healthcare utilization in children with cystic fibrosis. *J Pediatr* 2009;155:634–9.e1–4.
- VanDevanter DR, Pasta DJ, Konstan MW. Improvements in lung function and height among cohorts of 6-year-olds with cystic fibrosis from 1994 to 2012. *J Pediatr* 2014;165:1091–1097.e2.
- Isles A, Macluskay I, Corey M, Gold R, Prober C, Fleming P, Levison H. *Pseudomonas cepacia* infection in cystic fibrosis: an emerging problem. *J Pediatr* 1984;104:206–210.
- Muhdi K, Edenborough FP, Gumery L, O'Hickey S, Smith EG, Smith DL, Stableforth DE. Outcome for patients colonised with *Burkholderia cepacia* in a Birmingham adult cystic fibrosis clinic and the end of an epidemic. *Thorax* 1996;51:374–377.
- Lipuma JJ. The changing microbial epidemiology in cystic fibrosis [review]. *Clin Microbiol Rev* 2010;23:299–323.
- Kaminski R, Nazareth D. A successful uncomplicated CF pregnancy while remaining on ivacaftor. *J Cyst Fibros* 2016;15:133–134.
- Goss CH, VanDevanter DR. CFTR modulators and pregnancy: our work has only just begun. *J Cyst Fibros* 2016;15:6–7.
- Quan JM, Tiddens HA, Sy JP, McKenzie SG, Montgomery MD, Robinson PJ, Wohl ME, Konstan MW; Pulmozyme Early Intervention Trial Study Group. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001;139:813–820.
- Murphy TD, Anbar RD, Lester LA, Nasr SZ, Nickerson B, VanDevanter DR, Colin AA. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatr Pulmonol* 2004;38:314–320.