Outcome Measures for Development of New Therapies in Cystic Fibrosis

Are We Making Progress and What Are the Next Steps?

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Since the discovery of the gene encoding the cystic fibrosis transmembrane regulator protein (CFTR) in 1989, rapid expansion in our understanding of the basic defect has afforded the cystic fibrosis (CF) community the opportunity to develop new therapies to correct the pathobiological consequences of absent or defective CFTR and to improve the lives of patients (1). Over the same time period, the number of multicenter clinical studies directed at correcting the secondary consequences of dysfunctional CFTR has rapidly increased, with 453 clinical studies identified by PubMed (www.pubmed.gov) that were published in 2006 compared with 19 studies published in 1990. Clinical trials have led to the U.S. Food and Drug Administration (FDA) approval of two therapies (2, 3) for the treatment of CF lung disease (Pulmozyme and TOBI) and to the current evaluation of at least two new therapies in pivotal phase 3 studies (4, 5). In addition, dozens of potential therapies are making their way through earlier stages of the therapeutic pipeline. Although no approved therapies currently treat the underlying genetic defect, promising approaches to correct CFTR are currently in early-phase trials (6–8).

In spite of this enormous progress in both basic and clinical science, CF remains a challenging field for the development of new therapies. First, this illness falls within the orphan disease designation (www.rarediseases.org), with approximately 30,000 identified individuals in the United States (9), and thus a finite number of patients are available for clinical trials in any geographic location. Thus, the conduct of pivotal phase 3 trials requiring more than 500 patients often requires multinational participation, adding significant complexity and cost. Second, improved life span and stabilization of progression of lung disease, albeit encouraging, are resulting in an evolution of clinical end points. With median survival of almost 40 years, mortality is no longer a realistic outcome. A surrogate measure for mortality, median FEV₁ as a function of age, has also improved over the past two decades (9). This change makes it increasingly difficult to detect a meaningful treatment effect except in large studies of long duration (10). Thus, there is an increasing need to validate new outcome measures and to improve the assessment of existing outcome measures.

Beginning in the early 1990s, the Cystic Fibrosis Foundation (CFF) (Bethesda, MD) realized the need to develop clinical end points for therapeutic trials. A group of CF specialists and FDA representatives convened in 1992 to review the state of the art for outcome measures at that time (11). Eight key issues were

recommended as top priorities: (1) definition of a pulmonary exacerbation; (2) broadly applicable measures of testing pulmonary function in small children; (3) a comprehensive severity of disease score for young children; (4) reliable methods of quantifying chest X-rays and computerized tomography (CT) scans in young patients; (5) simple, inexpensive measures of lung inflammation; (6) centralized uniform approach to establishment of data monitoring committees; (7) quality of well-being scales for small children; and (8) reliable, reproducible aerosol delivery systems. Although not all these issues have been resolved, this symposium will elucidate some areas of significant progress, including infant and toddler pulmonary function testing, imaging in young children, quality-of-life measures, definitions of pulmonary exacerbation, and improved measures of lung inflammation.

Advances in outcome measures development have been the result of joint efforts of CF researchers worldwide, who have collaborated in the development of standard procedures for measurements such as infant pulmonary function testing (12) and CT imaging (13). Another CFF initiative was the establishment in 1998 of the Therapeutics Development Network (CFF TDN) to enable the rapid evaluation of new therapies for CF (14). A key component of the CFF TDN mission has been the validation of clinical outcome measures for therapeutic trials conducted at multiple centers. While most outcomes are initially tested in small, single-site studies, the transition toward use of an outcome measure at multiple sites can be a complex and often overlooked process. This transition requires the development of standardized procedures, training of research staff, and in some cases establishment of a central interpretive center or core laboratory. Through these processes, intra- and intersite variability can be reduced and thus the statistical power to see a therapeutic effect is enhanced. Since 1998, the CFF TDN, composed of 18 clinical sites and a central coordinating center, has established processes and central reading centers for microbiology, inflammatory markers, nasal potential difference measurement, sweat testing, chest imaging, and infant pulmonary function testing. These processes and standard operating procedures are available to all CF researchers worldwide on request (tdncc@seattlechildrens.org). In addition, outcome measures working groups within the network have been established to address issues such as quality improvement, new assay developments, and statistical methodologies. At the CFF TDN annual meeting in Seattle, Washington, in April 2006, these working groups were asked to carefully assess the current “state of the art” of a range of commonly used clinical end points in CF and to define the next steps required for further validation or improvement. The deliberations of these groups are summarized in this symposium.

Before the groups met, they were given a framework for their discussions in a keynote address, summarized in the first article by Mayer-Hamblett and colleagues. This article presents an overview of outcome measures currently used in CF clinical studies defined and categorized by the three main classes of end points: clinical efficacy measures, surrogate end points, and biomarkers.

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The article then defines the principles to be followed in the ongoing process of evaluating, improving, and validating existing and emerging end points for clinical research and recommends that the CF community adopt a consistent and rigorous approach to this process. The key characteristics for which CF outcome measures should be evaluated include (1) clinical and biological relevance, (2) sensitivity and specificity to treatment effects, (3) reproducibility, and (4) feasibility. The reader will see that these themes are carried throughout the subsequent articles focused on each of the working group reports.

One working group focused on clinical efficacy measures based on patient-reported outcomes (PROs) and is summarized in the article by Goss and Quittner. There is a general discussion of PRO development and validation consistent with FDA guidance (<http://www.fda.gov/cder/guidance/>), followed by a review of existing measures used in CF to characterize the functional, physical, and emotional outcomes of the disease. These measures are divided into three categories: health-related quality of life, respiratory symptom scores, and signs and symptoms defining a pulmonary exacerbation. The article also defines the critical next steps to validate measures in each of these categories.

The remaining four articles focus on a range of biomarkers and potential surrogate markers that are currently used or being developed for all phases of therapeutic development. The article by Rowe and coworkers is a comprehensive review of *in vivo* measures detecting the presence and physiologic functioning of CFTR with particular emphasis on nasal potential difference (NPD) and sweat chloride. Both of these techniques are well established as diagnostic markers of CF (15) and have been widely used to define genotype and phenotype correlations (16). The next step is to optimize and validate these assays for use as biomarkers in multicenter clinical trials to assess treatment effects. This article reviews the current strengths and limitations of NPD and sweat chloride as well as future studies required to further validate these measures.

The next biomarker of physiologic function presented in this symposium is mucociliary clearance (MCC) by Donaldson and coworkers. Because ion transport abnormalities in CF reduce airway surface liquid (17), and secondarily impair MCC, many new therapies are targeted to correction of this important biologic function. Evidence suggesting that the change in MCC is associated with clinical efficacy (18, 19) has led to renewed interest in this biologic efficacy measure. This article outlines current steps to further validate this measure and to standardize procedures and increase the feasibility of using this measure across multiple sites for future studies.

Sagel and coworkers review the use of an array of biomarkers (both cellular and soluble mediators) to monitor the impact of therapies on airway inflammation, a key factor leading to progressive structural damage (e.g., bronchiectasis). The focus of the article is on markers derived from sputum collected after hypertonic saline induction, argued to be the safest and most promising source of relevant biological fluid. Significant efforts to standardize specimen collection, processing, and centralized interpretation leading to reduced variability and improved reproducibility are described. The authors propose a lung injury biomarker panel relevant to CF therapeutic trials and the necessary steps to validate this panel.

The final article, by Davis and coworkers, provides a comprehensive update on improved outcome measures for young children (less than 6 years of age) with CF. Since the 1992 conference, significant progress has been made in methodologies for infant and toddler pulmonary function testing and CT in this age group. Infection and inflammation of early lung disease have also been well defined through longitudinal studies based on bronchoalveolar lavage. The article reviews the use of these

end points in more recent studies and the next validation steps required.

It is recognized that the breadth of CF outcome measures goes well beyond what is covered in this symposium, and thus the included articles focus on several key outcome measures for which some of the most significant activity has occurred over the last decade. For example, pulmonary function testing in older patients and airway microbiology are reviewed in the Mayer-Hamblett article but were not the focus of working group reports because standard procedures for these end points are well established for multicenter studies (20, 21). In addition, development of imaging biomarkers is the focus of the other symposium on cystic fibrosis that appears in the first section of this issue of *PATS* (22), and therefore discussion in this symposium was limited to children younger than 6 years of age.

Although no working group was focused on the definition of a pulmonary exacerbation (PE), this important clinical outcome measure is discussed herein in the articles by Goss, Mayer-Hamblett, Davis, and colleagues (23–25). Since the CFF–FDA conference in 1992, several PE definitions have been published and have been used as key clinical efficacy measures in phase 3 trials (2, 3, 26–28). Two review articles have summarized the current status of this clinical end point in CF (29, 30). The currently available PE definitions consist of constellations of patient symptoms, physical findings, and laboratory data. They have helped in the validation process (26) but have not resulted in a universally accepted definition by clinicians and researchers (31). One limitation of all published definitions is that they are physician-derived, rather than patient-derived, interpretations of health-related symptoms. In response to the FDA guidance on PROs, the CFF is supporting efforts to incorporate patient (parent)-reported changes in symptoms and functioning into future definitions of PE (23).

The efforts of these working groups have led to continued enthusiasm in the CFF TDN for optimizing clinical end points. There has been particular interest in finding opportunities to validate these end points within the context of therapeutic trials. For example, development of a multicenter study to evaluate the impact of hypertonic saline on infant pulmonary function testing over an 18-month period has been proposed as a means to test the sensitivity of this outcome for capturing response to therapy in this young age group. It is hoped that readers involved in CF-related research will find these reviews helpful in developing their next clinical studies, both in terms of defining the appropriate outcome measures and recognizing opportunities to further the validation process. More generally, the processes, procedures, and statistical considerations for end-point validation that are presented are widely applicable to the development of outcome measures across all pulmonary diseases. Thus, readers in a multitude of clinical settings beyond CF will benefit from the outcome measures development approaches reviewed in this symposium.

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