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Review

Physiologic endpoints for clinical studies for cystic fibrosis

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Abstract

The cystic fibrosis (CF) drug development pipeline promises many exciting new treatments for patients with CF, all which will require clinical studies to prove their benefits on CF lung disease. Historically many pivotal CF studies have used the Forced Expiratory Volume in 1 s (FEV_1) as the primary outcome measure, and after demonstrating significant improvements in the treatment group relative to placebo have led to regulatory approval of therapies for routine clinical care. Widespread implementation of these therapies has subsequently led to significant improvements in outcomes for patients with CF. While preserving lung function has obvious benefits to CF patients, as more patients maintain FEV_1 in the normal range, it has become increasingly difficult to conduct clinical trials using FEV_1 as the primary outcome measure. With multiple concurrent trials competing to enroll from the same pool of patients, there is a need for novel approaches to study end points as well as new physiological outcomes for CF therapeutic trials. In this review we will discuss some of the limitations of FEV_1 in the current era of CF care, describe alternative physiological endpoints and outline areas for further research.

Keywords: Cystic fibrosis; Lung function; Clinical trials; Outcomes

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1. Introduction

The cystic fibrosis (CF) drug development pipeline promises many exciting new treatments for patients with CF, which will require clinical studies to prove their benefits on CF lung disease. While endpoints vary between studies, the most commonly reported surrogate outcome for CF clinical trials to date has been the Forced Expiratory Volume in 1 s (FEV_1), measured by spirometry. Many pivotal studies have used FEV_1 as the primary outcome measure, demonstrating significant improvements in the treatment arm relative to the placebo arm, which in conjunction with supporting evidence from other outcome measures has led to regulatory approval. Implementation of these treatments into routine clinical care has led to significant improvements in outcomes for patients with CF. As a consequence, not only life expectancy, but also clinical severity of lung disease has changed over time [1,2]. Improvements in outcomes have shifted the phenotype of patients with CF across the lifespan, such that many patients now maintain normal lung function well into early adulthood. Preserving lung function has obvious benefits to CF patients, but has made it increasingly difficult to conduct clinical trials using FEV_1 as the primary outcome measure. On one hand larger study populations are needed to demonstrate smaller treatment effects in patients that are already heavily treated. On the other hand proportionally fewer patients are in the range of disease severity commonly included into clinical trials to prove efficacy in CF patients. With multiple concurrent trials competing to enroll from the same pool of patients, there is a need for novel approaches to study end points as well as new physiological outcomes for CF therapeutic trials. In this review we will discuss some of the limitations of FEV_1 in the current era of CF care, describe alternative physiological endpoints and outline areas for further research.

2. FEV_1

Spirometry is the hallmark physiological test for respiratory disease diagnosis, management and research studies. FEV_1 is the primary spirometric output used to monitor patients with CF in clinical practice, and the primary outcome measure in many CF clinical trials. Spirometry equipment is readily available in all CF centers and there are standardized testing protocols and certified commercial devices available [3]. FEV_1, in particular, is a very reproducible and repeatable outcome; however the variability is not constant across all ages, or across the spectrum of disease severity [4]. Most CF patients 6 years or older, the age group in whom the test is performed routinely in the clinic, are familiar with the test, and with appropriate training accurate measurements are easy to obtain. FEV_1 is considered an appropriate surrogate outcome for CF studies since low FEV_1 values are strongly associated with increased mortality, and decreased quality of life [5–7].

3. How much improvement in FEV_1 can we expect in the current era of CF care?

Many of the therapies that are now the standard of clinical care in patients with CF were investigated in randomized trials where the FEV_1 was the primary outcome measure (Table 1). While patient characteristics and treatment duration were fairly comparable, treatment effects have varied and except for the remarkable improvements in FEV_1 observed in patients with class III gating mutations treated with Ivacaftor [8], the magnitude of the FEV_1improvement observed, either in absolute or relative terms, have been smaller than the threshold used to assess short term treatment response to interventions such as bronchodilators in patients with asthma or COPD [9] (Table 1). As lung function of the CF population further improves, and more patients with normal lung function are

Table 1
Summary of treatment responses using FEV_1 as an outcome measure for 6 landmark randomized control trials in patients with CF.

Publication	Treatment	Duration (weeks)	Sample Size (N)	Primary Outcome	Secondary Outcomes
Fuchs H.J. et al. NEJM (1994) [10]	Dornase Alfa	24	968	Reduction in pulmonary exacerbations	Relative change in FEV_1 (5.8% ± 0.7SE once daily; 5.6% ± 0.7SE)
Ramsey B.W. et al. NEJM (1999) [11]	Tobramycin	20	520	Relative change in FEV_1% predicted (12%)	
Elkins M.R. et al. NEJM (2006) [12]	Hypertonic Saline	48	164	Linear rate of change in FEV_1 from baseline (0.3 ml/week, 95%CI −1.3; 1.8)	Absolute change in FEV_1 (0.068 L); Relative change in FEV_1 (3.2%)
Saiman L. et al. JAMA (2010) [13]	Azithromycin	24	260	Absolute change in FEV_1 (0.020 L, 95%CI −0.05; 0.08)	Relative change in FEV_1% predicted (2%)
Ramsey B.W. et al. NEJM (2011) [8]	Ivacaftor	24	161	Absolute change in FEV_1% predicted (10.6%)	Relative change in FEV_1 (17.2%); Absolute change in FEV_1 (0.361 L)
Wainwright C.E. et al., NEJM (2015) [14]	Ivacaftor + Lumacaftor	24	1108	Absolute change in FEV_1% predicted (2.8% -3.3%)	Relative change in FEV_1 (4.8% -5.6%)