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Review

Cystic fibrosis and the role of gastrointestinal outcome measures in the new era of therapeutic CFTR modulation ☆

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Abstract

With the development of new drugs that directly affect CFTR protein function, clinical trials are being designed or initiated for a growing number of patients with cystic fibrosis. The currently available and accepted clinical endpoints, FEV1 and BMI, have limitations.

The aim of this report is to draw attention to the need and the ample possibilities for the development and validation of relevant gastrointestinal clinical endpoints for scientific evaluation of CFTR modulation treatment, particularly in young children and infants.

The gastrointestinal tract offers very good opportunities to measure CFTR protein function and systematically evaluate CF related clinical outcomes based on the principal clinical gastrointestinal manifestations of CF: intestinal pH, intestinal transit time, intestinal bile salt malabsorption, intestinal inflammation, exocrine pancreatic function and intestinal fat malabsorption.

We present a descriptive analysis of a variety of gastrointestinal outcome measures for clinical relevance, reliability, validity, responsiveness to interventions, feasibility in particular in young children and the availability of reference values.

Keywords: Cystic fibrosis; Outcome measures; End points; Gastrointestinal; Clinical trials; Intestinal pH; Intestinal transit time; Bile acid metabolism; Intestinal inflammation; Exocrine pancreatic insufficiency; Fat malabsorption

Contents

☆ The views expressed in this article are those of the authors and do not necessarily reflect official positions or policies of the European Medicines Agency.

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1. Introduction

In recent years great progress has been achieved in therapeutic Cystic Fibrosis Transmembrane Corrector (CFTR) protein modulation. Current CFTR modulation treatment is based on the use of small molecules, that either improve gating of ions ("CFTR potentiators") or restore folding ("CFTR correctors") of the CFTR protein to improve its function. Clinical trials testing CFTR modulators have proven their success by showing significant clinical improvement, including sustained improvement in lung function as measured by forced expiratory volume in 1 s (FEV1), and an increase in body mass index (BMI) [1,2].

To date the major accepted and established clinical outcome measures for cystic fibrosis (CF) are FEV1, body weight and body mass index (BMI). However, unlike previous symptomatic treatment approaches for cystic fibrosis, therapeutic CFTR modulation offers the prospect of early intervention and possible preemptive treatment. As a consequence, clinical trials to prove efficacy will be performed in increasingly younger cystic fibrosis patients [3]. Young children and infants with cystic fibrosis, in particular those diagnosed via neonatal screening, may have well preserved lung function and normal growth. Therefore, development and validation of clinical outcome measures applicable in this young age group are imperative.

The gastrointestinal tract offers opportunities to measure CFTR protein function and systematically evaluate CF related clinical outcomes for clinical trials. Clinical signs of CFTR dysfunction in the gastrointestinal tract often occur earlier in disease development than in the respiratory tract. Meconium ileus is almost pathognomonic for CF. Meconium ileus will usually be symptomatic before neonatal screening results are available. Exocrine pancreatic insufficiency can present at birth or develop in weeks to months during the first year of life [4]. Additionally the same pathophysiological triad of obstruction, infection, and inflammation that causes disease in the airways also causes disease in the intestine [5].

In this position paper we systematically discuss gastrointestinal outcome measurements for cystic fibrosis that are available to date. We describe clinically measurable outcome parameters and methods to directly measure CFTR protein function in gastrointestinal tissues. The aim of the report is to draw attention to the need and the ample opportunities for the development and validation of relevant clinical endpoints for scientific evaluation of CFTR modulation treatment, particularly in young children and infants.

2. Methods

After an expert group assessment we systematically discuss potential high-impact gastrointestinal outcome measurements based on a retrospective literature analysis. We structured our search for potential GI outcome measures on the principal clinical gastrointestinal manifestations in CF: intestinal pH, intestinal transit time, intestinal bile salt malabsorption, intestinal inflammation, exocrine pancreatic function and intestinal fat malabsorption. We present a descriptive analysis of gastrointestinal outcome measures for clinical or disease relevance, reliability, validity, responsiveness to interventions, feasibility in particular in young children and the availability of reference values. The results are summarized in the Table 1.

3. Results

3.1. Measurements of clinical gastrointestinal manifestations of cystic fibrosis

3.1.1. Intestinal pH profile

Physiologically, gastric acid is buffered by secretion of bicarbonate by the pancreas and by the enterocytes of the proximal small intestine. CFTR is essential for adequate pancreatic and duodenal bicarbonate secretion. In patients with CF, the pancreatic and duodenal bicarbonate secretion is insufficient to neutralize the gastric acid load [6,7]. Hence, the duodenal pH is (on average) 1–2 units lower in CF patients compared with healthy controls. Accordingly, CF patients have significantly longer postprandial periods in which the duodenal pH is below 4 [8]. In the proximal intestine, acidification may interfere with absorption both by inhibiting pancreatic enzyme activity [9] and by causing intraluminal precipitation of bile acids with impaired mixed micelle formation [10]. More distally in the small intestine, the pH values of jejunal and ileal contents from CF patients vary from lower to similar pH values compared with healthy controls. Bicarbonate secretion is tightly tied to fluid secretion [11] and in the CF mouse intestine is essential to allow mucins to unfold and become fluid [12,13]. Thus, the excess acidity in the intestine may contribute to obstruction.