TITLE PAGE

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Gastrointestinal outcome measures before and after Orkambi therapy in Cystic Fibrosis (CF) Patients carrying the F508del mutation on both alleles

or

Official Swedish title:

Gastrointestinal studie vid Orkambi-behandling hos cystisk fibros-patienter

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Synopsis

Ivacaftor caused a significance increase in weight in patients carrying the G551D mutation and the etiology of this has largely remained unknown but may be due to improved function of the gastrointestinal tract. The combination therapy of Orkambi has been recently approved for subjects with Cystic Fibrosis homozygous for F508del mutation. This provides an opportunity to examine if there are any improvements in gastrointestinal function. We aim to investigate various aspects of gastrointestinal and pancreatic function before and 6 months after the commencement of Orkambi therapy.

Objective

To examine the entire intestinal mucosa via capsule endoscopy before and 6 months after Orkambi therapy to ascertain if the inflammatory changes in the intestine have improved. A marker of intestinal inflammation measured in the stool, Calprotectin, will be examined before and 6 months after Orkambi treatment. We hypothesize that the result will be reduced on therapy.
A marker of pancreatic exocrine function, pancreatic elastase, will be examined before and 6 months after therapy to examine if the result has increased indicating improvement of exocrine pancreatic function

Study Population

All subjects with CF homozygous for the F508del mutation in Sweden. There is a total of 145 patients with this mutation in Sweden and 60 at Stockholm CF Center; we aim to examine 20 patients.

Study Duration

The duration will be 6 months.

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.
The CFTR modulator Ivacaftor already has proven to improve clinical status in children and adults with the G551D CFTR gating mutation. Clinical trials have shown significant clinical improvement, including sustained improvement in lung function as measured by forced expiratory volume in 1 second (FEV1), and an increase in body mass index (BMI) and other parameters including intestinal pH and insulin secretion (1,2,3,).
In a recent study of 213 patients with the G551D mutation there was a significant improvement in nutritional status after 48 weeks of treatment with Ivacaftor in children and adults (4). This is a most

relevant finding considering that decreased mortality has been associated with greater body weight and BMI in patients with CF (5) This observation opens the window of opportunity to investigate how the improvement in CFTR function affects the function of the gastrointestinal tract in CF.
Less emphasis has been given to the development of gastrointestinal outcome measures for therapeutic trials in cystic fibrosis than for pulmonary outcome measures. This was partially due to the presumed irreversible character of CF gastrointestinal manifestations, for example exocrine pancreatic insufficiency. Different from pulmonary disease, some GI manifestations of CF do not present with clinically recognizable and relevant disease. Ivacaftor has been shown in a few studies to have systemic benefit on the gastrointestinal tract (2,4).
The current studies with CFTR modulators offer new and promising opportunities to implement GI outcome measures for cystic fibrosis, and the use of GI outcome measures can provide evidence of the systemic action of these medications. In fact, we do not have a good explanation as to why the BMI increases after Ivacaftor treatment. This may be due to rectification of gastrointestinal pathology caused by CFTR dysfunction (2,4). As these drugs are systemically absorbed, it is reasonable to assume they will have a systemic benefit.

An exciting new development has been that the combination therapy of Ivacaftor and Lumacaftor (Orkambi) has been recently approved for CF patients homozygous for F508del (6).

To date the major accepted and established clinical outcome measures for CF are FEV1, 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. Therefore, clinical trials to prove efficacy will be performed in increasingly younger cystic fibrosis patients (7)

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 can 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 (8). Additionally, the same pathophysiologic triad of obstruction, infection, and inflammation that causes disease in the airways also causes disease in the intestine (9)

In this protocol, we systematically examine 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 protocol is to draw

attention to the need and the ample opportunities for the development and validation of relevant clinical endpoints for scientific evaluation of Orkambi modulation treatment.

In this study, we propose that patients who are eligible to receive Orkambi will provide a stool sample for Calprotectin and fecal elastase 1 and undergo a capsule endoscopy intestinal examination before and 6 months after commencing treatment.

Materials and Methods

Measurements of clinical gastrointestinal manifestations of cystic fibrosis

Intestinal inflammation

Several studies have shown evidence of intestinal inflammation in cystic fibrosis, particularly in patients with pancreatic insufficiency. The underlying pathophysiology of intestinal inflammation is not completely understood. Data from cystic fibrosis mouse models suggest that the intestinal inflammation is related to CFTR dysfunction in the intestinal tissues, which leads to mucus accumulation, disturbed motility, small bowel bacterial overgrowth and inflammation with altered innate immune responses. It is to be expected that these different factors interact with one another (10)

I) Fecal calprotectin

To date several fecal biomarkers are available of which fecal calprotectin is the most studied and used in the clinical practice (11, 12). Calprotectin is a very stable protein originating from inflammatory neutrophils. Several studies have demonstrated significantly increased fecal calprotectin levels in cystic fibrosis patients compared to healthy controls. The fecal calprotectin levels do not seem to be related to the presence of small intestinal bacterial overgrowth frequently observed in cystic fibrosis patients (13). Clinical trials using probiotics to treat intestinal inflammation in cystic fibrosis patients have shown a therapeutic responsiveness of fecal calprotectin indicating the potential of this marker as a clinical endpoint (14)

II) Fecal elastase-1

Fecal elastase-1 is one of the proteolytic pancreatic enzymes. In the intestine elastase-1 is not subject to degradation. It is pH and temperature stabile and is excreted via the feces. A small fecal sample can easily be obtained and stored. Elastase-1 has no cross reactions with chymotrypsin of animal sources that is present in exogenous submitted pancreatic enzymes (PERT). For this reason, elastase-1 can still be used a marker of exocrine pancreatic function during PERT use. In the case of exocrine pancreatic insufficiency fecal elastase-1 is decreased. Reference values of fecal elastase-1 have been established (16). There have been reports of Ivacaftor improving exocrine pancreatic insufficiency in patients with G551D mutation (personal communication -Prof Kevin Gaskin, Sydney, Australia). We hypothesize that there may be improvement in patients with delF508 after Orkambi treatment.

III) Small bowel capsule endoscopy

A relatively new option for making the diagnosis of intestinal inflammation is small bowel capsule endoscopy (SBCE). The primary indication of SBCE is to examine areas of the small intestine that cannot be inspected by other types of endoscopy. SBCE has been performed in CF patients. One study from Israel reported SBCE results in CF patients (15). The study showed that most cystic fibrosis patients had varying degrees of diffuse areas of inflammatory findings in the small bowel including edema, erythema, mucosal breaks, and frank ulcerations. The method of SBCE has been well established as a descriptive diagnostic tool for intestinal inflammation. However, systematic quantitative evaluation of SBCE is not easy and not yet well established. SBCE has been used as an outcome measure in clinical trial but not yet in therapeutic trails for cystic fibrosis. Due to the size of the video capsule SBCE cannot be applied in young children and infants.

Blood tests

Inflammatory markers in blood, such as CRP, sedimentation rate and serum electrophoresis, as well as liver function tests will be taken in this study.

Inclusion Criteria

1. Patients with CF with F508del homozygote eligible for Orkambi therapy
2. Males and females
3. >12 years of age

Exclusion Criteria

1. Patients who the patency capsule does not pass within 48 hours
2. FEV1 <30%
3. Pregnancy and breastfeeding women
4. Liver function blood tests > 3 times the normal value
5. Bilirubin > 2 times normal value
6. AST or ALT alone more than 5 times normal value
7. Patients who have had a lung transplant

Dosing of Orkambi

This study is being carried out in patients who are receiving Orkambi for clinical and non-research indications. Orkambi will be administered according to the approved label in Sweden. There will be no changes in dosing because of this study.

Dosage Adjustment for Patients with Hepatic Impairment.

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A dose reduction to 2 tablets in the morning and 1 tablet in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) is recommended for patients with moderate hepatic impairment (Child-Pugh Class B).
Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening (lumacaftor 400 mg/ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment

Safety Monitoring

Monitoring will be carried out in accordance with GCP regulations and according to the general protocol for patients receiving Orkambi as per label. This includes monitoring liver function blood tests after 3 months. Ophthalmological assessment will be performed to rule out cataracts and liver function tests will be performed at the start of the study and at the end.
Adverse events will be recorded and following local laws and regulations reported to GlobalPatientSafety@vrtx.com

Statistical Analysis

This study is a prospective observation on the gastrointestinal tract before and after Orkambi treatment. Each patient will act as his or her own control and changes will be compared from baseline. Lesions which will be seen on the capsule endoscopy will be assessed according to the Maiden criteria (erythema, petechiae, mucosal erosions, ulcerations) (15) before commencement of Orkambi and at the second capsule endoscopy examination.

Study in Detail

After informed consent the subject will undergo physical examination and females will provide a urine sample for a pregnancy test. The subjects will provide a stool sample for:
1- Calprotectin and fecal elastase – the stool will be placed in a freezer at -4degrees.
2- The patients will perform liver function tests.
3- The first phase of the capsule endoscopy is the patency capsule to ensure that there is no obstruction in the intestine. The patency capsule is the same size as the "real" capsule but is made of a biodegradable lactose polymer. If it is not seen in the intestine after 48 hours the subject is able to ingest the capsule. The preparation for the patency capsule is a liquid only diet from midday on the day prior to the test and fasting from 12 midnight before the test.
The subject will then swallow the patency capsule which is a placebo SBCE. The subject will notice the capsule in the stool. If not the subject reports back to the study nurse who will examine the abdomen with a non-radiation emitting scanner.
If the capsule is not present the subject will proceed to the next stage -swallowing the capsule (SBCE).
4-The preparation is somewhat different as the mucosa needs to be as clean as possible. Once again the subject takes a liquid diet the day before the capsule but in the evening before the subject with ingest one sachet of laxative (picosalax). This will cause the subject to have increased bowel movements.
The following morning the subject with ingest the capsule endoscopy which will take pictures for 8-10 hours. The readings are collected on a belt worn by the subject for this entire time.
5-The subject will return the belt to the study nurse within 2 to 3 days at their convenience.
The data will be read by a gastroenterologist trained in reading the capsule endoscopy by Rapid Software (Medtronic).
The subject will receive Orkambi.
6 months after commencing Orkambi the subject will perform the following tests:
Stool sample for calprotectin and elastase to be stored at -4 degrees and liver function tests.
The subject will have Picosalax preparation the evening before the capsule endoscopy
The subject will swallow the capsule wearing the belt as before

Study Endpoints

The results of SBCE, stool calprotectin and pancreatic elastase 6 months after commencement of Orkambi therapy will be compared to baseline. Findings at capsule endoscopy including mucosal erythema, petechiae, erosions and ulcerations will be recorded before and after 6 months of treatment.

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