TAAI Erasmus Research Initiative to Fight CF: Monitoring Inflammation in CF Lung disease into a new Era

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON54176

Source
ToetsingOnline

Brief title
TERRIFIC-MILE

Condition

- Respiratory disorders congenital
- Gastrointestinal conditions NEC
- Congenital respiratory tract disorders

Synonym
cystic fibrosis, mucoviscidosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Stichting TAAI

Intervention

Keyword: Breathomics, Cystic fibrosis, Lung Inflammation, Monitoring

Outcome measures

Primary outcome

Primary endpoint is the comparison of VOCs, measured by GC-MS, during ETI treatment compared to control group over time during 3 different study visits.

Secondary outcome

Secondary endpoints:

- The correlation of VOCs by GC-MS breath profiles/VOCs, measured by eNose, inflammatory markers in induced sputum (IL-8, free neutrophilic elastase (NE), calprotectin and myeloperoxidase, plus a predetermined cytokine panel), blood (IL-18, IL-1β, TNF, hsCRP, sCD14, calprotectin, HGMB-1, amyloid and miRNA), urine and, lung function, quality of life and symptom scores at baseline (if available) and overtime during 3 consecutive study visits.
- Change of VOCs by GC-MS and eNose from baseline till 3 months of ETI treatment.

Study description

Background summary

Progressive destruction of the lungs is the main cause of shortened life expectancy in cystic fibrosis (CF). Inflammation and respiratory infections play a key role in CF lung disease. Previous studies have shown that an increase in inflammatory markers predicts structural lung damage like bronchiectasis in infants with CF. Close monitoring of people with CF (pwCF) is crucial to adequately provide optimal care. Pulmonary management of pwCF is

focused on treating infections and pulmonary exacerbations, and maintaining lung health by doing sports and stimulation of muco-ciliary clearance, to prevent or at least slowdown progressive structural lung damage. To evaluate treatment and incite timely interventions it is important for the pulmonary physician to be well informed about the condition of the lungs. The main monitoring tools in regular CF care are lung function, sputum cultures, symptom reporting and more recently imaging by chest computed tomography (CT-scan) or magnetic resonance imaging (MRI). Strangely enough, there are currently no monitoring tools used in clinics to measure inflammation in the lung, although this is a main factor for progressive lung disease. We are on the edge of a new era for CF. The recently approved highly effective modulators therapy (HEMT) such as elexacaftor/tezacaftor/ivacaftor [ETI, Kaftrio®] will change the course of the disease. ETI has shown to be highly effective by improving lung function substantially and reducing pulmonary exacerbations by 3-fold. In studies with the first cystic fibrosis transmembrane conductance regulator (CFTR) modulators, like ivacaftor and lumacaftor/ivacaftor, it is shown that although lung function improves and pulmonary exacerbations are reduced, that inflammation in the lungs is still present. Long term follow-up with the first generation of CFTR modulators shows a decline in lung function overtime, although it is less steep than before treatment. For ETI there is no long term follow-up data yet, and it is also not known how inflammation in the lungs will change by using ETI. Monitoring pwCF on HEMT may be different than before, as lung damage seen on chest-CT will be less apparent and lung function will improve considerably, therefore not being adequate markers anymore for subtle changes in the lungs. Thus, the focus of monitoring in the era of highly effective CFTR modulators needs to change preferably focussing on changes in inflammation in the lungs. A good monitoring tool should be minimally invasive, quick and give an accurate value with good sensitivity and specificity. Currently inflammatory markers in sputum and broncho-alveolar lavage (BAL) are now the most commonly used methods to assess inflammation in the lungs. But BAL entails a bronchoscopy which is rather invasive, and sputum is not always available. Breathomics, which is analysis of volatile organic compounds (VOC*s) in exhaled breath, has great potential as a non-invasive test to monitor inflammation in the lungs. This can be done by using either an electronic nose (eNose) or gas chromatography-mass spectrometry (GC-MS). Other promising markers and techniques are: inflammatory markers in blood (cytokines and micro-RNA (miRNA)) and urine. Therefore, we aim to develop innovative minimally invasive monitoring techniques that can identify lung inflammation in pwCF when using highly effective CFTR modulators (ETI), compared to patients who are not on CFTR modulators. For validation these innovative techniques will be compared to inflammatory markers in sputum, spirometry and validated symptom and quality of life scores.

Study objective

The overall aim of the study is to develop innovative minimally invasive monitoring techniques that can identify lung inflammation in pwCF when using

highly effective modulators, compared to patients whom are not eligible for CFTR modulators (control group) yet.

Primary objective is to assess whether measuring VOCs with GC-MS is a sensitive method to monitor changes in lung inflammation in pwCF.

Secondary objectives are:
- To assess whether eNose is a sensitive method to monitor changes in lung inflammation in pwCF.
- To explore the usefulness of other inflammatory markers in blood and urine.

Study design

Explorative cohort study aimed to develop innovative minimally invasive monitoring techniques that can identify lung inflammation in pwCF when using highly effective CFTR modulators. (eNose, GC-MS, inflammatory markers in urine and blood), compared to a control group: pwCF not using CFTR modulators. Furthermore, we will in compare this techniques with inflammatory markers in induced sputum, conventional spirometry, symptom and quality of life scores.

Study burden and risks

The burden of this study is considered low. PwCF who are eligible to start with ETI will be included, and a group of patients who are not. The start of ETI is part of the routine care, and is already approved by the European medicines agency (EMA) for this indication. The study visits will be combined with the routine checks as much as possible. At the study visits there will be extra tests for the study, next to the routine care, which will entail around 30 min-1 hour extra time next to the clinic visit. To limit their burden of the study for the age group 6-11, we will not conduct all measurements.
Patients >12 years: At all visits there will be exhaled breath sampling, 3 extra vials of blood with a blooddraw, induced sputum, urine sample and 2 questionnaires.
Patients <12 years: At all visits there will be exhaled breath sampling and 1 questionnaire will be done through a interview with the child. On the last visit 2 extra vials of blood will be collected. For patients 6-18 years of age a multiple breath washout (MBW) for LCI will be scheduled at study visits.
Exhaled breath and urine sampling will cause a negligible burden. For pwCF receiving ETI treatment a laboratory blood tests are part of routine patient care. For pwCF, whom are not eligible to receive ETI treatment, a blood draw is not always part of routine care. If so, they can opt out for an extra blooddraw for the study if this is not performed during routine care. Induced sputum will be obtained by inhaling hypertonic saline and after that sputum needs to be coughed up with airway clearance techniques. This is something that patients need to do daily themselves at home, so this will cause only a minor burden. LCI mainly cost time, but no burden, because it does not require

contrast administration. Subjects may opt out for blood, induced sputum, LCI and urine samples, but there always need to be an exhaled breath sampling with eNose and GC-MS. For none of the tests any risks are associated. There will be no direct benefits for the participating subjects, but the study will provide valuable information for future development of non-invasive monitoring techniques.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all

of the following criteria:

Diagnosed with cystic fibrosis (CF), either by abnormal sweat test and/or confirmed with 2 CF causing mutations found by genetic analysis, either from heel-prick screening or diagnosed later in life. Furthermore, they have to be older than 6 years (i.e. children and adults). Age appropriate written informed consent is required.

In addition, patients need to meet the criteria of one of the following study groups:

Group 1: CF patients, whom are eligible to start elexacaftor/tezacaftor/ivacaftor treatment or who are already using it.
Group 2: CF patients, whom are not eligible to receive elexacaftor/tezacaftor/ivacaftor treatment. This group will function as controls.

Exclusion criteria

- Patients who cannot follow instructions

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-03-2022
Enrollment:	103
Type:	Actual

Medical products/devices used

Generic name:	SpiroNose
Registration:	No

Ethics review

Approved WMO Date:	21-03-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL79377.078.21