Getting insight in the exposure effect relationship of Elexacaftor/ Tezacaftor/Ivacaftor treatment in people with cystic fibrosis

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Primary objective: To compare the exposure of ETI in a group of pwCF with the highest decrease in sweat chlorid and the lowest decrease in sweat chloride as result of ETI therapy.

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

Summary

ID

NL-OMON56478

Source
ToetsingOnline

Brief title
The exposure effect relationship of ETI treatment in pwCF

Condition

- Respiratory disorders congenital
- Congenital respiratory tract disorders

Synonym
Cystic fibrosis, Mucoviscoidosis

Research involving
Human

Sponsors and support

Primary sponsor: HagaZiekenhuis

Source(s) of monetary or material Support: Overige subsidie aanvragen

Intervention

Keyword: Cystic fibrosis, Elexacaftor/Tezacaftor/Ivacaftor, pharmacology, Sweat Chloride

Outcome measures

Primary outcome

The study will involve the determination of the trough concentration (Ctrough)

of ETI in all 20 collected blood samples for statistical analysis. We will

compare Ctrough of the group with the highest absolute sweat chloride decrease

to C trough levels of the group with the lowest absolute sweat chloride

decrease. Since our study group is small, we will use a non-parametric,

Mann-whitney u test to compare the Ctrough of ETI in both groups.

Secondary outcome

not applicable

Study description

Background summary

On January 1st, 2022, the use of Elexacaftor/Tezacaftor/Ivacaftor (ETI) has been reimbursed in Netherlands for adult people with cystic fibrosis (pwCF) and at least one copy of the F508del mutation. The treatment involves taking 2 tablets of ETI in the morning and 1 tablet of ivacaftor in the evening. ETI is a combination of two correctors, Elexacaftor and Tezacaftor, and one potentiator, Ivacaftor.

Treatment with ETI has shown an impressive clinical effect. However, despite its effectiveness at group level, there is a high level of variability in the response to treatment among individuals with the same Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene mutation, even with standardised dosages. In daily practice, more side effects have been observed than expected based on registration studies. Adverse effects such as elevated transaminase, bilirubin, creatine kinase, rashes and mental problems have been

observed in pwCF treated with ETI.

There is currently limited information available on how exposure to CFTR modulators affects the clinical effect of these drugs, and the relationship between exposure and (side) effects is still not clear. To improve our understanding of this relationship, we will compare the serum concentrations of ETI in 10 people with CF who show the highest clinical effect, with those of 10 people with CF who show the lowest clinical effect.

Sweat chloride will be used as a clinical endpoint because sweat chloride can be used as a substitute biomarker for CFTR function, since its quantity indicates the activation of the CFTR protein. Although the reproducibility of the sweattest is moderate, it has the advantage of being independent of the severity of CF disease, as sweat glands do not appear to be susceptible to the progression of CF. In this study, we hypothesize that pwCF who have a greater reduction in absolute sweat chloride levels also have a higher concentration of ETI in their blood compared to those with less reduction in their absolute sweat chloride levels.

Study objective

Primary objective: To compare the exposure of ETI in a group of pwCF with the highest decrease in sweat chlorid and the lowest decrease in sweat chloride as result of ETI therapy.

Study design

This study is a single-centre study in which 20 pwCF will be included. The 10 patients with the highest absolute sweat chloride decrease and the 10 patients with the lowest absolute sweat chloride decrease, who are currently undergoing treatment with ETI will be selected for the study. After that we will ask them for participation in the study. Patients who are interested will be referred to the principal investigator, who will inform them about the study and ask for their consent. All participants will receive an information letter and an informed consent form and will be given at least 2 days to decide about their participation. If the patients agree to participate, a visit for blood sample collection will be scheduled. If possible, we will combine their study visit with their conventional appointment on the outpatient clinic.

Intervention

The sole intervention in this study is a single venous puncture for the collection of 5 ml of blood.

Study burden and risks

Included pwCF will visit the hospital once. One blood sample will be collected before their daily dose of ETI by venepuncture.
We do not consider the study to be high-risk since the patients with cystic fibrosis included in the study will continue with their existing ETI treatment, which is approved by both the FDA and EMA, and is already being used by the patients on a daily basis. The dose used in the study will be the same as the standard dose. The only intervention is that during the study, one blood sample will be taken by venepuncture and participants are asked to take their morning ETI dose after venapunction in the hospital. Their visits will therefore be scheduled in the morning.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 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:
1.Cystic fibrosis based on DBC code (specialisme: 0322 ; Diagnose: 1403)
2.Use of Kaftrio tablets with dosage of 75/5-/100mg and ATC code: R07AX32
3.Use of standard dose of ETI (2 tablets in the morning) and Ivacaftor (1 tablet in the evening).
4.Availability of a baseline and on ETI treatment sweat chloride value
5.A homozygous F508del mutation in the CFTR gene
6.A stable clinical condition defined as no pulmonary exacerbation in a period of 4 weeks before study visit

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Solid organ transplantation
2. The use of concomitant medications with CYP3A4 interactions during the period of determining the trough concentration of ETI
3. Pregnancy
4. Liver cirrhosis

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-03-2024
Enrollment:	20
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	13-02-2024
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL85749.058.23