The effect of Ivacaftor in CF patients with a class III mutation

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

Summary

ID

NL-OMON41740

Source
ToetsingOnline

Brief title
TICTAC II study

Condition

- Respiratory disorders congenital

Synonym
Cystic Fibrosis, Mucoviscidosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,NCFS

Intervention

Keyword: CFTR activation, Cystic Fibrosis, Ivacaftor, Treatment

Outcome measures

Primary outcome

Sweat chloride concentration before and after receiving Ivacaftor.

Secondary outcome

Secondary endpoints will include: • Difference in lung function (%FEV1), NO fraction of exhaled air and airway resistance (Rint and bodybox) before and after the use of Ivacaftor; • Change in microbioom (in sputum and oro- and nasopharyngeal swabs) before (till one year) and after the use of Ivacaftor; Difference in BMI before and after the use of Ivacaftor; • Difference in quality of life (measured with CFQ-questionnaire) before and after the use of Ivacaftor; • Bile salt measurements in plasma and the feces before and after the use of Ivacaftor; • Elastase measurements in the feces before and after the use of Ivacaftor; • Measurement of CFTR function in blood (PBMC's and monocytes) before and after the use of Ivacaftor • Correlation between individual Ivacaftor induced CFTR function in vitro (organoid-based measurements) and in vivo effect (lung function, SCC); • The CFTR stimulating ability of the concentration of Ivacaftor in the patient*s blood samples, examined by in vitro testing (in the organoid model), we will also determine the plasma levels of Ivacaftor.

Study description

Background summary

The cystic fibrosis trans membrane conductance regulator (CFTR), a chloride and bicarbonate channel encoded by the CFTR gene, is essential for fluid and electrolyte homeostasis at the epithelial surfaces of many organs, including the lung, intestine, and sweat gland. Over 1900 CFTR mutations have been identified causing impaired protein production (class I), folding (class II), channel gating (class III), conductance (class IV), or reduced synthesis (class V). The CFTR potentiator-drug Ivacaftor will be approved for the treatment of CF patients with a mutation associated with residual CFTR function, probably by the beginning of 2015. Introduction of this drug in clinical treatment of these patients is to be expected shortly after approval. The estimated costs of this treatment are ¤ 200.000 per patient per year.
Currently, several CF patients with gating mutations are using curcumin and genistein because of anecdotally reported beneficial effects of these self-administered food supplements. Using various primary cell models from CF patients (organoids), we also found the combination of natural food components curcumin and genistein to synergize in potentiating CFTR mutants with a channel gating defect, (e.g. F508del; S1251N), thereby enhancing function of these mutants significantly. Based on these findings we currently perform the TICTAC-I study. In this study we evaluate the therapeutic potential of these food supplements. In the TICTAC-II study we will objectively evaluate the therapeutic effect of Ivacaftor in patients with a class III mutation. The introduction of Ivacaftor is the ideal moment to measure this therapeutic effect because we can perform a before and after measurement without changing the treatment of a patient.

Study objective

Primary objective is to objectively investigate the therapeutic potential of Ivacaftor in Dutch CF patients carrying a mutation associated with residual CFTR function. A secondary objective is to evaluate the correlations between individual Ivacaftor induced CFTR function in vitro (organoid-based measurements) and the in vivo treatment effect. Other secondary objectives are: to assess the colonization status and microbiome of the airways before and after introduction of Ivacaftor treatment, to evaluate the concentration of Ivacaftor in the patient*s blood samples and CFTR stimulating ability of this concentration. We will examine this by measuring serum concentrations and by in vitro testing (in the organoid model). The last secondary objective is to compare the therapeutic potential of Ivacaftor with the therapeutic potential of the natural food components curcumine and genistein.

Study design

A multicenter observational study

Study burden and risks

Patients participating in this study will visit the hospital for two study visits.The following tests will be done during each study visit: Quality of Life Questionnaire, a brief anamnesis, physical examination, sweat test (SCC), lung function (FEV1%), NO fraction of exhaled air and airway resistance (Rint and bodybox). We will also ask patients to bring a feces sample at both visits, collect a blood and sputum sample at both visits and perform oro-and nasopharyngeal swabs. In addition, patients are asked to perform a FEV1 measurement at home with a small FEV1 meter once a week and to fill out a diary about using their Ivacaftor.
By the start of the study Ivacaftor will be an approved treatment in the Netherlands. In this project we propose to measure the therapeutic effect of the regular treatment with Ivacaftor in CF patients with a mutation associated with residual CFTR function. The introduction of Ivacaftor is the ideal moment to measure this therapeutic effect because we can perform a before and after measurement without changing a patients treatment. A number of CF patients with a class III gating mutation already use Ivacaftor as part of a compassionate use program and they report a clear diminution of their CF symptoms.

When our hypothesis that curcumin and genistein turn out to improve the CFTR function in patients with a class III gating mutation similar to Ivacaftor and therefor diminish CF symptoms is confirmed, this is a major benefit not only for the patient but also for society because of the much lower costs of curcumin and genistein in comparison with Ivacaftor (¤ 500 per year per patient versus ¤200.000 per year per patient). When this study also confirms our hypothesis that organoids can predict clinical responders, this is a major benefit not only for the individual patient but for the entire CF-population. With the use of organoids we will then be able to generate optimal treatment strategies for individuals based on (combinations of) current and future drugs with only limited patient discomfort.

Contacts

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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

• CFTR genotype associated with residual CFTR function;
• Already had a rectal biopsy to produce an organoid;
• Start a treatment with Ivacaftor;
• Male and female patients, aged 6 years or older on the date of informed consent;
• Signed informed consent form (IC), and where appropriate, signed assent form.

Exclusion criteria

• Use of curcumin and or genistein at start or within two weeks prior to start of the study;
• Inability to follow instructions of the investigator.

Study design

Design

Study phase:	4
Study type:	Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-05-2015
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	25-11-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-03-2015

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 26309
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL50276.041.14
OMON	NL-OMON26309

Study results

Date completed:	28-08-2015
Actual enrolment:	16