Peripheral targeting of inhaled rhDNase in stable CF patients.

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Primary Objective: To investigate the effect of treatment with nebulized rhDNase targeted to the peripheral airways compared to rhDNase targeted to the central airways on FEF75 in children with CF who are on maintenance treatment with rhDNase....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON33580

Source
ToetsingOnline

Brief title
PIPES-study (Pulmozyme Inhalation to the PEripheral airways in Stable CF.

Condition

- Respiratory disorders NEC

Synonym
Cystic Fibrosis (CF)

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Investigator initiated research. Roche Nederland B.V. ondersteunt dit onderzoek m.b.v. een unrestricted grant ,Roche Nederland B.V.

Intervention

Keyword: Cystic Fibrosis, Inhalation, Peripheral airways, rhDNase

Outcome measures

Primary outcome

Primary endpoint will be the change in FEF75 compared to baseline after one month of treatment. FEF75 is the most suitable endpoint since it is sensitive to peripheral airways obstruction.

Secondary outcome

Secondary endpoints will include:

Lung clearance index (LCI) measurements as assessed by multiple breath washout;

Other values obtained in the flow volume curve: MMEF25-75, FEV1, FVC.

Other study parameters, such as use of antibiotics and number of exacerbations (if applicable)

Study description

Background summary

Respiratory disease in patients with cystic fibrosis (CF) is characterized by an abnormal composition of the epithelial lining fluid. As a result patients develop chronic airway infection and inflammation which start early in life[1-3]. The sputum in CF is rich in leukocyte-derived DNA which greatly contributes to abnormal viscoelasticity of the CF sputum. This purulent, infected sputum can obstruct the airways. RhDNase is an identical copy of the native human DNase. RhDNase cleaves extracellular DNA through hydrolyses and reduces the viscoelasticity of CF sputum in vitro. RhDNase has been shown to reduce sputum viscosity, improve pulmonary function, and reduce the number of pulmonary exacerbations in patients with moderate lung disease. Similar effects have been demonstrated in patients with mild disease, making rhDNase currently the only mucolytic in CF with proven efficacy.
Lung damage In CF is thought to begin by mucus impaction predominantly localized in the peripheral airways. Chronic infection and chronic airway

inflammation lead to structural damage. To prevent this damage from occurring sputum mobilization using physiotherapy techniques is important in the treatment of CF pulmonary disease. Daily nebulization of rhDNase facilitates the mobilisation of mucus from the airways. However, relatively little of the inhaled drug is deposited in the peripheral airways. Hence this compartment of the lung is thought to be relatively under treated. Mucus clearance from peripheral airways can probably be improved by targeting rhDNase selectively to these airways. Therefore we hypothesize that rhDNase targeted to the peripheral airways can improve lung function in children with CF.

Study objective

Primary Objective: To investigate the effect of treatment with nebulized rhDNase targeted to the peripheral airways compared to rhDNase targeted to the central airways on FEF75 in children with CF who are on maintenance treatment with rhDNase.
Secondary Objective(s): To investigate the effect of treatment with nebulized rhDNase targeted to the peripheral airways compared to rhDNase targeted to the central airways on lung clearance index (LCI), and on spirometry parameters (MMEF25-75, FEV1 and FVC) in children with CF who are on maintenance treatment with rhDNase.

Study design

This study will be a multi centre, randomized controlled clinical trial.

Intervention

Nebulization of rhDNase targeted to the peripheral airways, using the Akita nebulizer.

Study burden and risks

The target population of this study are children rather than adults, because CF is a genetic disease leading to pulmonary problems starting in early childhood. Recent studies have suggested that inflammation and infection in the CF lung develops very early in life, even in asymptomatic infants. This warrants early treatment of patients with CF. In addition, elevated DNA concentrations have been found in bronchoalveolar lavage fluid from infants with CF, suggesting a role for early treatment with rhDNase. Predominantly the peripheral airways are damaged and filled with sputum in CF. Therefore, additional benefit may be expected from treatment targeted to these peripheral airways.
Participating in this study may be beneficial for CF patients. A possible benefit of the nebulization of rhDNase targeted to the peripheral airways could be an improvement in lung function and/or symptoms on top of the treatment effect of regular maintenance therapy. For patients randomized to nebulization

targeted to the central airways, no additional benefits over regular maintenance therapy with rhDNase are to be expected.
The risks associated with participation are small. RhDNase is a registered drug since 1994 for the treatment of mucous impaction in CF. RhDNase is registered for use in children over 5 years of age and in adults. Administration of rhDNase to children for chronic or acute respiratory symptoms is proven to be safe in multiple studies.
Serious and life threatening side effects have not been described. Side effects were mild and included pharyngitis, rhinitis and hoarseness, which resolved spontaneously. A more efficient delivery of rhDNase to the peripheral airways theoretically could reduce the above mentioned side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

The criteria of inclusion will be the following:
- Age between 6 and 18 years old;
- Diagnosis of CF confirmed by sweat-test and/or DNA analysis and/or electro physiology testing (nasal potential difference measurement);
- Routine treatment with rhDNase once daily, started at least one month before enrolment in the study;
- Stable condition, in this study defined as: condition of patient judged to be stable by the treating physician AND no i.v antibiotics (hospital or at home) in the previous month and constant medication regime during the previous 2 weeks (for example: no additional antibiotics course, no newly started inhaled or systemic corticosteroids etc).
- Ability to perform lung function tests (assessed by trained lung function technician);
- Lung function: FVC > 40% predicted;
- Signed written informed consent.

Exclusion criteria

The following exclusion criteria will be used:
- Inability to follow instructions of the investigator;
- Inability to inhale rhDNase;
- Concomitant medical conditions that effect inhaled treatment (e.g. cleft palate, severe malacia);
- Current respiratory tract infection;
- Pulmonary complications that might put the patient at risk to participate in the study;
- Neuromuscular disease;
- Poor compliance with treatment as assessed by the patient*s paediatrician;
- Active ABPA (allergic bronchopulmonary aspergillosis) defined as an oral course of prednisone for ABPA within the last three months.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-09-2007
Enrollment:	25
Type:	Actual

Medical products/devices used

Generic name:	Akita2 nebulizer system (with Apixneb nebulizer)
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Pulmozyme
Generic name:	rhDNase
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	26-03-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	26-04-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	13-03-2009
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
EudraCT	EUCTR2007-000935-25-NL
ISRCTN	ISRCTN64225851
CCMO	NL15632.078.07