Targeting Antibiotics to Pseudomonas Aeruginosa in Small airways (TAPAS) study in patients with cystic fibrosis

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Primary objective:To compare the change in small airways obstruction (FEF75%) in patients with CF when inhaling one ampule of inhaled tobramycin with the Akita® compared to standard of treatment (twice daily nebulization of one ampule using standard...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON41894

Source
ToetsingOnline

Brief title
TAPAS study in patients with CF

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Bacterial infectious disorders
- Respiratory tract infections

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: Chiesi Farmaceutici,Fondsen van H.A.W.M. Tiddens;o.a. bestaande uit een unconditional grant van Chiesi Farmaceutici S.p.A.

Intervention

Keyword: Cystic fibrosis, Efficacy, Inhalation, Tobramycin

Outcome measures

Primary outcome

Primary endpoint: change in FEF75 (Z-score and L/s) after 4 weeks of targeted treatment

Secondary outcome

Secondary endpoints will include:

• Change in FEV1, FVC, FEF25, FEF50, MMEF25-75 (Z-scores and absolute values);

• Change in Lung Clearance Index (LCI) measurements as assessed by multiple breath washout;

• Change in Pa bacterial CFUs (defined as the log10 value for the number of Pa CFUs per millilitre of sputum, either expectorated or collected by suction of the oropharynx);

• Change in the following conditions: Eradication = elimination of Pa; Persistence = persistence of Pa detected at previous visit; Superinfection = appearance of a pathogen (other than Pa) not detected at previous visit; Re-infection = re-appearance of Pa detected at screening and previously eradicated.

• Change in percentage of trapped air on MRI (% of total lung volume);

• Change in FEV1 before and after nebulisation (safety parameter);

• Systemic bioavailability of inhaled tobramycin, defined by trough level;

• Change in creatinine and blood urea nitrogen (BUN) values as measure of early

renal toxicity;

• Change in hearing function (measured by HFPTA);

• Compliance rate;

• Patient satisfaction (use of device);

• Cystic Fibrosis questionnaire-revised (CFQ-R): respiratory symptoms scale

scores and treatment burden scale scores.

Study description

Background summary

Small Airways Disease (SAD) plays an important role in the pathophysiology of cystic fibrosis (CF). Chronic infection and airway inflammation lead to structural tissue damage. Obstruction and destruction of small airways lead to air-trapping, hypoperfusion and bronchiectasis. When Pseudomonas aeruginosa (Pa) is acquired, even faster deterioration of the airways results. Inhaled tobramycin is an antibiotic used to treat Pa infections and is shown to be effective for eradication and for chronic treatment. Unfortunately, small airways are difficult to reach with standard nebulizer therapy. The newly introduced smart nebuliser Akita® is more efficient. It improves lung deposition from 10-15% of the loading dose with standard nebulizer therapy to 70%, with an increased deposition in the small airways. Peripheral targeting has been shown to reduce small airways obstruction (FEF75%) when delivering dornase alpha. Furthermore, it can record adherence to therapy electronically. Since nebulizer therapy is time-consuming and cumbersome, adherence is thought to be poor. Traditionally inhaled tobramycin is dosed twice daily, but no true dose finding studies are performed for inhaled tobramycin. For intravenous use, tobramycin once daily is shown to be as effective as thrice daily, and results in less toxicity. The bactericide efficacy of aminoglycosides, such as tobramycin, improves with higher peak levels. Inhalation of the double dose in a single inhalation presumably leads to higher peak levels, which might result in the same or even better efficacy of tobramycin therapy and may lead to better compliance. We hypothesize that once daily inhaled tobramycin with an efficient nebulizer is more effective in treatment of small airways, and more effective in suppressing Pa infection compared to standard of treatment.

Study objective

Primary objective:
To compare the change in small airways obstruction (FEF75%) in patients with CF when inhaling one ampule of inhaled tobramycin with the Akita® compared to standard of treatment (twice daily nebulization of one ampule using standard nebulizer equipment)

Secondary objective:
1. To compare changes in lung function parameters (FEV1, FVC, FEF25-75%, MMEF25-75) and LCI.
2. To compare changes in bacterial CFUs and the following conditions (eradication, persistence, superinfection and re-infection) of Pseudomonas aeruginosa in sputum between both treatment arms.
3. To compare the effect on *trapped air* between both treatment arms as depicted by spirometer controlled expiratory chest Magnetic Resonance Imaging (MRI).
4. To assess safety of Akita® tobramycin inhalation therapy in CF-patients by monitoring trough levels of tobramycine, ototoxicity and nephrotoxicity.

Study design

Open label, international, multi centre, randomised controlled cross-over trial.

Intervention

26 patients will be inhaling tobramycin at home for 2x28 days in a cross-over setting: one month with the Akita® nebuliser (once daily 300 mg tobramycin) and the other month with their own nebulizer equipment (twice daily 300 mg tobramycin).

Study burden and risks

The target population in this study are adults as well as children since the chronic Pa infection starts in childhood in many patients. Inflammation and infection in the CF lung is suggested to develop very early in life and therefore early treatment is necessary. In children and adults with CF a more effective and efficient nebulizer is likely to improve quality of life.
Participating in this study is likely to be beneficial for CF patients. More efficient nebulization of tobramycin targeted to the peripheral airways could reduce small airways obstruction, improve lung function and reduce symptoms on top of the treatment effect of maintenance therapy.
The risks associated with participation are small. Tobramycin (BRAMITOB®) is a registered drug since 2007 for treatment of chronic Pa lung infections in CF-patients 6 years and older. Inhalation of tobramycin in children with CF is proven to be effective and safe in multiple studies. The Akita® nebulizer is used off label by many patients for inhalation of tobramycin and dornase alpha,

in both children and adults. However, information on the efficacy of nebulized tobramycin in combination with the Akita® on SAD is lacking. To date no serious or life threatening side effects have been described.
Since the Akita® is more efficient compared to conventional nebulizers, dosing in our study is aimed to keep the daily dose to the patient equal to that of routinely administered tobramycin. It has been well described that only in the order of 10% of the inhaled tobramycin is systemically absorbed. Systemic exposure therefore will be in the order of only 5% of the doses used for intravenous treatment. In addition we will check through levels to exclude high through levels. Hence, the risk for toxic effects is expected to be small.

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)
Elderly (65 years and older)

Inclusion criteria

• Age >= 12 years
• Clinical diagnosis of CF and a positive sweat test or two CF-related mutations;
• Chronic Pseudomonas aeruginosa colonization requiring maintenance therapy with inhaled tobramycin, defined according to the Leeds criteria (>50% Pseudomonas aeruginosa positive airway cultures over last 12 months);
• Small airways obstruction present on spirometry (defined as follows: dissociation between FVC and FEF75 values (i.e. FEF75 at least 20% (absolute percent predicted) less than FVC);
• Ability to breathe through a mouthpiece and to use the inhaler;
• Ability to perform lung function tests;
• Written informed consent (12-18 years: child and parents; >= 18 years: patient).

Exclusion criteria

• Severe acute exacerbation of pulmonary infection (needing intravenous treatment) within one month prior to start or during the study;
• Known impaired kidney function (estimated creatinine clearance < 60 ml/min);
• Known aminoglycoside hypersensitivity;
• Evidence of impaired auditory function (auditory threshold in either ear above 20 dB at frequencies between 250 and 8000 Hz);
• Start of nephrotoxic or ototoxic drugs, e.g. aminoglycosides, within 1 month prior to start or during the study;
• Use of systemic steroids (at a dose >= equivalent of 10 mg/day of prednisone) in the previous 2 weeks;
• Therapy (e.g. furosemide) or disease which may complicate evaluation of the study protocol, as judged by the investigator;
• Pregnancy or breast feeding;
• Participation in another drug-investigating clinical study at the start or within 1 month prior to the start;
• Inability to follow instructions of the investigator.
• Use of Tobramycin Inhalation Powder as part of the maintenance therapy;• Participation in another drug-investigating clinical study at the start or within 1 month prior to the start;
• Inability to follow instructions of the investigator.
• Use of Tobramycin Inhalation Powder as part of the maintenance therapy

Study design

Design

Study phase: 4

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-05-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

Generic name:	Akita Nebulizer
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Bramitob
Generic name:	Tobramycin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-05-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	29-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	22-09-2015
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	EUCTR2014-001401-41-NL
CCMO	NL48806.078.14