RANDOMIZED CONTROLLED TRIAL (RCT) TO DETERMINE THE EFFICACY AND SAFETY OF AZITHROMYCIN (AZN) MAINTENANCE THERAPY FOR 6 MONTHS IN SUBJECTS WITH PCD - A DOUBLE-BLIND, PARALLEL GROUP STUDY

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To determine if maintenance therapy with AZN will provide significant improvements in PCD lung disease, compared to placebo: reduction in respiratory system exacerbations and improvement in lung function, ventilation inhomogeneity, improvement in...

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

Summary

ID

NL-OMON42237

Source
ToetsingOnline

Brief title
Azithromycin in PCD

Condition

- Hearing disorders
- Respiratory tract infections

Synonym
immotile cilia syndrome, Primairy Ciliary Dyskinesia

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: EU

Intervention

Keyword: azithromycin, lung function, PCD, respiratory symptoms

Outcome measures

Primary outcome

To determine the efficacy of 6 months of maintenance treatment with AZN on

respiratory system exacerbations in subjects with PCD, 7-40 years of age.

An exacerbation is defined as:

1. Respiratory symptoms leading to start of systemic antibiotic treatment,

irrespective of results of bacterial culture.

2. A decline in FEV1predicted of *10% relative to the avarage of FEV1 %

predicted at Visit 1 and Visit 2, whether or not antibiotics are prescribed

Secondary outcome

Difference in FEV1 % predicted, FVC % predicted and FEF25-75 % predicted

between treatments in the pre- to post-intervention period.

Difference in RV % predicted, RV/TLC % predicted and Raw % predicted between

treatments in the pre- to post-intervention period.

Difference in Lung Clearance Index (LCI), Sacin and Scond between treatments in

the pre- to post-intervention period.

Difference in Respiratory symptoms, Sinus symptoms and Ear & Hearing symptoms

on the QOL-PCD between treatments in the pre- to post-intervention period.

Difference in hearing threshold between treatments in the pre- to post-intervention period.

Difference in tympanometry between treatments in the pre- to post-intervention period.

Difference in inflammatory markers between treatments in the pre- to post-intervention period.

Difference in sputum microbiology between treatments in the pre- to post-intervention period.

Adverse Events (AE) and Serious Adverse Events (SAE).

Study description

Background summary

Primary ciliary dyskinesia (PCD) is a rare, congenital disease manifesting in the neonatal period or in early childhood and progressing throughout adulthood. Organelles termed cilia, which line the respiratory epithelium, are either immotile or dyskinetic and cannot generate coordinated ciliary beating necessary to expel mucus. As a result, excessive mucus may form plaques and plugs in the airways that can serve as a nidus for infection. Recurrent lower respiratory tract infections progress to chronic infection that ultimately leads to bronchiectasis. PCD causes progressive loss of lung function and in severe cases can result in chronic respiratory failure with lung transplantation as the final therapeutic avenue. No orphan drugs are currently available for the treatment of PCD, and for those therapeutics currently used in the management of PCD, there have been no randomized controlled clinical trials (RCTs) to determine their efficacy and safety. *Best* treatments are anecdotal and largely derived from treatments for patients with other chronic respiratory disorders, notably cystic fibrosis (CF) and asthma, and therefore based on distinct pathophysiology of these diseases. Maintenance therapy with azithromycine in cystic fibrosis has been shown to be safe and efective in reducing the number of exacerbations and maintaining lungfunction. Consequently, many lung physicians and pediatric lung physicians already use azithromycine maintenance therapy in many chronic respiratory disorders, including PCD. However, the effectiveness and safety has never been studied in

PCD.

Study objective

To determine if maintenance therapy with AZN will provide significant improvements in PCD lung disease, compared to placebo: reduction in respiratory system exacerbations and improvement in lung function, ventilation inhomogeneity, improvement in respiratory symptoms and hearing impairment.

Study design

Multicentre, double blind, randomized, placebo controlled parallel group study.

Intervention

Oral tablets of AZN 250/500 mg according to body weight (of placebo administered three times a week (Monday-Wednesday-Friday) for 6
months

Study burden and risks

As part of the trial the patients will have to take azitromycine or placebo during a period of 6 months. Antibiotics may have side-effects, predominantly gastro-intestinal complaints. As the dosage is generally lower than the therapeutic dosage, we expect this to occur less frequently than normal. Participation in the trial will result in about two visits more than usual for a PCD patient during a period of 7 months. Due to a few more procedures than during a routine visit each visit will last about 1-1* hours longer than a standard routine visit (Visit 2 and Visit 5 are about 45 minutes longer than Visit 1, 3 and 4). Interview, physical examination, sampling of sputum for microbiological analysis and spirometry are part of the routine clinical practice performed at the regular visits for PCD patients. QOL-PCD questionnaire, N2 MBW, urine pregnancy test, body plethysmography, audiometry, tympanometry and blood samples are extra procedures performed due to participation in the trial (audiometry, tympanometry and blood samples will only be performed at Visit 2 and Visit 5).
The individual subject receiving AZN in the trial may benefit of receiving the trial drug in possibly having fewer respiratory system exacerbations and improvement in lung function, health related quality of life and hearing impairment during the treatment period, according to the hypothesis.

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

A confirmed diagnosis of PCD: Characteristic clinical symptoms and high speed video microscopic recordings of abnormal ciliary beat pattern and/or frequency;
and either abnormally low nasal NO production, and/or abnormal ciliary ultra-structure demonstrated by transmission electron microscopy analysis or high resolution immunofluorescence (not incl. isolated IDA) and/or an unequivocal genetic mutation recognized to cause PCD.
Age * 7 years and * 50 years at inclusion;
Ability to swallow tablets;
At least 30 days treatment with antibiotics prescribed against respiratory tract infections/pulmonary exacerbations in the previous 2 years;
No AZN treatment within 1 month prior to screening (visit 1);
No current therapy with systemic, inhaled maintenance antibiotics
FEV1 % predicted > 40 % at screening (Visit 1)

Ability to perform spirometry and Multiple Breath Washout (MBW);
Personally provide, or have a legal guardian provide written informed consent to participate in the trial, according to local regulations.

Exclusion criteria

Known infection with Nontuberculous Mycobacteria (NTM) (found in sputum in the past 6 months prior to screening (Visit 1), Achromobacter xylosoxidans, Burkholderia cepacia or chronic infection with Pseudomonas aeruginosa;
Be currently participating in, or have participated in another investigative drug trial within four weeks prior of screening (Visit 1);
A history of allergic reaction to macrolide antibiotics incl. ketolide antibiotics, peanut, or to any of the excipients of *Azithromycine CF 250 mg* or to any of the ingredients of the placebo.
Liver disease with Alanine transaminase (ALT) twice or more the upper limits of normal or history of portal hypertension ;
Known kidney disease with serum creatinine > 150 µmol/l and/or Glomerular Filtration Rate (GFR) < 50 ml/min;
Known congenital or documented acquired prolonged QT-interval, cardiac arrhythmia, clinical relevant bradycardia, severe heart failure, or electrolyte disturbances.
Known myasthenia gravis.
Current treatment with ciclosporin, coumarin-like oral anticoagulants (e.g. warfarin), digoxin, ergotamine derivatives (e.g. methylergometrine), nelfinavir, rifabutin and active substances known to prolong QT interval such as amiodarone and other class *A and class *** antiarrhythmics, cisapride, terfenadin, antipsychotic agents such as pimozide, antidepressants such as citalopram and fluoroquinolones such as moxifloxacin and levofloxacin;;* Be pregnant or breastfeeding; plan to become pregnant whilst in the trial; or be female of childbearing potential (at the discretion of the investigator) using an unreliable form of contraception;
* Requirement of home oxygen (not incl. supplemental oxygen for use only when exercising, mountaineering or travelling by air) or assisted ventilation;
or;
* Have any concomitant medical, psychiatric, or social condition that, in the Investigator*s opinion, would put the subject at significant risk, may confound the results or may significantly interfere with the subject*s participation in the trial.

Study design

Design

Study phase: 4

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-02-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Azithromycine
Generic name:	Azithromycine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	31-10-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	01-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	07-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	19-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-004664-58-NL
CCMO	NL48965.029.14