A European multi-centre, randomised, double-blind trial of pirfenidone in bronchiolitis-obliterans-syndrome grade 1-3 in lung transplant recipients.

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Primary objectiveThe primary objective is to evaluate the effect of Pirfenidone on the change in FEV1 over 6 months in lung transplant recipients with BOS, who are treated with Azithromycin.Secondary objectives The secondary objectives involve the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON47103

Source
ToetsingOnline

Brief title
EPOS Trial

Condition

- Bronchial disorders (excl neoplasms)

Synonym
BOS (bronchiolitis obliterans syndrome), narrowing and scarring of airways

Research involving
Human

Sponsors and support

Primary sponsor: Rigshospitalet

Source(s) of monetary or material Support: Funded by the Industry Roche

Intervention

Keyword: bronchiolitis-obliterans syndrome, lungtransplantation, pirfenidone

Outcome measures

Primary outcome

Primary Endpoint

The primary endpoint is the change in FEV1 at 6 months.

Secondary outcome

Secondary Endpoints

The secondary endpoints will be the results of the change in lung function

tests, the number of treatment failures, the change in BOS grade, the number of

hospital admissions, the rate of death or re-transplantation and the change in

the health questionnaire score at the end of the 6 month study period.

Study description

Background summary

The EPOS trial is an investigator initiated study to look at the effect of Pirfenidone on patients who have had a double lung transplant and who have been diagnosed with Bronchiolitis Obliterans Syndrome (BOS).
BOS is the result of chronic rejection of the donor lungs in patients who have had a transplant. The rejection leads to narrowing and fibrosis of the airways which creates shortness of breath and a dry cough. There is a progressive and irreversible decline in the FEV1 (the amount of air that can be exhaled in one second). BOS is the leading cause of death after 1 year post transplant. The treatment options for BOS are limited and not always effective. The usual treatment is with drug therapy (Azithromycin) and bronchodilators (drugs to help open up the airways). Photopheresis (treatment of the blood using ultraviolet light) has been used to damage the immune cells to try and slow down the rejection of the donor lungs.
Recent clinical trials in patients with Idiopathic Pulmonary Fibrosis (IPF)

have shown that Pirfenidone can be effective in increasing the lung function; IPF is a lung condition where scarring occurs in the lung tissue leading to difficulty in breathing. Pirfenidone is now approved for use in Europe for IPF. BOS is similar to IPF in that the airways become narrowed due to swelling and scarring. It is thought that Pirfenidone will help reduce the swelling and scarring in the airways, in a similar way to IPF.
Approximately 80 patients will take part in this study at 11 lung transplant centres across Europe. Seven countries will be involved: Denmark, Sweden, Norway, Germany, The Netherlands, Belgium and the United Kingdom. Patients who are regularly treated within these 11 lung transplant centres will be considered for the EPOS study.
The study has been organized by a group of expert physicians and the sponsor of this study is the lead physician in the University Hospital of Copenhagen.
There is no industrial sponsor for this study.

Study objective

Primary objective
The primary objective is to evaluate the effect of Pirfenidone on the change in FEV1 over 6 months in lung transplant recipients with BOS, who are treated with Azithromycin.

Secondary objectives
The secondary objectives involve the changes seen in the different lung function tests over the 6 months of the study. In addition, the secondary objectives will look at the number of patients with treatment failure, with a change in BOS grade and with any hospital admission. The rate of death or re-transplantation will be assessed as well as the change in the health questionnaire score.

Study design

Study Design:
Randomized double blinded, placebo controlled study. Eligible patients are to be randomized in a 1:1 ratio to receive either Pirfenidone 2403 mg/d or the matching placebo treatment for 6 months.

Study Procedures
All study procedures are the same as the routine tests that are done for patients with BOS except for one health questionnaire.
Screening
Patients will be screened for the study if they have had a double lung transplant only. Patients who have other transplants will not be eligible for the study. The screening process will use the results of diagnostic tests that the patient will routinely have had due to their condition and their symptoms

of BOS. These diagnostic tests will include the following:
* Chest x-ray
* Lung function tests (spirometry to measure the volume of air inhaled and exhaled)
* ECG (measure the heart rhythm)
* Bronchoscopy with bronchoalveolar lavage (BAL) according to standard international criteria. This is an endoscope that passes into the lungs and saline is flushed in and out to wash the airways and check if there are bacteria and fungi present.
* Transbronchial biopsy * a biopsy of the large airways
* Blood samples (haematology and chemistry) including liver function tests
* Drug monitoring for immuno-suppressive treatment
Patients who are eligible for the study need to be taking the currently accepted treatment for BOS * Azithromycin.

Start of Study
Once the patient has signed the consent form, they will have a series of diagnostic tests that are routine for BOS:
* measurement of weight,
* lung function tests
o spirometry * measure the volume of air inhaled and exhaled to determine the FEV1
o plethysmography * lung function test to calculate how much air is left in the lungs after exhalation
o diffusion capacity (DLco) * test to show the movement of oxygen from the air sacs of the lungs into the blood, after inhalation.
* 6 minute walk test - a test to see the best distance that the patient can walk in 6 minutes,
* blood tests to check the amount of blood cells, kidney function, liver function and signs of infection.
* Female patients, who are of child bearing age, will have a pregnancy test done, before they can enter the study.

In addition, a 2 page health questionnaire will be completed.

The patient will be randomised to receive either Pirfenidone or a placebo. This is a double blind study, so neither the doctor nor the patient will know which treatment they are receiving. If there are any safety concerns for a patient during the study, there will be a possibility to unblind the study treatment. The patient will be given a bottle of tablets to take home and will be told to escalate the dose over the 4 weeks as shown in the table below.

Treatment Day Number of capsules
1-7 1 (three times a day with food)
8-14 2 (three times a day with food)
15 + 3 (three times a day with food)

Months 1-4
The patient will come back to the clinic every month for the first 4 months. Their supply of the treatment will be renewed and they will have a series of routine tests (weight measurement, spirometry, blood tests). At the 4 month visit, you will be given enough study drug for 2 months.

Month 5
A blood test will be done to check the condition of the liver. This test may be done at the study centre or at the family doctor or local clinic.

Month 6
The 6 month visit is the last study visit. The patient will be asked to fill out the health questionnaire again and also to have a number of routine tests:
* measurement of weight,
* lung function tests (spirometry, plethysmography, diffusion capacity),
* chest x-ray
* 6 minute walk test
* blood tests

A chest CT scan may be arranged but only if this is routine practice for the clinic. The next routine follow up visit will be arranged as per routine practice. If a patient wishes to withdraw their consent or if the physician wishes to change their treatment due to a deterioration in BOS, they will be withdrawn from the study and will undergo the tests in the 6 month visit.

Subjects who wish to receive open label pirfenidone at the end of the 6 month EPOS trial, will be offered treatment for 1 year. Safety blood tests will be done once a month for the first 6 months of open label treatment and then at 3 monthly intervals. The blood results and all spirometry measurements that are done within this 1 year open label period will be collected for a safety analysis.

Study burden and risks

Side Effects

Severe side effects may include the following: allergic reaction (such as swelling of the face, lips and/or tongue, difficulty breathing or wheezing); skin reaction to sunlight (blistering and/or large amount of peeling of the skin); signs of an infection such as a sore throat, fever, mouth ulcers or flu-like symptoms and signs of liver problems (yellowing of the eyes or skin or dark urine). Severe allergic reaction and difficulty in breathing are uncommon and may affect up to 1 in a 100 people.

Very common side effects (may affect more than 1 in 10 people) include: skin reactions, feeling sick, tiredness, diarrhoea and indigestion or stomach upset.

Common side effects (may affect up to 1 in 10 people) include: throat infections, sinusitis (infection of the sinus) or infection of the airways going into the lungs, bladder infections, weight loss, loss of apetite, difficulty sleeping, dizziness, headache, changes in taste, hot flushes, shortness of breath, cough, muscle pain, aching joints/joint pains and chest pain.

Rare side effects (may affect up to 1 in 1000 people) -blood tests may show a decrease in the white blood cells

Patients will be encouraged to contact someone on the study team if they experience any side effects.

Treatment failure
Treatment failure will be considered as one of the following:
* New transplantation needed
* Death due to respiratory causes
* Stop study treatment due to need for a rescue therapy (change treatment for worsening of BOS)

Benefits of the study
There are very few treatment options for patients with BOS. Recent clinical trials in patients with Idiopathic Pulmonary Fibrosis (IPF) have shown that Pirfenidone can be effective in increasing the lung function; IPF is a lung condition where scarring occurs in the lung tissue leading to difficulty in breathing. Pirfenidone is now approved for use in Europe for IPF.
BOS is similar to IPF in that the airways become narrowed due to swelling and scarring. It is thought that Pirfenidone will help reduce the swelling and scarring in the airways, in a similar way to IPF.

Safety considerations
Patients will not be included in the study if they have restarted smoking after their lung transplant. They will also not be allowed to smoke during the study as this can reduce the effect of the active drug. They are not allowed to drink grapefruit juice and they need to keep the same bronchodilator (drug administered in an inhaler) throughout the study. As Pirfenidone increases the sensitivity to sunlight, patients will be advised to wear clothes that cover their arms and legs and to wear sunblock if they go outside.

The Investigator*s Brochure has a section on how to treat the patient if there are side effects. The study treatment can be stopped for up to 2 weeks, if there are severe side effects, but the dose escalation will be repeated to restart the study drug if there has been a 2 week break.

Female patients of child bearing ability will need to use 2 methods of contraception during the study to avoid becoming pregnant.

An independent Data Safety Monitoring Board will be reviewing the safety aspects of the trial during the study. In addition to this, the steering committee will review all enrolled patients to ensure that they were eligible for entry into the study; this information will be prepared so that each reviewer is unaware in which centre the patients were enrolled and so that the reviewer does not review his own patients. The steering committee will also take on the role of the Clinical Events Committee to review all serious adverse events; this will be done in the same way as the patient review.

Contacts

Public
Rigshospitalet

Blegdamsvej 9 not applicable
Not applicable not applicable
DK
Scientific
Rigshospitalet

Blegdamsvej 9 not applicable
Not applicable not applicable
DK

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients >18 years of age;2. Azithromycin therapy for at least 4 weeks prior to study start, with an Azithromycin dose of minimum 250mg /day at least 3 times per week;3. Double lung

transplantation is required; ;4. Patients must be at least 6 months after transplantation and must have documented post-transplant, base-line value of FEV1 (mean of the 2 highest values measured at least 3 weeks apart according to ISHLT criteria);5. Patients must have BOS grade 1 -3. ;6. Patients must have documented progressive disease as demonstrated by:;* At least 3 FEV1 measurements in the last 6 months each at least 3 weeks apart;* a total decline of at least 200mL in FEV1 in the last six months;* a mean decline of at least 50 mL in the last two measurements

Exclusion criteria

1. Patients with redo lung transplantation or combined transplantation (including heart and lung transplantation) Or Single lung recipients ;2. Patients with any severe comorbidity complicating BOS which might determine the prognosis and functional level of the patient (e.g. invasive aspergillosis, active malignant disease within last 12 months (i.e. disease free since at least 12 months));3. FEV1 decline related to other non BOS causes (eg pneumothorax, bronchial stenosis, effusion, etc.);4. Screening ECG shows QTc > 500 ms ;5. Patients who on Thorax CT at entry demonstrate new significant findings which are not compatible with BOS like interstitial fibrosis, consolidation, appearances suggesting restrictive Allograft Syndrome (RAS) and acute pulmonary infection as cause of decline in lung function;6. Documented acute perivascular rejection higher than grade A1 or findings compatible with antibody mediated rejection at the last trans bronchial biopsy performed.;7. Pregnancy or lactation.;8. Renal insufficiency (Creatinine clearance <30 ml/min calculated by the CKD-Epi formula).;9. Any of the following liver test criteria above the specified limit:;* Total bilirubin above the upper limit of the normal range (ULN), except in patients with predominantly unconjugated hyperbilirubinemia (e.g., Gilbert*s syndrome);* Aspartate or alanine aminotransferase (AST or ALT) >3 × ULN
* Subjects with severe liver impairment (Child Pugh C);10. Known allergy or hypersensitivity to Pirfenidone;11. Ongoing use or expected use of any of the following therapies:;* Strong inhibitors of CYP1A2 (fluvoxamine or enoxacin)
*Moderate inhibitors of CYP1A2 (mexiletine, thiabendazole, oral contraceptives or phenylpropanolamine [Note: ciprofloxacin will be allowed only at doses *500 mg BID])
*Moderate inducers (montelukast, phenytoin)
*Cimetidine
*Previous treatment with Pirfenidone after transplantation;12. Patients who have resumed smoking after transplantation
13. Initiation of a new bronchodilator therapy or treatment with Montelukast within 4 weeks prior to randomization

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-01-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	03-11-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-06-2015

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-09-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2014-002022-12-NL
ClinicalTrials.gov	NCT02262299
CCMO	NL50918.042.14