An exploratory, randomized, double-blind, placebo controlled study to assess the efficacy of multiple doses of omalizumab in cystic fibrosis complicated with allergic bronchopulmonary aspergillosis

Published: 24-09-2008
Last updated: 10-08-2024

A clinical research study to find out if Xolair is safe and has beneficial effects in adolescents (12 years old and above) and adults with cystic fibrosis (CF) and ABPA. All patients entering the study will be taking oral corticosteroids (steroid...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital respiratory tract disorders
Study type	Interventional

Summary

ID

NL-OMON33750

Source
ToetsingOnline

Brief title
none

Condition

- Congenital respiratory tract disorders

Synonym
mucoviscidosis/cystic fibrose

Research involving

Human

Sponsors and support

Primary sponsor: Harrison Clinical Research Benelux
Source(s) of monetary or material Support: Novartis

Intervention

Keyword: allergic bronchopulmonary aspergillosis, cystic fibrosis, omalizumab

Outcome measures

Primary outcome

To assess the efficacy of Xolair in adolescent and adult patients with cystic fibrosis (CF) complicated by chronic or acute allergic bronchopulmonary aspergillosis (ABPA)

• as measured by the proportion of patients requiring rescue with corticosteroids following 6 months of study treatment.

• as measured by time to deviation from the protocol prescribed steroid tapering regime.

Safety objective: to explore the safety and tolerability of higher doses of Xolair in this patient population.

Secondary outcome

1. To assess the ABPA exacerbation rates during the treatment periods

2. To assess the changes in FEV1 from baseline, measured after 3 and 6 months of study treatment, and in particular the changes between FEV1 measured before and after the

first dose in both the blinded and open label treatment periods

3. To assess the proportion of patients responding to Xolair treatment, where a

responder is

defined by a reduction in systemic corticosteroid dose of 50% or more compared

to

baseline

4. To measure the time to steroid free state

5. To assess the change from baseline over time in the average dose of rescue

corticosteroid

6. To assess the proportion of patients in each treatment group

(Xolair/placebo) responding

to Xolair whose steroid dose has reduced to 5mg following 6 months of treatment

7. To measure the number of steps needed to reduce the steroid dose to zero (or

to 5mg or

less) following 6 months of treatment

8. To measure Immunogenicity (anti-omalizumab antibodies)

9. To measure PK/PD: Total omalizumab levels, Free & Total IgE

Study description

Background summary

Allergic bronchopulmonary aspergillosis (ABPA) is a severe complication in children, adolescents and adults with cystic fibrosis (CF). Estimates of ABPA prevalence range as high as 15%. The consequent inflammatory and obstructive bronchopulmonary injury can accelerate clinical deterioration in CF. Treatment currently consists of long-term oral and inhaled corticosteroid
(OCS, ICS) usage, which are titrated against clinical response, adverse effects

and the measurement of total serum IgE levels. Oral itraconazole and/or inhaled amphotericin are used by some centers to attempt to reduce the need for OCS, but this continues to be controversial.

Study objective

A clinical research study to find out if Xolair is safe and has beneficial effects in adolescents (12 years old and above) and adults with cystic fibrosis (CF) and ABPA. All patients entering the study will be taking oral corticosteroids (steroid pills) for ABPA.
We want to assess if taking Xolair will:
• help patients to stop (or reduce) steroid pills
• improve breathing as measured by lung function tests (spirometry)
• reduce the number of times a patient gets an ABPA flare
• be safe and acceptable for patients
This is an exploratory clinical research study. Doctors have given Xolair to patients with CF and ABPA with encouraging results, but this is the first time it will be tested in a research study in patients with CF & ABPA.

Study design

The aim of this exploratory study is to assess the efficacy, safety, and tolerability of omalizumab (Xolair), and the impact on oral corticosteroid reduction in adolescent and adult patients with cystic fibrosis (CF) complicated by chronic or acute allergic bronchopulmonary aspergillosis (ABPA). Other safety and efficacy endpoints will also be assessed, as outlined in the synopsis.

Intervention

The two groups we are comparing in this study are:
1. Patients who receive Xolair treatment
2. Patients who receive placebo treatment
That means that out of the 60 people in the study 40 will receive Xolair, and 20 will receive placebo for 6 months. This is the first part of the study (double blind).
Everyone in the study will be offered treatment with Xolair for the last 6 months of the study. This is the second part of the study (open label).

Study burden and risks

Some possible side effects from taking the study medicine (Xolair):
• Allergic reactions - these are the most serious reactions to have been reported in patients taking Xolair, but they are unusual.
Most of these allergic reactions happened after the first dose of Xolair between 1* and 2 hours after the injections. Some reactions started later than

the first 2 hours and some even started 24 hours after the injection.

• Skin rash - associated with allergic reactions have been reported - only a few patients reported severe skin rashes.
• Injection site reactions - (usually happen within 1 hour of injection) bruising, redness, stinging, itching and/or pain have been reported. Although common, injection site reactions have not been troublesome enough to most patients for them to stop treatment.
• Unknown problems or side effects could also occur.

• Reducing steroid pills - reducing your steroid pills may cause patients to have symptoms of an ABPA flare. The investigator will supervise the steroid treatment during the study. While patients are taking steroid pills their blood levels will be checked to make sure that it is safe to continue reducing your steroids.

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

1. Males/females age >= 12 years
2. Cystic Fibrosis diagnosed by either gene profiling and/or sweat test
3. ABPA previously diagnosed according to the Cystic Fibrosis Foundation Consensus Conference recommendations - minimal diagnostic criteria for diagnosis of ABPA in cystic fibrosis (Stevens et al, 2003) defined as:
i) Acute or sub-acute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, or increased sputum production) not attributable to another etiology.
ii) Total serum IgE concentration of >500 IU/mL (1200 ng/mL).
iii) Immediate cutaneous reactivity to Aspergillus (prick skin test wheal >3mm in diameter with surrounding erythema, while the patient is not being treated with systemic antihistamines) or in vitro demonstration of IgE antibody to A.fumigatus.
iv) One of the following:
a)precipitans to A.fumigatus or in vitro demonstration of IgG antibody to A.fumigatus
or
b)new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that has not cleared with antibiotics and standard physiotherapy.
3. Total serum IgE level of > 500 IU/ml (will be measured locally at Screening Visit). Screening IgE levels will determine the dose throughout the study.
4. Patients who are being treated for ABPA by any oral corticosteroid (for at least 8 weeks prior to the first dose of study treatment - with an OCS entry dose of minimum 5mg/maximum 40mg per day in prednisolone equivalence). Patients must have a history of at least one unsuccessful attempt to taper steroids defined as in the clinician*s judgment, an ABPA exacerbation during taper (chronic ABPA group)
OR
Patients who present with an acute episode of ABPA, either as a first presentation or as a recurrence, and who were taking a maximum dose of prednisolone of 20mg/day (or equivalent) prior to the ABPA flare (acute ABPA group)
5. Patients must have an FEV1, as measured at the Baseline Visit, of no lower than 90% of their previous best FEV1 as measured at Screening Visit
6. FEV1 >40% of predicted in patients aged < 16 years old, and FEV1 of >30% of predicted is acceptable in patients aged >= 16 years old as measured after 12 hour washout of LABA \ 6 hours of SABA
7. Female subjects of childbearing potential must be advised that systemic corticosteroids pose a known risk to mother and fetus. Xolair is FDA pregnancy category B. This medication is not expected to be harmful to an unborn. However, patients are advised to use adequate methods of contraception, (e.g. hormonal contraceptive plus condom, intrauterine

device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not adequate methods of contraception
8. Female subjects who report surgical sterilization must have had the procedure at least six (6) months prior to initial dosing. Surgical sterilization procedures should be supported with clinical documentation made available to the sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the CRF
9. Postmenopausal females must have had no regular menstrual bleeding for at least one (1) year prior to initial dosing. Menopause will be confirmed by a plasma FSH level of >40 IU/L at screening.
10. Prior to administration of any study procedures, eligible patients (and parents for patients below age 16) must provide written informed consent
11. Subjects must be able to communicate well with the investigator; understand and comply with the requirements of the study; and understand and sign the written informed consent (parental consent and assent for minors, if applicable).

Exclusion criteria

1. History of cancer in the past 10 years (except surgically-cured basal cell or squamous cell skin cancer).
2. Any previous history of anaphylaxis.
3. Any other medical condition that in the opinion of the investigator may cause the patient to be unsuitable for completion of the study or place the patient at potential risk from being in the study.
4. Pregnant women.
5. Prior Xolair exposure.
6. Lung or other transplant.
7. Participation in any clinical trial within four (4) weeks prior to initial dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.
8. Hemoglobin levels below 10.0 g/dl at screening.
9. History of immunodeficiency diseases.
10. Significant illness other than CF/ABPA within two (2) weeks prior to initial dosing.
11. A past medical history of clinically significant ECG abnormalities.
12. Patients who are known to be positive for chronic atypical Mycobacteria and Burkholderia cepacia including subspecies.

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-01-2010
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	placebo
Generic name:	placebo
Product type:	Medicine
Brand name:	Xolair
Generic name:	Omalizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-09-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2009
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2010
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	EUCTR2007-006648-23-NL
CCMO	NL24314.029.08