ISRCTN90016959 https://doi.org/10.1186/ISRCTN90016959

Omalizumab in non-atopic asthma

Submission date 29/04/2010	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 16/06/2010	**Overall study status** Completed	
Last Edited 21/09/2017	**Condition category** Respiratory	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT01113437

Protocol serial number
Omalizumab/2009/01

Study information

Scientific Title

The effect of a humanised monoclonal anti-IgE antibody (omalizumab) on disease control and bronchial mucosal inflammation in non-atopic ('intrinsic') asthma: a double-blind, randomised, placebo-controlled trial

Acronym
XONAA

Study objectives
Anti-IgE monoclonal antibody, omalizumab (Xolair®), is effective on disease control and bronchial mucosal inflammation in non-atopic asthma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Guy's Research Ethics Committee, 22/06/2009, ref: 09/H0804/43

Study design
Randomised double-blind placebo-controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Asthma

Interventions
Overview:
This will be a double-blind, placebo-controlled, parallel-group proof-of-principle study. Patients will be randomized to receive omalizumab or placebo therapy for 12 weeks, following which their inhaled corticosteroid therapy will be normalized and reduced in two stages over a subsequent 8 week period while omalizumab/placebo therapy is continued. Any additional IgE produced within the circulation or the bronchial mucosa as a result of this reduction in therapy will be bound immediately by the anti-IgE in the actively treated patients, thus theoretically preventing end organ effects.

Subjects:
We will randomize 40 moderate/severe, non-atopic asthmatics to active (omalizumab) or matching placebo therapy in a 1:1 ratio.
Patients attending the relevant clinics of the participating investigators or recruited otherwise (advertisement, poster etc.) will be approached by members of the research team and information sheets will be given to them. Those who are willing to participate will be invited to attend for a screening visit.

Clinical protocol:
Visit 1 - Screening visit:
Informed consent will be obtained before screening starts. All patients will have a complete history taken and a full medical examination. Clinical testing will include measurement of

weight, skin prick testing for atopic status, blood samples for full blood count, coagulation screen (prior to fibre-optic bronchoscopy) and serum total IgE concentration. Patients will be given a home peak flow meter and blank diary forms and asked to document daily morning /evening peak flow, usage of rescue medication and day and night symptoms from this point until the end of the study. Patients anti-asthma medication will not be changed at this stage but they will be encouraged to take any such medications as prescribed.

Visit 2 - First fibre-optic bronchoscopy and commence omalizumab/placebo therapy:
This will be arranged with eligible patients no more than 4 weeks after the screening visit. Patients will be asked not to eat or drink anything (save sips of water to take tablets if necessary) and omit long-acting inhaled bronchodilator therapy if possible on the morning of attendance. Assuming that it is safe to proceed with fibre-optic bronchoscopy, as determined by the study physicians based on the results of prior testing and lung function records, patients will be randomized to omalizumab/placebo therapy and asked to hand in and renew their diaries, complete a validated asthma quality of life questionnaire and undergo spirometry with reversibility and exhaled nitric oxide measurement. Following this they will undergo fibre-optic bronchoscopy with bronchial biopsy. During this procedure 30 ml of venous blood will be collected, allowed to clot and the serum stored. Following bronchoscopy, patients will receive a subcutaneous injection of omalizumab (75-300 mg, depending on body weight & serum total IgE) or matching placebo with supervision for 2 hrs afterwards. This dosage will be in accordance with that recommended for normal therapeutic usage of omalizumab in atopic asthma, according to the manufacturer's SPC, and will be sufficient to bind to all free serum IgE in these non-atopic patients.

According to the manufacturer's recommendations, dosage and intervals of omalizumab administration (2 or 4 weekly) are dictated by the patient's body weight and serum total IgE concentration (see Appendix). We expect that, since in this study the patients are non-atopic and will have low total serum IgE concentrations, for most patients dosing will be 4 weekly. Nevertheless there may be some patients who require 2 weekly dosing (9 doses at 2 weekly intervals instead of 5 at 4 weekly intervals as shown in the study flow chart below). Flexibility of +/- 1 week (for 4 weekly dosing) or +/- 3 days (2 weekly dosing) will be allowed on the dates of these dosages so that patients are able to schedule appointments conveniently.

Visits 2a, 3, 3a, 4, 4a, 5 - Further dosages of omalizumab/placebo:
Patients will receive 3 (or 6) further, identical injections of omalizumab or placebo and undergo clinical assessment at intervals of 4 +/- 1 weeks (in the case of 4 weekly dosing) or 2 weeks +/- 3 days (in the case of 2 weekly dosing). They will continue to fill in their diary cards and take their usual anti-asthma medication. At each visit, in addition to the injections with supervision afterwards for 2 hours, patients' diary cards will be collected and renewed.

Visit 6 - Second fibre-optic bronchoscopy and reduce anti-asthma medication:
Within 2 weeks of visit 5, patients will attend for a further fibre-optic bronchoscopy as described previously. Prior to the procedure subjects will once again complete a validated respiratory quality of life questionnaire and undergo spirometry with reversibility and exhaled nitric oxide measurement. Commencing the day following the procedure, patients will be asked to substitute their existing anti-asthma medication with budesonide/formoterol combination therapy (Symbicort® 100/6 Turbohaler 2 puffs twice daily). Thorough instruction in the use of the device will be given to those patients not familiar with it. In addition, patients will be given a short-acting beta-2-agonist (terbutaline (Bricanyl®) Turbohaler 250 mcg/puff) to use in addition to the Symbicort as required for the immediate relief of symptoms. These procedures will be explained during the bronchoscopy visit.

Visit 7 - Dosage of omalizumab/placebo if appropriate and clinical assessment:
Regardless of the precise date of visit 6, patients will be asked to return within 2 weeks +/- 3 days of visit 5. Patients on 2 weekly dosages of omalizumab/placebo will receive their injections at this visit. All patients will have clinical examination and discussion of their symptoms and medication with the study physician.

Visit 8 - Final dosage of omalizumab/placebo and reduce anti-asthma medication:
This visit will be arranged 2 weeks +/- 3 days after visit 7. During this visit, after clinical examination and discussion of their symptoms and medication with the study physician and collection of their diaries, patients will receive their 5th or 9th and final injection of omalizumab /placebo. They will be instructed to reduce the dosage of Symbicort® 100/6 Turbohaler to one puff twice daily, and continue to use Bricanyl Turbohaler 'as required' for symptoms.

Visit 9 - End of study:
This visit will be arranged within 4 +/- 1 weeks of visit 8. After clinical examination and discussion of their symptoms with the study physician and collection of their diaries, patients will complete a third validated asthma quality of life questionnaire and undergo spirometry with reversibility and exhaled nitric oxide measurement. We will check the symptoms, peak flow diary and clinically examine the patient. Patients will be instructed to resume their regular anti-asthma medication from the day following this visit.

Visit 10 - Follow up visit:
A follow-up appointment will be arranged 2 weeks later to check the patients' well being, symptom control and to ask about any adverse reactions.

At any time during the study, patients will be treated for asthma exacerbations, if these should occur, with a 10 day course of prednisolone 30 mg/day instituted by the study physician in consultation with the patient. Such patients will leave the study, resume their regular anti-asthma medication and be followed up in 2 weeks or earlier if necessary by arrangement with the patient.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Omalizumab (Xolair®)

Primary outcome(s)
1. Prior to reduction of existing anti-asthma therapy (first 12 weeks of study):
Differences in changes in pre-bronchodilator FEV1 after 12 weeks of treatment with omalizumab or placebo
2. During anti-asthma therapy reduction phase (subsequent 8 weeks of study):
The primary outcome measure will be disease exacerbation, defined as a need for rescue oral corticosteroid medication for worsening of symptoms and/or deterioration in lung function, as agreed between the patient and the study physician

Key secondary outcome(s))

Clinical secondary efficacy parameters
1. Prior to reduction of existing anti-asthma therapy (first 12 weeks of study):
Differences in changes in:
1.1. Morning and evening peak expiratory flow
1.2. Exhaled nitric oxide
1.3. Day and night time symptom scores
1.4. Total dosages of rescue beta-2-agonist
1.5. Total symptom free days
1.6. Validated asthma Quality of Life scores

2. During anti-asthma therapy reduction phase (subsequent 8 weeks of study):
Secondary outcome measures will include all those measurements listed in section (1) above, unless they cannot be measured because of disease exacerbation (the primary outcome measure)

3. Laboratory efficacy parameters
Differences in changes in the following variables after 16 weeks of treatment with omalizumab or placebo:
3.1. Lay down of collagen types I, III, IV and V and tenascin
3.2. Area of vascular structures and expression of angiogenic stimuli (collagen type IV, CD31 and human VEGF
3.3. Infiltration of inflammatory cells (eosinophils, T cells, B cells, plasma cells, macrophages, neutrophils, mast cells)
3.4. Relative area of goblet cells (stained using monoclonal anti-Muc-5AC antibody)
3.5. Mucosal expression of immunoglobulin E and its high- and low-affinity receptors
3.6. Cytokine concentrations in homogenised biopsies

Completion date
30/08/2012

Eligibility

Key inclusion criteria
1. Males and females aged 18 to 60 years inclusive
2. Moderate/severe non-atopic asthma as defined below treated with inhaled corticosteroid for at least 6 months
2.1. Daytime & night-time symptoms at least 3 days/week in the last 3 months prior to screening visit (despite taking inhaled corticosteroids with or without long-acting β2- agonist or leukotriene blockers
2.2. Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) 40-80% predicted; reversibility of ≥12% in FEV1 in response to inhaled β-agonist documented at any time within the past 2 years
2.3. Negative skin prick and/or in vitro IgE tests to a range of 12 common aeroallergens
2.3.1. pollens:
2.3.1.1. grass
2.3.1.2. hazel
2.3.1.3. alder
2.3.1.4. birch
2.3.2. danders:
2.3.2.1. cat
2.3.2.2. dog

2.3.3. dust mite:
2.3.3.1. D.pteronyssinus
2.3.3.2. D. farinae
2.3.4. moulds
2.3.4.1. Cladosporium
2.3.4.2. Aspergillus
2.3.4.3. Alternaria

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Smoking within the past year or total smoking history 0.5 pack years
2. Pregnant or lactating females or those at risk of pregnancy
3. Treatment with more than 2000 µg/day beclometasone, 1600 µg/day
4. Budesonide or1000 µg/day fluticasone by inhalation or regular systemic corticosteroid at screening
5. Hospitalisation for asthma or exacerbation requiring systemic corticosteroid therapy within 3 months of the screening visit
6. History of life-threatening asthma, defined as an asthma episode that required intubations and /or was associated with hypercapnia, respiratory arrest and/or hypoxic seizures
7. Patients in whom, in the opinion of the study investigators, omalizumab therapy might normally require precaution (a history of autoimmune disease, renal or hepatic impairment, hyper immunoglobulin E syndrome, Allergic bronchopulmonary aspergillosis and diabetes mellitus)

Date of first enrolment
12/05/2010

Date of final enrolment
30/08/2012

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Guy's Hospital
London
United Kingdom
SE1 9RT

Sponsor information

Organisation
King's College London (UK)

Organisation
Guy's and St. Thomas' NHS Foundation Trust (UK)

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Charity

Funder Name
Guy's and St. Thomas' Charity (UK) - (Charity No: 251983)

Alternative Name(s)
Guy's and St Thomas' Charity, Guy's and St Thomas' Foundation, GSTTFoundation

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location

United Kingdom

Funder Name
Novartis UK Ltd (UK)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/12/2016		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes