Evaluation of the anti-inflammatory effects of glycopyrronium added to indacaterol/mometasone on the allergen-induced late asthmatic response

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The purpose of this study is to assess the anti-inflammatory effects of Indacaterol/glycopyrronium/Mometasone (QVM) 150/50/80 µg once daily versus Indacaterol/Mometasone (QMF) 150/160 µg once daily on the allergen-induced late asthmatic response in…

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

Summary

ID

NL-OMON49783

Source
ToetsingOnline

Brief title
Anti-inflammatory effects of Glycopyrronium

Condition

- Bronchial disorders (excl neoplasms)

Synonym
asthma; bronchitis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Novartis

Intervention

Keyword: allergen, anti-inflammatory, asthma

Outcome measures

Primary outcome

The primary endpoint is the reduction in the percentage of sputum eosinophils 24 hours after allergen challenge at the end of each treatment period vs. control allergen challenge.

Secondary outcome

Change from baseline after allergen challenge of:

• Cell differential counts in blood and sputum 24 hours after allergen challenge.

• Bronchial and alveolar nitric oxide.

• Multiple Breath Nitrogen Washout (Lung Clearance Index (LCI), Scond, Sacin).

• Lung function (FEV1, FEV1/FVC, FEF25, FEF50, FEF75, FEF25-75).

• Body plethysmography (RV (% predicted), RV/TLC % predicted).

• Impulse Oscillometry. Resistance (R5, R20, R5-20) and Reactance at 5 Hertz (IOS).

• Genome-wide mRNA and miRNA expression in sputum and in epithelial cells derived from nasal epithelial brushes.

Study description

Background summary

Current treatment for patients with asthma includes inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA). The long-acting muscarinic antagonist (LAMA) tiotropium has recently been registered for the treatment of asthma. Clinical trials have shown beneficial effects on lung function by addition of tiotropium to standard treatment in moderate and severe asthma. In addition, treatment with tiotropium reduces the number of severe exacerbations, suggesting that anticholinergics exerts anti-inflammatory effects in these patients.

Anti-inflammatory effects of anticholinergics have extensively been demonstrated in in vitro and in vivo studies using various experimental models. In vitro, anticholinergics exert direct anti-inflammatory effects on T cells, macrophages, epithelial cells, and on airway smooth muscle cells. Moreover, in vivo animal models have demonstrated inhibitory effects of tiotropium or muscarinic M3 receptor knockout on ovalbumin-induced inflammation, the anti-inflammatory effects of tiotropium being comparable to those of the corticosteroid budesonide.

The effects of the combination of anticholinergics with ICS/LABA on airway inflammation are currently largely unknown. In vitro, it has been shown that the anticholinergic glycopyrronium acts synergistically with budesonide in inhibiting tumor necrosis factor α (TNF-α) release from isolated monocytes, suggesting that the combination of anticholinergics and corticosteroids might be more effective than the monotherapies in vivo. In addition, we recently demonstrated that the combination of the anticholinergic tiotropium with the corticosteroid ciclesonide is more effective than either compound alone in inhibiting allergen-induced airway inflammation and remodelling in a guinea pig model of chronic asthma. It is currently unknown whether treatment with anticholinergics added to ICS/LABA has anti-inflammatory effects in patients with asthma.

Study objective

The purpose of this study is to assess the anti-inflammatory effects of Indacaterol/glycopyrronium/Mometasone (QVM) 150/50/80 µg once daily versus Indacaterol/Mometasone (QMF) 150/160 µg once daily on the allergen-induced late asthmatic response in patients with asthma.

Study design

Study design: This study will be a double-blind, randomized, two-way cross-over

study.
Study population: A total of 28 patients with mild to moderate severe asthma (GINA steps 1-3) will be randomized for treatment.

Intervention

Indacaterol/glycopyrronium/Mometasone (QVM) 150/50/80 µg once daily versus Indacaterol/Mometasone (QMF) 150/160 µg once daily

Study burden and risks

This study has no specific benefits for the participating patients. The study also has no major risks. Minor risks for participants in this study are:
• Nasal epithelium collection may cause a temporary nose bleed.
• Allergen inhalation can cause dyspnea. After the challenge subjects may take an inhaled bronchodilator when necessary.
• Blood collection may cause bruising.
• All drugs may cause side effects.

When patients use inhaled corticosteroids and certain types of medication for asthma (SAMA, B2-agonists + corticosteroids, short-acting B2-agonists + short-acting anti-cholinergic, theophylline, leukotriene antagonist) at visit 1, they will be asked to stop their inhaled corticosteroid for a short period of time (4-5 weeks). This is considered to be in mild to moderately severe asthma (GINA treatment step 1-3). In previous studies stopping the asthma medication for a short period has never led to serious problems and after the provocation test and sputum induction every patient will get a bronchodilator. When lung function has dropped by more than 20% at visit 2 compared to visit 1 (after stopping inhaled corticosteroids), patients will be withdrawn from the study so they can start using their own medication again.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female adult patients aged between 18 and 65 years old.
3. Patients with a diagnosis of asthma for at least 6 months prior to Visit 1 with current asthma severity of step 1-3 (GINA 2018).
4. Patients with presence of allergy against house dust mite, cat or grass pollen.
5. PC20 methacholine <= 8 mg/ml.
6. Drop in FEV1 of 20% or more during the early asthmatic response and drop in FEV1 of 15% or more during the late asthmatic response, i.e. between 3-8 hours after allergen challenge.
7. Patients able to produce sputum of sufficient quality for evaluation of cell differential counts 24 hours after the baseline allergen challenge at Visit 3.

Exclusion criteria

1. Patients who have a smoking history >= 10 pack-years (Note: 1 pack is equivalent to 20 cigarettes. 10 pack years = 1 pack/day x 10 years or * pack/day x 20 years). Ex-smokers are eligible for inclusion if they quit smoking for at least 6 months prior to Visit 1.
2. Patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD).
3. Patients with severe airway obstruction at baseline, FEV1 < 70% of predicted or < 1.5 liters.
4. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1. If patients experience an asthma attack/exacerbation requiring systemic

steroids or hospitalization or emergency room visit, they may be re-screened 6 weeks after recovery from the exacerbation.
5. Patients who have had a respiratory tract infection or clinical significant asthma worsening as defined by Investigator within 4 weeks prior to Visit 1. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
6. Patients who have ever required intubation for a severe asthma attack/exacerbation.
7. Patients who have a clinical condition which is likely to be worsened by ICS administration (e.g. glaucoma, cataract and fragility fractures) who are according to investigator*s medical judgment at risk participating in the study.
8. Patients treated with a LAMA for asthma within 3 months prior to Visit 1.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-09-2020
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	QMF149
Generic name:	Mometasone furoate / Indacaterol
Product type:	Medicine
Brand name:	QVM149

Generic name:	Mometasone furoaat / Indacaterol/Glycopyrronium

Ethics review

Approved WMO Date:	02-07-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-07-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	14-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-09-2022
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	EUCTR2019-001762-14-NL
CCMO	NL70842.042.19