*Differences in effect of treatment with mepolizumab and benralizumab on resident and inflammatory eosinophils.

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To test the hypothesis: the mode of action of benralizumab being ADCC will target both resident and inflammatory eosinophils whereas mepolizumab only targets inflammatory eosinophils. This will achieved by a head-to-head comparison of the presence...

Ethical review	Not approved
Status	Will not start
Health condition type	Allergic conditions
Study type	Observational invasive

Summary

ID

NL-OMON49549

Source
ToetsingOnline

Brief title
DIMENSION

Condition

- Allergic conditions
- Bronchial disorders (excl neoplasms)

Synonym
asthma, shortness of breath

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: GlaxoSmithKline

Intervention

Keyword: asthma, benralizumab, eosinophil, mepolizumab

Outcome measures

Primary outcome

Number of eosinophils per high power field in rectal biopsies

Secondary outcome

1. Number of eosinophils in the peripheral blood (million/ml)

2. Kinetics of eosinophils in tissue and blood.

Study description

Background summary

Overall rationale: the production of eosinophils in the bone marrow is not dependent on IL-5, but reactive eosinophilia is. The prevailing idea is that eosinophil progenitors are formed independently of IL-5 but the cells express the IL-5R (IL-5 KO mice have terminally differentiated eosinophils in the peripheral blood). When IL-5 is produced during T2 inflammation this cytokine acts as growth/proliferation factor for these IL-5R-positive cells. This implicates that anti-IL-5 therapy can only act on reactive eosinophilia.
The situation with benralizumab is different. This antibody is directed against IL-5R and kills these cells by antibody-dependent cellular cytotoxicity (ADCC). This implicates that benralizumab kills all IL-5R positive cells (eosinophils and basophils)(1).
The recent study and review by Mesnil et al (2) again shows the presence of resident eosinophils in homeostasis in healthy tissues as well as in the lung. Following the above-mentioned reasoning these cells are likely not sensitive for IL-5 targeted therapy whereas they are sensitive for benralizumab therapy. Conus et al. (3) supports this hypothesis as treatment with mepolizumab does not affect eosinophil numbers in duodenal mucosa. In addition, the expected depletion of eosinophils in the gut tissue by benralizumab has been recently demonstrated in patients with HES (4,5)..

Study objective

To test the hypothesis: the mode of action of benralizumab being ADCC will target both resident and inflammatory eosinophils whereas mepolizumab only

targets inflammatory eosinophils. This will achieved by a head-to-head comparison of the presence of (healthy) resident eosinophils in the rectal (gut) tissue.

Study design

Investigation part 1: comparative study between 20 patients treated with mepolizumab (Nucala) and 20 patients treated with benralizumab (Fasenra).

Investigation part 2: longitudinal cross over study with 12 (2x6) biological naïve patients that either start with mepolizumab and cross after 6 months to benralizumab or vice versa

Study burden and risks

Burden is limited:

Cross-sectional study (part 1):
Three visits: 1 initiation visit (1 hr), 1 day in UMCU (glucose labeling), 1 visit for taking biopsies/2 hr
Total: 6-26 days depending on the length of the labeling: 11 hrs in total
Clinical samples: 4 small rectal biopsies, 1 tube of NaHep blood and 6 finger pricks

Prospective cross-over study (part 2)
Four visits: 1 initiation visit (1 hr), 3 visits for taking biopsies/2 hr and 10 short visits for determination of weight and blood differentiation
Total: 4 visits in 52 weeks: 17 hrs in total
Clinical samples: 4 small rectal biopsies, 3x1 tube of NaHep blood and 3x1 urine sample

There are very small risks associated with
1. Venipuncture: potential small leakage of blood, bruise
2. Rectal biopsy: potential small leakage of blood
3. 2H-gluocse: no known side effects at doses used in this investigation
4. Treatment with Nucala en Farenza: mild complaints such as head ache, colds, low fever.

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

* Age * 18
* Diagnosis of severe refractory eosinophilic asthma
* Eligible for mepolizumab or benralizumab therapy according the national recommendations for severe asthma of the Dutch society for lung diseases and tuberculosis (NVALT guideline 2013): Patients with asthma, for whom alternative diagnoses are excluded, comorbidity optimally treated, provoking factors minimized and therapy compliance optimized, but despite this still have insufficient asthma control (* 1.5 ACQ-7 or other questionnaire) or frequent (*2 annually) severe exacerbations (systemic CS needed) while routinely using high-dose asthma medication (* 1000 mcg/day fluticasone propionate equivalent and/or daily OCS in combination with LABA or other controller medication); or patients who can achieve asthma control only with systemic CS and are therefore are risk for adverse effects or the corticosteroids.
* Treated with mepolizumab or benralizumab for at least 4 months.
* Before treatment with biologics a blood eosinophilia (* 150 eosinophils/microl blood) irrespective of steroid use

Exclusion criteria

* Any infection (eg. HIV, Hepatitis, STDs)
* Insulin dependent diabetes
* Smoking at present or in the last 12 months and/or a past history of more than 10 pack years
* Proven allergic bronchopulmonary aspergillosis
* Auto-immune diseases
* Use of medication, excluding:
o Anticonceptives
o Pain killers, if used on average less than once a week
* exuberant alcohol consumption (for males > 36 glasses per week, for females >24 glasses per week)
* Drug use
* History of cancer
* Use of biologicals other than mepolizumab or benralizumab
* daily oral steroid therapy during the three months preceding inclusion

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	72
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	Fasenra
Generic name:	benralizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nucala
Generic name:	mepolizumab
Registration:	Yes - NL intended use

Ethics review

Not approved

Date:	26-06-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2019-004676-18-NL
CCMO	NL72258.041.20