Eosinophils in the treatment of asthma

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Outline
- Eosinophils in the treatment of asthma -

• How important are eosinophils in the diagnosis of asthma?
• How important are eosinophils in the treatment of asthma?
The Dogma
There are many phenotypes of asthma,
- but not all asthma is associated with eosinophils
Asthma: defining of the persistent adult phenotypes

- No non-allergic in children?
- Or are all children non-allergic and only a subgroup allergic?

non-allergic vs. allergic? What about the rest?
What is asthma?

- Asthma phenotypes
  - Ask 2 physicians, get 3 answers ...
  - Phenotype stability ?
  - Prognosis in adult asthma
- Endotypes
  - „The emperor’s new clothes“
  - invisible to those unfit for their positions, stupid, or incompetent
The multiple “phenotypes” of asthma

**Onset**
- Early-onset (< 12 y)
- Late-onset (> 12 y)

**Severity**
- Symptoms
- Obstruction
- Hyperresponsiveness (Methacoline/Histamine/Cold Air/other agents)

**Control**
- Treatment-resistant
- Treatment-sensitive
- Brittle asthma

**Exacerbations**
- Exacerbation-prone or not

**Triggers**
- Allergic
- Non-allergic
- Aspirin-sensitive
- Occupational
- Menses-related
- Exercise induced

**Inflammation**
- Eosinophilic
- Neutrophilic
- Paucigranulocytic
- High or low Exhaled NO

**IgE-Levels**
- High IgE-levels
- Medium IgE-levels
- Low IgE-levels
# Extrinsic and intrinsic Asthma: Clinical features

<table>
<thead>
<tr>
<th></th>
<th>Allergic Asthma</th>
<th>Intrinsic Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>before age 30</td>
<td>after age 40</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Other atopic manifestations</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Seasonal symptoms</strong></td>
<td>based on sensitisation</td>
<td>-</td>
</tr>
<tr>
<td><strong>Perennial symptoms</strong></td>
<td>based on sensitisation</td>
<td>+</td>
</tr>
<tr>
<td><strong>Asthma attacks</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Skin-prick-tests</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total IgE</strong></td>
<td>elevated</td>
<td>normal</td>
</tr>
<tr>
<td><strong>Specific IgE</strong></td>
<td>detectable</td>
<td>-</td>
</tr>
<tr>
<td><strong>Eosinophilia</strong></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>Sputum-eosinophilia</strong></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>Chronic sinusitis</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Nasal/sinus polyps</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Aspirin-induced asthma</strong></td>
<td>rarely</td>
<td>+</td>
</tr>
<tr>
<td><strong>Response to therapy</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Steroid-free intervals</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Steroid-requirement</strong></td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Non-eosinophilic phenotype

More frequently associated with:

- Occupational asthma
- Elite athletes
- Obesity
- Post-menopausal women
- others

⇒ steroid resistant asthma?

Asthma Phenotypes according to Factor-Analysis

Discordant Symptoms

- EARLY SYMPTOM PREDOMINANT
  - Early onset, atopic.
  - Normal BMI.
  - High symptom expression.

- OBESITY NON-EOSINOPHILIC
  - Later onset, female preponderance.
  - High symptom expression.

Concordant Disease

Primary Care Asthma

- EARLY ONSET ATOMIC ASTHMA
  - Mixed middle-aged cohort.
  - Well controlled symptoms and inflammation. Benign prognosis.

- INFLAMMATION PREDOMINANT
  - Late onset, greater proportion of males.
  - Few daily symptoms but active eosinophilic inflammation.

Discordant Inflammation

- MONITORING INFLAMMATION allows down-titration of corticosteroids.
- Symptom-based approach to therapy titration may be sufficient.
Eosinophils in the treatment of asthma

- Diagnosis -

<table>
<thead>
<tr>
<th>43 y/o male</th>
<th>Normal red and white BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma since 6-8 y</td>
<td>No eosinophilia (1.3%)</td>
</tr>
<tr>
<td>Tx with Symbicort</td>
<td>Neutrophilic sputum</td>
</tr>
<tr>
<td>Last 1.5 y no Tx</td>
<td>with 100k Strep. pneum. CFU</td>
</tr>
<tr>
<td>Hx: chronic rhinosinusitis</td>
<td>CRP 5.0</td>
</tr>
<tr>
<td>Smoking Hx: 15py, &gt; 7 y ago</td>
<td>Vit D 59.1 nmol/l</td>
</tr>
<tr>
<td>Vital signs normal</td>
<td>Total IgE 19.6 kU/l</td>
</tr>
<tr>
<td>norm. Temp</td>
<td>Neg. SPT</td>
</tr>
<tr>
<td>Upper airways w/o pathol.</td>
<td>FENO 7 ppb</td>
</tr>
<tr>
<td>Severe wheezing on auscult.</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis & management of asthma in adults

FEV1: 1.08 L (27% of pred)
RV: 4.28 L (216.1 % of pred)
DLCO normal
FEV1: 1.08 L (27% of pred)  
RV: 4.73 L (238.9% of pred)  
DLCO normal  

After 3 weeks of high dose systemic steroids Flut/Salm, Montelukast and Amoxicillin/Clav. and high dose Vit D
What is this?

Very severe, steroid refractory asthma?

Or something else?

Haldar P, et al. AJRCCM 2008; 178; 218-224
Diagnosis & management of asthma in adults
Diffuse Panbronchiolitis

FEV1: 1.65 L (41.6% of pred)
RV: 3.99 L (198.9 % of pred)
DLCO normal

Marked improvement
on daily Clarythromycin 500mg
How many of such and/or similar patients have the label „asthma“?
Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

## Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>69 (32.9)</td>
</tr>
<tr>
<td>One or more positive skin tests for atopy — no./total no. (%)</td>
<td>175/200 (87.5)</td>
</tr>
<tr>
<td>Age at visit 1 — yr</td>
<td>42.2±12.3</td>
</tr>
<tr>
<td>Duration of asthma — yr</td>
<td>26.1±14.1</td>
</tr>
<tr>
<td>Weight at visit 1 — kg</td>
<td>88.3±25.3</td>
</tr>
<tr>
<td>Body-mass index at visit 1†</td>
<td>31.4±8.8</td>
</tr>
</tbody>
</table>

Asthma and Tiotropium

- Obesity has been associated with false positive results on measurements of BHR ...
- an accelerated decline in FEV$_1$ ...
- a reduced response to inhaled glucocorticoids ...


We agree with Lommatzsch et al. that the relationships between obesity and asthma are intriguing. In fact, we have planned a formal analysis of our study results to take into account the effects of body-mass index. The average FEV$_1$/FVC ratio for the randomized subjects was 68%.

Management of asthma in adults

In cases of insufficient treatment response and reduced FEV1 despite adequate therapy:

• Rule in Co-morbidities
• Rule in other diseases / differential diagnosis
• Including
  • HR-CT
  • Bronchoscopy
  • Lung biopsy
In a patient without eosinophilia the diagnosis of asthma should be challenged!

Lack of eosinophilia predicts an insufficient treatment response!
Phenotype stability ?
Asthma phenotypes: consistency of classification using induced sputum

- Sputum phenotype stability of asthma studied in two clinical trials:
- Participants' sputum frequently changed between eosinophilic and non-eosinophilic inflammation.
  - Study 1 (n=28): only one of 8 pat. with non-eosinophilic sputum after placebo treatment remained non-eosinophilic
  - Study 2 (n=26 pat. with non-eos.-asthma): all pat. had at least one eosinophilic sputum sample. Neutrophilic asthma was uncommon in both studies and was also inconsistent
- Changes occurred spontaneously and in response to treatment.
- A diagnosis of non-eosinophilic, asthma should not be based on a single sputum sample

Hancox RJ, et al. Respiration 2011; (Epub ahead of print)
Open questions:

• Are patients without eosinophilia asthmatics?
• What is the long term cause of eosinophilia in asthma?
Pathophysiology of chronic airway changes in asthma

Environmental Factors
- Pollutants, Viruses, Smoke, etc.
- Mast cell
- Intact Epithelium
- Injury

Pollutants, Viruses, Smoke, etc.
- pDCs mDCs
- Mast cell
- Intact Epithelium
- Injury

Bronchial Hyperresponsiveness
Airflow Obstruction
Asthma-Symptoms

Chronic Inflammation
- Neutrophils
- Eosinophils
- ATP
- Chitinases
- IL-4, IL-13, IL-5, etc.

Growth factors and Cytokines
- TGF-β
- Activation of Myofibroblasts
- Increase in smooth muscle

Cytotoxic (regulatory?) T-cells
- Granzyme/Perforin

Neutrophils
- Neurotrophins

CysLTs ↔ PGE₂

Neuronal Remodeling

Neurotrophins
Asthma Phenotypes
- Qualitative or quantitative Differences -

Inflammation
- Duration Severity 2\textsuperscript{nd} hit

Prodromal
- atopic
- eosinophilic
- "Scar"

Functional impairment
- Inflammatory
- Sensitised
- Paucigranular

Reversibility
- Structural Airway changes
- Fixed airflow obstruction

Easy to treat
- Inactive ?
- Intrinsic ?
- Neutrophilic ?
- No NO ?

Refractory to treatment
How important are eosinophils in the treatment of asthma?
Total eosinophil counts in the management of bronchial asthma

- 52 patients with asthma had eosinophilia (>350/mm$^3$ off and >85/mm$^3$ on steroids), suggesting that eosinophilia is an important diagnostic feature of bronchial asthma
- In 14/60 patients counts were inversely correlated with specific airway conductance ($r = 0.74$)
- Total eosinophil counts reflect asthmatic activity and are useful for regulating steroid dosage and for early detection of exacerbations.
Eosinophil cationic protein (ECP) in sputum and airflow obstruction / reversibility

Longitudinal Association between activated T-cells, Eosinophils, Cytokines and Pulmonary Function

Sputum Eosinophils to Guide Therapy
- Results -

- Fewer Asthma Exacerbations (35 vs 109, p=0.01)
- Less need for oral steroids (24 vs 73, p=0.008)
- Inhaled Steroid-Dose was not different between the two groups

Green, Lancet 2002;360:1715
Evaluate clinical significance of sputum eosinophilia and long-term treatment outcomes related to sputum eosinophilia in Korean asthmatics.

201 steroid-naive asthmatics with induced sputum treated as suggested by GINA. 53 patients completed 24 months of follow-up. Sputum eosinophilia was defined as >3%.

97 patients had NEA and 104 had eosinophilic asthma (EA). Only 52% had elevated baseline sputum eos levels. Higher percentage of sputum eos was associated with a lower PC20 ($r = -0.193; p = 0.009$), but not with FEV1.

The change in FEV1 was lower in NEA than in EA at 6, 12, 18, and 24 months ($p < 0.05$). The NEA group had no significant improvement in FEV1 at 6, 12, 18, or 24 months ($p > 0.05$).

Conclusion:
A higher sputum eosinophil percentage correlates with a higher airway hyperresponsiveness. Compared with EA patients, NEA patients had poor treatment outcomes in the 2-year follow-up of a Korean asthma cohort population.

FENO ?
FENO to predict response to therapy

Shaw DE, et al. AJRCCM 2007; 176:231-7


546 12-20 y/o inner city asthmatics, NAEPP or FENO

108 pat with asthma BTS or FENO

Shaw DE, et al. AJRCCM 2007; 176:231-7

Allergic Asthma
- Segmental Allergen Challenge -

before

5 min following allergen challenge
Endobronchial inflammation and eosinophils
Segmentale Allergenprovokation bei allergischem Asthma
Zelluläre Verteilung in der BAL vor und nach segmentaler Provokation

C = Kontrolle (NaCl) 18 h nach Provokation
10 min = Lavage 10 min nach Provokation
18 h = Lavage 18 h nach Provokation

Segmental Allergen Challenge in Allergic Asthma

TH\(_1\) and TH\(_2\) Cytokines in BAL before and after Challenge

TH\(_1\)

IL-2 (pg/ml)

IFN-\(\gamma\) (pg/ml)

C = Control (NaCl) 18 h after Challenge

10 min = Lavage 10 min after Challenge

18 h = Lavage 18 h after Challenge

TH\(_2\)

IL-4 (pg/ml)

IL-5 (U/ml)

Virchow JC Jr., et al.
Am J Respir Crit Care Med
1995; 151:960-8
Dissociation between Airway Inflammation and Airway Hyperresponsiveness in Allergic Asthma

Monoklonale anti-IL-5-Antikörper (SB-240563) zur Therapie der inhalativen Allergenprovokation

Novel treatments
Eosinophils and Exacerbations in Asthma

29 placebo/27 mepolizumab (449 screened)
- 70% atopic
- 1/3 nasal polyps
- FEV₁ 78%
- Sputum eosinophils 5.46/6.84%
- Blood eosinophils 320/350/microl
- ICS 2038/1711microg.

Mepolizumab monthly for 1 year

Halder P, et al NEJM 2009; 360:973-84
Pitfalls


- Only 12% of screened patients could be included
- Single center
- Optimal Placebo?
- Results partially due to the influence of pat. With recurrent exacerbations.
Eosinophils and Exacerbations in Asthma

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Mepolizumab monthly for 1 year

Halder P, et al NEJM 2009; 360:973-84
Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D., Melanie Kjarsgaard, R.R.T., Mark D. Inman, M.D., Ph.D., Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D., Frederick E. Hargreave, M.D., and Paul M. O’Byrne, M.B.

Patient population:

• Less than 3% of the 800 adult patients with severe asthma
• In all but two of the patients, more than 3% of cells in an induced sputum sample were identified as eosinophils,
• despite daily treatment for at least 4 weeks with prednisone (at a dose of 5 to 25 mg) and an
• Inhaled corticosteroid at a high dose (equivalent to 600 to 2000 µg of fluticasone)

Proportion of Patients without an Asthma Exacerbation during the Study

11 placebo
9 mepolizumab
Sputum eosinophils
- 4.0 / 16.6
Prednisone
-10mg median

mepolizumab (750 mg) or an identical placebo (normal saline diluent) i.v. over 30min at weeks 2, 6, 10, 14, and 18

Pitfalls

- Only 3% of patients with severe asthma included
- Low number
- Single center
- Optimal Placebo?

Treatment of nasal polyps with mepolizumab
CT scores improvement from baseline at week 8

Percentage of patients with improvement on CT scan

Treatment of nasal polyps with mepolizumab
CT scan improvement from baseline at week 8

Baseline

8 weeks post 1st Mepo dose

Reslizumab for Poorly Controlled, Eosinophilic Asthma

479 screened, 109 included
53 reslizumab 3mg/kg, 53 placebo
- Poorly controlled (AQC) despite >440 mg of fluticasone bid +/- short- or long-acting b-agonists, +/- leukotriene antagonists, +/- DNCG
- Sputum eos ≥ 3%

- ...significantly greater reductions in sputum eosinophils, improvements in airway function, and a trend toward greater asthma control than those receiving placebo ...

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CRTH2 is a G-protein-coupled receptor that mediates the activation of Th2 lymphocytes, eosinophils and basophils in response to prostaglandin D(2)

Selective CRTH2 antagonist, OC000459 orally 200mg bid (N=65) or a placebo (N=67) for 4 weeks

- ΔFEV(1) was 7.1% on OC000459 vs. 4.3% on placebo (n. s.) in ITT and 9.2% vs. 1.8% (P=0.037) in PP
- ΔAQLQ(S) total score of 0.29, p=0.0113 and 0.37, p=0.0022,
- Night-time symptom scores (mean reduction of 0.36 vs. 0.11, P=0.008, FA population; 0.37 vs. 0.12, P=0.022, PP population).
- Mean sputum eosinophil from 2.1% to 0.7% (P=0.03) but not significant to placebo (p=0.37)

CRTH2 receptors contribute to airflow limitation, symptoms and eosinophilic airway inflammation in asthma

Future anti-IL-5/anti-eosinophil approaches

- Reslizumab IL-5 Ab
- Mepolizumab IL-5 Ab
- Benralizumab – mAb IL-5R-antagonist

Pathogenesis of persistent allergic Asthma

Recruitment of Eosinophils

“activated” T-Cell TH2-cell

IL-4 IL-5, IL-13

CCR3

anti-IL-4 anti-IL-5

Adhesions-Inhibitors
VLA-4 Antagonists
Selektin-Antagonists
(Bimosiamose-TBC1269, IPL512602)
Leukotrien-Receptor-Antagonists

Chemotaxis
Eotaxin
RANTES
MCP-4

Viability
IL-3, IL-5
GM-CSF
IL-4, IL-13
TNF-α, IFN-γ

Neurotrophins

Cell damage Leukotrienes

CCRs3-Antagonists
(YM-344031, -355179)
TPI ASM8
met-RANTES
VLA-4 (Valategrast)

BHR Inflammation

Corticosteroids
Lidocaine
p38 MAPK Inhibitors

Novel approaches an the treatment of asthma

Immunosuppressiv
Therapy
CyA
Tacrolimus
Rapamycin
Mycophenolat
Brequinar

CCR3

Asthma

Neurotrophins

Cell damage Leukotrienes

CCR3-Antagonists
(YM-344031, -355179)
TPI ASM8
met-RANTES
VLA-4 (Valategrast)

BHR Inflammation

Corticosteroids
Lidocaine
p38 MAPK Inhibitors

Novel approaches an the treatment of asthma
Eosinophils in the treatment of asthma

Summary and conclusion

- Eosinophil granulocyte and their markers/mediators are elevated in peripheral blood, sputum, and airway tissue of patients with asthma
  - in patients w/o eosinophilia the diagnosis of asthma should be entertained with great caution
  - unclear if there is neutrophilic/paucigranulocytic asthma
  - consider alternative diagnosis

- Eosinophils are closely associated with asthma pathogenesis
  - In extrinsic as well as intrinsic asthma
  - Eos only reliable predictor of response to antiasthmatic treatment
  - Promising target for novel treatments

- Are not the sole feature responsible in asthma pathogenesis
EAACI Congress 2012
Geneva, Switzerland

European Academy of Allergy and Clinical Immunology
16 – 20 June 2012
Geneva, Switzerland

Abstract Submission Deadline: 18 January 2012

www.eaaci2012.com