Phenotypes of asthma; implications for treatment

Medical Grand Rounds Feb 2018

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No conflicts to declare
Objectives

• To understand the varied clinical forms of asthma
• To understand the pathobiologic basis for asthma
• To familiarize yourself with the biomarkers of asthma and their therapeutic implications
• To be aware of novel biologics
Questions?

• What are the useful blood tests for the assessment of severe asthma?
• Is asthma always allergic in nature?
• If patients are using maximal inhaled medication and are still uncontrolled, is oral steroid the only recourse?
Defining characteristics of asthma

Asthma is a heterogeneous disease based on variable contributions from

- Inflammation
- Bronchoconstriction
- Airway hyperresponsiveness
- Loss of lung function (airway remodeling)
Inflammation

• Local
  – essential in the pathogenesis of asthma

• Systemic
  – Increased circulating leukocytes (and their progenitors) and pro-inflammatory markers in the blood

• Bone marrow
  – Activation by blood borne signals
Bronchoconstriction

Smooth muscle can maintain force for long periods but at low energy cost. Contraction may be hard to reverse. Muscle is pro-inflammatory.

Gijs Ijpma et al. Amer J Physiol 2017
Airway hyperresponsiveness

<table>
<thead>
<tr>
<th>Step</th>
<th>Pred</th>
<th>Act1</th>
<th>Act2</th>
<th>Act3</th>
<th>Act4</th>
<th>Act5</th>
<th>Act6</th>
<th>Act7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc</td>
<td>4.46</td>
<td>3.41</td>
<td>3.25</td>
<td>3.21</td>
<td>3.07</td>
<td>2.78</td>
<td>2.59</td>
<td>3.59</td>
</tr>
</tbody>
</table>

PC[-20] FEV 1: 2 mg/ml Conc.
Pathological changes in the airways in asthma
Clinical phenotypes

• Allergic asthma (Extrinsic)
• Non-allergic asthma (Intrinsic)
• Exercise induced asthma
• Aspirin intolerant asthma
• Asthma in the obese
• Asthma in the elderly
• Catamenial asthma
• Severe asthma
  – Asthma with chronic airflow limitation
  – Brittle asthma
Cluster analysis and clinical asthma phenotypes

P Haldar et al. Amer J Respir Crit Care Med, 2008
What factors determine asthma phenotypes?

- Genes
- Environment

Pathobiology

Response to treatment

Clinical expression of disease
How is airway inflammation engendered?

• Allergic inflammation
  – Adaptive immune mechanisms

• Non-allergic inflammation
  – Epithelial derived mediators
  – Innate lymphoid cells
Dendritic cells and T cells

Dendritic cells *en face*

Dendritic cells and T cells co-localize

Van Rijt and Lambrecht, 2005.
The adaptive immune response and Th2 inflammation
Non-allergic airway inflammation
Th2 inflammation and phenotypes

Woodruff P et al Amer J Respir Crit Care M, 2009
Th2 asthma is steroid responsive

Woodruff P et al Amer J Respir Crit Care M, 2009
Definition

A biomarker has been defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention’. (NIH Working Group- 2001)
Potential utility of biomarkers

• Diagnostic purposes
• Measure of severity
• Predictor of future events (e.g. decline in lung function, exacerbations)
• Phenotyping and personalization of treatment
What has been looked at up to now?

- Lung function
- \( F_{E\text{NO}} \)
- Sputum leukocytes
- Sputum lipid mediators
- Sputum and tissue cytokines
- Serum IgE
- Blood eosinophils
- Cytokine-driven serum markers (periostin)
Granulocytes and asthma

Rosenberg et al, Nature Immunology, 2013.
Inflammation based on sputum examination

J Simpson et al, Respirology, 2006
What is severe asthma?

Despite usually optimal treatment asthma is

• Frequently symptomatic
• Recurring exacerbations
• Loss of lung function
Relationship of eosinophils in sputum to time of first exacerbation

CJ Walsh et al, CEA 2016
Relationship of neutrophils in sputum to time of first exacerbation

CJ Walsh et al, CEA 2016
FeNO and subsequent exacerbation

30 ppb threshold: Sens 69%, Spec 92%

23 ppb threshold: Sens 77%, Spec 76%

17 ppb threshold: Sens 85%, Spec 61%

ROC for FeNO (ppb) and subsequent exacerbation

B. Smith, unpublished
FeNO and exacerbations among subjects that exacerbate

>17 ppb
  • +LR: 2.2
  • -LR: 0.25

>23 ppb
  • +LR: 3.1
  • -LR: 0.30

>30 ppb
  • +LR: 8.5
  • -LR: 0.35

B. Smith, unpublished
Severe asthma; fixed and variable airway obstruction

A

Smooth muscle area

B

Subepithelial fibrosis

Kaminska et al, JACI 2009
## Subset definition and characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fixed obstruction (FEV1 &lt; 70)</th>
<th>Variable obstruction (FEV1 ≥ 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Age (y)</td>
<td>$49.8 \pm 11.7$</td>
<td>$45.9 \pm 11.0$</td>
</tr>
<tr>
<td>Sex (F//M)</td>
<td><strong>5//8</strong></td>
<td><strong>13//6</strong></td>
</tr>
<tr>
<td>Ex-smokers (n [pack-years])</td>
<td>4 ($4.5 \pm 7.7$)</td>
<td>9 ($4.3 \pm 7.4$)</td>
</tr>
<tr>
<td>Atopy (n)</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Duration (y)</td>
<td>$27.6 \pm 16.7$</td>
<td>$14.5 \pm 13.7^*$</td>
</tr>
<tr>
<td>ACQ score</td>
<td>$2.06 \pm 0.876$</td>
<td>$2.31 \pm 1.31$</td>
</tr>
<tr>
<td>Best FEV1 (% predicted)</td>
<td>$54.6 \pm 12.3$</td>
<td>89.2 $\pm 14.5^*$</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>$30.7 \pm 24.5$</td>
<td>$18.4 \pm 12.7$</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>$10.3 \pm 19.8$ (n=11)</td>
<td>$7.63 \pm 13.6$ (n=15)</td>
</tr>
<tr>
<td>Sputum neutrophils(%)</td>
<td>$63.9 \pm 28.3$ (n=11)</td>
<td>$49.1 \pm 31.6$ (n=15)</td>
</tr>
<tr>
<td>Daily ICS (µg)</td>
<td>$1353.9 \pm 391.5$</td>
<td>$1097.4 \pm 323.0^*$</td>
</tr>
<tr>
<td>Daily LABA (µg)</td>
<td>$153.9 \pm 49.9$</td>
<td>$107.9 \pm 24.4^*$</td>
</tr>
<tr>
<td>Subjects on oral corticosteroid (n [mg/d])</td>
<td>4 ($5.77 \pm 9.97$)</td>
<td>8 ($5.26 \pm 7.16$)</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD; *p < 0.05
Baseline and follow-up characteristics of subjects that had bronchoscopic biopsies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete long term follow-up N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50±8</td>
</tr>
<tr>
<td>Baseline FEV₁ - % predicted</td>
<td>77±23</td>
</tr>
<tr>
<td>Baseline FEV₁/FVC ratio</td>
<td>68±13</td>
</tr>
<tr>
<td>Follow-up interval – years</td>
<td>8±1</td>
</tr>
<tr>
<td>Follow-up FEV₁ - % predicted</td>
<td>73±22</td>
</tr>
<tr>
<td>ΔFEV₁ - % predicted†</td>
<td>-3±24</td>
</tr>
<tr>
<td>Airway smooth muscle area-mm²</td>
<td>0.16±0.13</td>
</tr>
<tr>
<td>Follow-up ACQ</td>
<td>1.6±1.2</td>
</tr>
<tr>
<td>ΔACQ score†</td>
<td>+0.1±1.2</td>
</tr>
<tr>
<td>Follow-up AQLQ</td>
<td>5.3±1.3</td>
</tr>
<tr>
<td>ΔAQLQ score†</td>
<td>+0.2±1.1</td>
</tr>
</tbody>
</table>

Plus minus values are mean ± standard deviation. †: Δ results calculated as follow-up minus baseline.

Ben Smith, unpublished
Baseline Smooth Muscle vs Δ(Follow Up – Baseline) FEV₁:
Males

Long term Δ % predicted FEV₁ (deviation from group mean)

Baseline smooth muscle area (mm²)

p=0.37

Ben Smith, unpublished
Baseline Smooth Muscle vs $\Delta$(Follow up – Baseline) $FEV_1$: Females

Long term $\Delta$ % predicted $FEV_1$
(deviation from group mean)

Baseline smooth muscle area (mm$^2$)

$\text{Ben Smith, unpublished}$
CTS treatment guidelines

2012 Asthma Management Continuum
Children (6 years and over) and Adults

Regularly Reassess
- Control
- Spirometry or PEF
- Inhaler technique
- Adherence
- Triggers
- Comorbidities
- Sputum eosinophils

Inhaled Corticosteroid (ICS)*
*Second-Line: Leukotriene Receptor Antagonist (LTRA)

Low Dose
≥12 yrs: ≤250 mcg/day†
6-11 yrs: ≤200 mcg/day†

Medium Dose
251 – 500 mcg/day†
201 – 400 mcg/day†

High Dose
>500 mcg/day†
>400 mcg/day†

SABA on Demand
SABA or ICS/LABA‡ on Demand

Environmental Control, Education and Written Action Plan
Confirm Diagnosis

Prendrine
Anti-IgE

≥12 yrs: Add LTRA
6-11 yrs: Add LABA*
6-11 yrs: Increase ICS

Adjusted Therapy to Achieve Control and Prevent Future Risk

† HFA Beclomethasone or equivalent; *Second-line: LTRA; † Approved for 12 years and over;
‡ Using a formulation approved for use as a reliever;
§ In adults 18 years and over with moderate to severe asthma.
Mast cells and immediate hypersensitivity reactions

Galli et al, Nature Medicine, 2012
Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma

Busse et al, JACI 2001
Monoclonal antibodies to inhibit IL-5 and the IL-5 receptor
Mepolizumab for prednisone-dependent asthma with sputum eosinophilia

P Nair et al, NEJM 2009
Mepolizumab treatment in patients with severe eosinophilic asthma

H.G. Ortega et al, NEJM, 2014

E. Bel et al. NEJM, 2014
Table 1. New potential drugs in the pipeline for asthma treatment and their target and developmental stage

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Drug target</th>
<th>Developmental stage</th>
<th>Estimated time of market launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>EMA and FDA approved</td>
<td>Already launched</td>
</tr>
<tr>
<td>QGE-031</td>
<td>IgE</td>
<td>Clinical phase III</td>
<td>2019</td>
</tr>
<tr>
<td>MEDI-4212</td>
<td>IgE</td>
<td>Clinical phase I</td>
<td>After 2020</td>
</tr>
<tr>
<td>Quilizumab</td>
<td>IgE</td>
<td>Clinical phase II</td>
<td>After 2020</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Ra</td>
<td>Clinical phase II</td>
<td>After 2020</td>
</tr>
<tr>
<td>Pitrakinra</td>
<td>IL-4 Ra</td>
<td>Clinical phase II</td>
<td>NA</td>
</tr>
<tr>
<td>Pascolizumab</td>
<td>IL-4</td>
<td>Suspended</td>
<td>–</td>
</tr>
<tr>
<td>Altrakincept</td>
<td>IL-4</td>
<td>Suspended</td>
<td>-</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>FDA approved</td>
<td>Already launched</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Clinical phase II</td>
<td>2016</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5 Ra</td>
<td>Clinical phase II</td>
<td>After 2020</td>
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<tr>
<td>MEDI-528</td>
<td>IL-9</td>
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<td>NA</td>
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<tr>
<td>Tralokinumab</td>
<td>IL-13</td>
<td>Clinical phase II</td>
<td>2017–2018</td>
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<tr>
<td>Lebrikizumab</td>
<td>IL-13</td>
<td>Clinical phase III</td>
<td>2017–2018</td>
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<td>QAX-576</td>
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<td>After 2020</td>
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<td>ABT-308</td>
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<td>CNTO 5825</td>
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<td>Clinical phase I</td>
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<td>GSK679586</td>
<td>IL-13</td>
<td>Clinical phase II</td>
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<td>Brodalumab</td>
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<td>2019</td>
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<td>Secukinumab</td>
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<td>Clinical phase II</td>
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<td>MT203</td>
<td>GM-CSF</td>
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<tr>
<td>Golimumab</td>
<td>TNF-α</td>
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<td>Infliximab</td>
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<td>GW766994</td>
<td>CCR3</td>
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<td>NA</td>
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<td>AMG 761</td>
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<td>GSK2239633</td>
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<td>AM211</td>
<td>CRTH2</td>
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<td>NA</td>
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<tr>
<td>ARRY-502</td>
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<tr>
<td>QAV 680</td>
<td>CRTH2</td>
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<td>NA</td>
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<tr>
<td>Setipirrant</td>
<td>CRTH2</td>
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<tr>
<td>RG7185</td>
<td>CRTH2</td>
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<td>NA</td>
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<tr>
<td>AMG 853</td>
<td>CRTH2/DPR</td>
<td>Clinical phase III</td>
<td>NA</td>
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<tr>
<td>AZD 1981</td>
<td>CRTH2/DPR</td>
<td>Clinical phase II</td>
<td>NA</td>
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<tr>
<td>AMG 157</td>
<td>TSLP</td>
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<td>NA</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Tyrosine kinases</td>
<td>Clinical phase II</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = No estimated time of market launch has been announced; – = there will be no market launch (see text).

1 Already launched/approved to treat chronic granulocyte leukemia.
Answers

• What are the useful blood tests for the assessment of severe asthma?
  – IgE and eosinophils

• Is asthma always allergic in nature?
  – No

• If patients are using maximal inhaled medication and uncontrolled, is oral steroid the only recourse?
  – No, biologics are available
The Montreal Chest Institute has a severe asthma clinic, lots of experience with biologics and wonderful nurses and technicians who monitor and educate.