T2 High/T2 Low Asthma

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University of Rochester, NY
Disclosures

Grant support – GSK

I will not be discussing off-label use for any drugs or devices
Objectives

- Appreciate the key differences between T2 high and T2 low asthma
- Using clinical characteristics and biomarkers, identify specific asthma phenotypes
- Formulate a targeted treatment plan for patients with asthma based on their ‘treatable traits’
Asthma

- Heterogenous
- Chronic airway inflammation
- Wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity
- Variable expiratory airflow limitation.

GINA 2018
Busse and Lemanske, NEJM, 2001
The Exposome & Asthma

Maternal transmission

Diet

Ozone

Air pollution: Particulates Sulfur dioxide Nitrogen dioxide

The Asthmatic Patient

Tobacco smoke

Pollens Molds

Medications Antibiotics

Pests

Pets

Dust mite

Microbiome

Thailand

Bangkok | 10-12 April

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Guidelines recommend stepwise approach to treatment of all asthma.
But…do not account for variability in response to medication
Old Paradigm: Asthma = Th2 disease

- Antigen
- APC
- Th0
- Th1
- Th2
- IL-4, IL-13
- IL-5
- Mast cell proliferation
- IgE synthesis
- Mucin secretion
- Eosinophilic airway inflammation
Complex gene/environment interactions result in different clinical expressions.
You evaluated the following patients in clinic last week and have requested testing to better characterize their asthma. Which ONE of your patients is UNLIKELY to have non-eosinophilic asthma?

- A 56 year old female with adult onset asthma, obesity and GERD
- A 45 year old male current smoker with late onset asthma and recurrent bronchitis
- A 32 year old female nonsmoker with asthma, nasal polyps and aspirin sensitivity
- A 63 year old female nonsmoker with late onset asthma and fixed airflow obstruction
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### T2 High
- Allergic, atopic
- Eosinophilic
- Steroid responsive
- TH2, ILC2

### T2 Low
- Non-atopic
- Non-eosinophilic
- Airway remodeling
- Poorly steroid responsive
- TH1, TH17
Understanding disease mechanisms may guide a more personalized approach to therapy

Type 2 inflammation in asthma

Brusselle GG, Maes T, Bracke K. Nature Medicine 2013
Biomarkers in T2 asthma

<table>
<thead>
<tr>
<th>Source</th>
<th>Measured characteristic</th>
<th>Developmental stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophil</td>
<td>Blood</td>
<td>Cell (eosinophil)</td>
</tr>
<tr>
<td>FeNO</td>
<td>Exhaled breath</td>
<td>Exhaled gas (nitric oxide)</td>
</tr>
<tr>
<td>IgE</td>
<td>Blood</td>
<td>Protein</td>
</tr>
<tr>
<td>Sputum eosinophil</td>
<td>Sputum</td>
<td>Cell (eosinophil)</td>
</tr>
<tr>
<td>Periostin</td>
<td>Blood</td>
<td>Protein</td>
</tr>
<tr>
<td>YKL-40</td>
<td>Blood</td>
<td>Protein</td>
</tr>
<tr>
<td>Transcriptomics</td>
<td>Blood, sputum, endobronchial biopsies</td>
<td>Gene</td>
</tr>
<tr>
<td>Metabolomics</td>
<td>exhaled breath, urine</td>
<td>Molecules</td>
</tr>
<tr>
<td>FD-PET-CT</td>
<td>Organ</td>
<td>Metabolic activity uptake</td>
</tr>
<tr>
<td>Hyperpolarized gas MRI</td>
<td>Organ</td>
<td>Ventilation defects</td>
</tr>
</tbody>
</table>
Biomarkers are probably not necessary to manage mild asthma

Sputum Strategy

FeNO Strategy

Mild asthma

Moderate-Severe Asthma

Mild-Moderate asthma

Jayaram L. et al. ERJ 2006; 27: 483
Calhoun W et al. JAMA 2012; 308: 987
Targets for Type 2 asthma

Brusselle GG, Maes T, Bracke K. Nature Medicine 2013

- Anti-IgE
- Anti-TSLP
- Anti-IL4/13
- Anti-IL5
- Anti-IL5R
## Biologics for Type 2 Asthma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Mechanism</th>
<th>FDA Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab (Xolair®, Genentech)</td>
<td>75-375 mg SC Q 2-4 weeks</td>
<td>Anti-IgE</td>
<td>Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens$^7$</td>
</tr>
<tr>
<td>Mepolizumab (Nucala®, GlaxoSmithKline)</td>
<td>100 mg SC Q 4 weeks</td>
<td>Anti-IL-5</td>
<td>Age ≥ 12 years with severe asthma and eosinophilic phenotype$^8$</td>
</tr>
<tr>
<td>Reslizumab (Cinqair®, Teva)</td>
<td>3 mg/kg IV Q 4 weeks</td>
<td>Anti-IL-5</td>
<td>Age ≥ 18 years with severe asthma and eosinophilic phenotype$^9$</td>
</tr>
<tr>
<td>Benralizumab (Fasenra™, AstraZeneca)</td>
<td>30 mg SC Q 4 weeks x 3, then Q 8 weeks</td>
<td>Anti-IL-5Rα</td>
<td>Age ≥ 12 years with severe asthma and eosinophilic phenotype$^{10}$</td>
</tr>
<tr>
<td>Dupilumab (Dupixent®, Sanofi/Regeneron)</td>
<td>200 mg SC Q 2 weeks, 300 mg SC Q 2 weeks</td>
<td>Anti-IL-4Rα</td>
<td>Age ≥ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma$^{11}$</td>
</tr>
</tbody>
</table>

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### Rate Ratio for exacerbations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.52 (0.37-0.73)</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>0.45 (0.36-0.55)</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>0.43 (0.33-0.55)</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>0.59 (0.51-0.68)</td>
</tr>
<tr>
<td>Dupilumab 200 mg</td>
<td>0.44 (0.34-0.58)</td>
</tr>
<tr>
<td>Dupilumab 300 mg</td>
<td>0.40 (0.31-0.53)</td>
</tr>
</tbody>
</table>

### Mean Difference AQLQ

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.26 (0.05-0.47)</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>NR</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>0.28 (0.17-0.39)</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>0.23 (0.11-0.35)</td>
</tr>
<tr>
<td>Dupilumab 200 mg</td>
<td>0.29 (0.15-0.44)</td>
</tr>
<tr>
<td>Dupilumab 300 mg</td>
<td>0.26 (0.12-0.40)</td>
</tr>
</tbody>
</table>

### Mean Difference ACQ

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>NR</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>-0.42 (-0.56 to -0.28)</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>-0.27 (-0.36 to -0.19)</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>-0.23 (-0.34 to -0.12)</td>
</tr>
<tr>
<td>Dupilumab 200 mg</td>
<td>-0.39 (-0.53 to -0.25)</td>
</tr>
<tr>
<td>Dupilumab 300 mg</td>
<td>-0.22 (-0.36 to -0.08)</td>
</tr>
</tbody>
</table>
Question

Which of the following is true about Type 2 Asthma?

A. The majority of patients with eosinophilic asthma are atopic and have early onset disease
B. AERD is a common cause of eosinophilic asthma
C. High (>2%) sputum eosinophils is noted in approximately 50% of late onset asthma
D. Eosinophilic asthma comprises at least 75% of all asthma
Question

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C. High (>2%) sputum eosinophils is noted in approximately 50% of late onset asthma
D. Eosinophilic asthma comprises at least 75% of all asthma
Sputum cytology

Neutrophilic

Pauci-Granulocytic

Mixed Granulocytic

Eosinophilic
• T2 biased inflammation, using airway epithelial transcriptomics, has been observed in
  • Only 50% of patients with mild-moderate asthma
  • Only 37% of patients with severe asthma
• Mechanisms of T2-low asthma are not well understood
  • Th1/Th17 pathway activation
  • Innate immune defects, barrier dysfunction
  • Tissue remodeling
  • Neurogenic inflammation
• Typically refractory to steroids
T2 low asthma is a common inflammatory phenotype across all severities of asthma

McGrath et al. AJRCCM 2012
- Repeated sputum analysis from 995 subjects with mild-mod asthma
- 47% of patients not on ICS were persistently non-eosinophilic

Lemière et al. JACI 2006
- Sputum analysis from 31 patients with severe asthma
- 58% with low sputum eosinophil count (<3%)

Hastie et al. JACI 2010
- 242 patients enrolled in SARP (Severe and Non-severe)
- 65% had NEA (36% Paucigranulocytic; 29% neutrophilic)
- No difference between ICS+ or ICS- groups

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Paucigranulocytic Asthma

Although most common phenotype in stable asthma
  • ~20% of PGA is severe refractory
Uncoupling of airway obstruction from airway inflammation
Airway smooth muscle dysfunction and AHR

Proposed mechanisms
  • Altered neural control of ASM contractility
  • Nonimmunologic mediators & critical signaling molecules
  • Upregulation of expression of specific asthma susceptible genes
  • Consequence of ‘burnout’ of AI in severe longstanding asthma
Bronchial Thermoplasty
AIR2 Trial

Randomized study with sham control
Primary endpoint AQLQ
79% of BT and 64% of sham subjects achieved changes in AQLQ > 0.5
6% more BT subjects hospitalized in the treatment period (up to 6 wk after BT)
In the post-treatment period (6–52 wk after BT), the BT group had fewer severe exacerbations, ED visits

AIR2 Extension: 5-yr follow-up
Bronchial Thermoplasty PAS 2 Study
Real world effectiveness – 3 year follow-up
Neutrophilic Asthma

- Associated with
  - Oxidative stress
  - Chronic infection
  - Smoking
  - High fat diet

- Impaired lung function with less bronchodilator reversibility
- Increased prevalence of GERD and Chronic Rhino-Sinusitis
- Impaired Glucocorticoid response
Azithromycin in asthma
AMAZES

N=420
Symptomatic asthma despite ICS/LABA
Azithromycin 500 mg thrice weekly vs placebo for 48 weeks

Gibson, Peter G et al. The Lancet 2017
Azithromycin in asthma
AMAZES

Gibson, Peter G et al. The Lancet 2017
Obesity associated asthma

**Mechanical factors**
- Increased peripheral airway closure
- Increased impedance
- Mass loading
- Decreased ERV

**Inflammation**
- High fat/low fiber diet
- Adipose tissue & adipokines
- Innate & adaptive immune function
- Gut microbiome

**Comorbidities**
- Anxiety/Depression
- GERD
- OSA
## Effect of dietary weight loss on asthma in obesity

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>N</th>
<th>Weight Loss</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dias-Junior, 2014</td>
<td>Diet + weight loss medication</td>
<td>22</td>
<td>7.5%</td>
<td>Improved asthma control</td>
</tr>
<tr>
<td>Scott, 2013</td>
<td>Diet + exercise</td>
<td>28</td>
<td>8.5%</td>
<td>Improved asthma control</td>
</tr>
<tr>
<td>Hernandez Romero, 2008</td>
<td>Diet</td>
<td>96</td>
<td>10.6%</td>
<td>Improved symptoms decreased medications</td>
</tr>
<tr>
<td></td>
<td>Diet</td>
<td></td>
<td>6.1%</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td>Johnson, 2007</td>
<td>Diet</td>
<td>10</td>
<td>8%</td>
<td>Improved asthma control</td>
</tr>
<tr>
<td>Stenius-Aarniala, 2000</td>
<td>Diet</td>
<td>19</td>
<td>14.5%</td>
<td>Improved lung function Improved symptoms</td>
</tr>
</tbody>
</table>
Which of the following cytokines is considered an “epithelial alarmin” and is being investigated as a treatment target for severe eosinophilic asthma?

A. Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF)
B. Thymic stromal lymphopoietin (TSLP)
C. Platelet-derive growth factor (PDGF)
D. Stem cell factor (SCF)
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B. Thymic stromal lymphopoietin (TSLP)
C. Platelet-derive growth factor (PDGF)
D. Stem cell factor (SCF)
Tezepelumab in Adults with Uncontrolled Asthma
Effect independent of Eos or Th status
Potential therapeutic targets in non-type 2 asthma

Asthma is a heterogenous disease with complex pathophysiology

- Multiple endotypes result in a myriad of phenotypes
- Eosinophilic inflammation can be allergic or non-allergic
- Current biologics target patients with T2 high asthma and biomarkers can help select most efficacious biologic
- NEoA or T2-low asthma is a common phenotype in adult asthma
- Neutrophilic inflammation is especially associated with corticosteroid-resistant severe asthma
- Urgent need for treatment options in T2 low asthma
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