New treatment approaches for airway diseases

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Asthma treatment costs and hospitalisation rates

Published hospitalisations for asthma, England, 2000/01 - 2007/08

Source: HESonline
New drug discovery in respiratory diseases

<table>
<thead>
<tr>
<th>Area</th>
<th>Drugs n</th>
<th>Market entry probability</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>108</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Dermatology</td>
<td>122</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Haematology</td>
<td>163</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>Neurology</td>
<td>192</td>
<td>73</td>
<td>47</td>
</tr>
<tr>
<td>Cancer</td>
<td>68</td>
<td>78</td>
<td>46</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>280</td>
<td>69</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory</td>
<td>165</td>
<td>68</td>
<td>31</td>
</tr>
</tbody>
</table>

Data are presented as %, unless otherwise stated. Adapted from [7].

Barnes et al. Eur Respir J 2015
Effect of monoclonal antibody to IL-5 (Mepolizumab) on sputum eosinophils and traditional outcomes in asthma

Flood-Page et al. AJRCCM 2007;176:1062-71
Getting the basics right
Environmental factors (i.e. allergen) and genetic factors

- Eosinophilic airway inflammation
  - Airway hyperresponsiveness
  - Variable airflow limitation
    - Symptoms

Asthma

Exacerbations

Environmental factors (i.e. smoking) and genetic factors

- Neutrophilic airway inflammation
  - Small airway fibrosis, mucus plugging and loss of support
  - Fixed airflow limitation
    - Symptoms

COPD
Cells
- Eosinophils
- Neutrophils
- Macrophages
- Lymphocytes
- Epithelial cells

Effector mediators
- LTC/D/E$_4$
- PGD$_2$
- Histamine

Cellular markers
- ECP
- Neutrophil elastase

Cytokines
- IL-8
Sputum eosinophil counts in asthma and COPD

Green et al. Thorax 2002; 57:875-879

Meijer et al. CEA 2002;32:1096-03
Which patient needs more steroids?

No serious attacks

Two near fatal attacks
Targeting sputum eosinophilia and severe exacerbations of asthma

Induced sputum eosinophil count (%)

FEV1 (litres)

Time (months)

*P=0.002

Severe exacerbations (cumulative number)

Time (months)

BTS guidelines (n=37)
6 patients admitted

Sputum guidelines (n=37)
1 patient admitted

*P=0.01

Green et al. Lancet 2002;360:1715-21
Eosinophilic inflammation

Exacerbations

Airway dysfunction

Airway remodelling

Cough, breathlessness and wheeze
Mepolizumab in severe eosinophilic asthma

- Parallel group, double blind, placebo controlled trial
- 61 patients with severe eosinophilic asthma randomised to IV mepolizumab 750 mg monthly or placebo for 12 months
- Primary outcome: severe exacerbations

Haldar et al. NEJM 2009;360:973-84
Effect of Mepolizumab (anti-IL-5) on airway inflammation and clinical parameters

Haldar et al. NEJM 2009;360:973-84
GSK announces outcome of US FDA Advisory Committee recommending approval of mepolizumab for the treatment of adults with severe asthma

11 June 2015
Issued: London UK

GlaxoSmithKline plc (LSE: GSK) today announced the outcome of the meeting of the Pulmonary Allergy Drugs Advisory Committee of the United States (US) Food and Drug Administration (FDA) regarding the Biologics Licence Application (BLA) for mepolizumab as an add-on maintenance treatment for severe asthma with eosinophilic inflammation.

The FDA Advisory Committee voted unanimously (14 yes, 0 no) that the efficacy and safety data for mepolizumab, an anti IL-5 monoclonal antibody delivered as a 100mg fixed dose via a subcutaneous injection every four weeks, supported approval in adults 18 years of age and older with severe asthma. The Committee also voted that the efficacy data provided substantial evidence of a clinically meaningful benefit in this population (14 yes, 0 no) and safety in adults with severe asthma had been adequately demonstrated (13 yes, 1 no).
Is biomarker directed, precision management ready for prime time?

• The validity and feasibility of assessing airway inflammation is not widely accepted
• Traditional disease labels and guidelines are deeply embedded
• Concern about complexity of approach
• Industry haven’t seen an opportunity
Simpler biomarkers

Type 2 cytokines are released as part of the inflammatory response

Eosinophils migrate into the airway lumen and can be measured in the airway lumen.

Eosinophils can be measured in sputum.

IL-5 induces eosinophil maturation.

IL-5

IL-13

IL-13

IL-13

IL-13/IL-4

Induction of iNOS, leading to increases in FeNO that can be measured in the breath.

FeNO

Secretion of periostin

Periostin is secreted basolaterally and enters the bloodstream.

PERIOSTIN

Bone marrow


Biomarkers, risk stratification and identification of steroid responsive disease

Risk of attack

Response to ICS

FE\textsubscript{NO} (ppb)

- >47
- 15-47
- <15


Smith et al. AJRCCM 2005;172:453-50
Mepolizumab: MENSA key results by higher blood eosinophils count (>500/mm³)

Reduction of Clinically Significant Exacerbations Across the 3 Treatment Groups at Week 32

Change From Baseline in Pre- and Post-bronchodilator FEV₁ Compared to Placebo at Week 32

## The new pharmacology of eosinophilic airway disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Biomarker</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab (GSK)</td>
<td>IL-5</td>
<td>Blood eos</td>
<td>+</td>
</tr>
<tr>
<td>Reslizumab (Teva)</td>
<td>IL-5</td>
<td>Blood eos</td>
<td>+</td>
</tr>
<tr>
<td>Benralizumab (AZ)</td>
<td>IL-5*</td>
<td>Blood eos</td>
<td>+</td>
</tr>
<tr>
<td>Lebrikizumab (Roche)</td>
<td>IL-13</td>
<td>Periostin</td>
<td>+</td>
</tr>
<tr>
<td>Tralokinumab (AZ)</td>
<td>IL-13</td>
<td>FeNO (?)</td>
<td>+</td>
</tr>
<tr>
<td>Dupilumab (Sanofi)</td>
<td>IL-13&amp;4</td>
<td>FeNO (?)</td>
<td>++</td>
</tr>
<tr>
<td>QAW039** (Novartis)</td>
<td>CRTH2</td>
<td>Blood eos (?)</td>
<td>++</td>
</tr>
</tbody>
</table>

*anti-IL-5 receptor

** Orally active
Precision management of airway disease

- **Benign disease**
  - LABA or LAMA

- **Inflammation predominant disease**
  - High dose ICS (oral CS)
  - Biologicals

- **Symptom predominant disease**
  - LABA/LAMA

- **Severe, concordant disease**
  - LABA/LAMA/High dose ICS
  - Biologicals

Risk assessed using biomarkers of eosinophilic airway inflammation

Pavord & Agusti. ERJ 2016 in press
Inhaled steroids and the risk of pneumonia in patients with COPD

The effect of addition of Fluticasone Furoate (FF) to Vilanterol (VI)

- Aim: to determine if the combination of FF and VI is more protective than VI alone against COPD exacerbations
- Two studies of identical design
- Baseline blood eosinophil count available

N=3255
- Diagnosis of COPD (ATS/ERS definition)
- Aged ≥40 years
- 4-week FP/Sal BD run-in period
- ≥1 COPD exacerbation in the year before screening

Randomise

FF/VI 46/22 mcg (n=820)
FF/VI 92/22 mcg (n=806)
FF/VI 184/22 mcg (n=811)
VI 22 mcg (n=818)

For 52 weeks
Once daily (in the morning) using a dry powder inhaler

The effect of addition of Fluticasone Furoate to Vilanterol by blood eosinophils in COPD


Blood eosinophil count (%)

- 0 to <2%
  - FF/VI, all doses: 0.79 (n=799)
  - Vilanterol 25mcg: 0.89 (n=299)
  - 10% diff p=0.280

- 2% to <4%
  - FF/VI, all doses: 0.92 (n=907)
  - Vilanterol 25mcg: 1.21 (n=302)
  - 24% diff p=0.005

- 4% to <6%
  - FF/VI, all doses: 0.84 (n=395)
  - Vilanterol 25mcg: 1.24 (n=113)
  - 32% diff p=0.013

- 6% or more
  - FF/VI, all doses: 0.95 (n=281)
  - Vilanterol 25mcg: 1.62 (n=85)
  - 42% diff p=0.002
1. Symptoms not due to airflow limitation
2. Attacks (and symptoms) not due to eosinophilic airway inflammation
Cough reflex hypersensitivity as a treatable trait

Yousaf et al. ERJ 2013
Cough reflex hypersensitivity and P2X3 antagonist

Abdulqawi et al. Lancet 2014
Is neutrophilic airway inflammation a target?

**COPD**

Albert et al. NEJM 2011;365:689-98

**Bronchiectasis**

Wong et al. Lancet 2012;380:660-7

**Asthma**

Simpson et al. AJRCCM 2008;177:148–155
CXCR2 antagonist as a means of investigating neutrophilic airway disease

- 1.3 vs 2.25 mild exacerbations/patient (p=0.15)
- 0.42 difference in change in ACQ (p=0.053)

Are there two types of neutrophilic airway disease?

<table>
<thead>
<tr>
<th>Subgroup (n)</th>
<th>HR</th>
<th>95% CI for HR</th>
<th>P Value*</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (1,113)</td>
<td>0.71</td>
<td>0.61–0.83</td>
<td>&lt;0.0001</td>
<td>0.75</td>
</tr>
<tr>
<td>Women (455)</td>
<td>0.69</td>
<td>0.55–0.87</td>
<td>0.001</td>
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<tr>
<td>Men (658)</td>
<td>0.72</td>
<td>0.59–0.89</td>
<td>0.002</td>
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</tr>
<tr>
<td>GOLD II (292)</td>
<td>0.55</td>
<td>0.40–0.75</td>
<td>0.0002</td>
<td>0.04</td>
</tr>
<tr>
<td>GOLD III (451)</td>
<td>0.71</td>
<td>0.56–0.90</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>GOLD IV (370)</td>
<td>0.64</td>
<td>0.65–1.00</td>
<td></td>
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<tr>
<td>Ex-smoker (867)</td>
<td>0.65</td>
<td>0.55–0.77</td>
<td>&lt;0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoker (246)</td>
<td>0.99</td>
<td>0.71–1.38</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

Han et al. Am J Respir Crit Care Med 2014;189:1503-8

Macrolides

CXCR2 antagonist

Rennard et al. Am J Respir Crit Care Med 2015;191:1001-1011
Conclusions

• Progress has required a rethink of basic concepts
• Biomarkers of eosinophilic airway inflammation identify risk and likely treatment responsiveness
• Clinical approach needs to move away from categorisation to analysis and identification of this and other treatable traits
• Industry is engaged
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