COPD: From Phenotypes to Endotypes

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Presenter Disclosures

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Consulting
- Novartis
- Boehringer Ingelheim
- GlaxoSmithKline
- AstraZeneca
- Sunovian

Research support
- NHLBI
- Novartis
Phenotypes: A New Definition

Clinical Commentary

Chronic Obstructive Pulmonary Disease Phenotypes
The Future of COPD


“A single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death).”

Phenotype is defined by symptoms, radiology, physiology, biomarkers

Ultimately we would hope that phenotypes would have similar biologic or physiologic mechanisms

Han, et al. AJRCCM 2010;182:598.
Ideal Phenotyping Construct: Paths to Phenotype Development

Han, et al. *AJRCCM* 2010;182:598.
Endotype: “Subtype of a condition, defined by a distinct functional or pathobiological mechanism. This is distinct from a phenotype, which is an observable characteristic or trait of a disease without any implication of a mechanism. It is envisaged that patients with a specific endotype present themselves within phenotypic clusters of diseases.”

“Treatable Trait”

Precision medicine is defined as “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical patients.”

# Treatable Traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>Diagnostic criteria</th>
<th>First-line Tx</th>
<th>Second-line Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airflow limitation</td>
<td>FEV1/FVC &lt;0.7</td>
<td>LABA/LAMA</td>
<td>ICS</td>
</tr>
<tr>
<td>Smooth muscle contraction</td>
<td>BD reversibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td>CT or DLCO</td>
<td>Smoking cessation</td>
<td>LVRS/transplant</td>
</tr>
<tr>
<td>Airway mucosal edema</td>
<td>CT</td>
<td>ICS</td>
<td>Anti IL-5, -13 and -4</td>
</tr>
<tr>
<td>Eosinophilic inflammation</td>
<td>Sputum/blood eos</td>
<td>ICS</td>
<td>Anti IL-5, -13 and -4</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>Symptom assessment</td>
<td>Smoking cessation</td>
<td>Macrolides, roflumilast</td>
</tr>
<tr>
<td>Airway bacterial colonisation</td>
<td>Culture/PCR</td>
<td>Antibiotics</td>
<td>Macrolides</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>CT</td>
<td>Chest PT</td>
<td>Macrolides, inhaled antibiotics</td>
</tr>
</tbody>
</table>

How do we make the transition from phenotypes to endotypes?

Clinical and Radiographic Phenotypes

Endotype A

Endotype B

Ultimately, Precision Medicine
• Diagnostic tests
• Targeted therapies
…based on the biology
How do we make the transition from phenotypes to endotypes?

Clinical and Radiographic Phenotypes

- Chronic Bronchitis – Roflumilast responsive COPD
- Th2/ Eosinophilic COPD

Endotype A

Endotype B
Evolution of Roflumilast Program
Identification of Target COPD Population

Early Phase III Studies
M2-111, M2-112
Subanalyses

Hypothesis
Generation

Confirmatory
Pivotal Studies
M2-124, M2-125

Treatment of COPD Associated
With Chronic Bronchitis in
Patients at Risk of Exacerbations
Roflumilast significantly reduced the rate of moderate or severe exacerbations on top of double/triple inhaled therapy


ITT = intent-to-treat; PP = per protocol

*Patients experiencing at least one exacerbation; †rate ratios, 95% CI and p-values are based on a negative binomial regression analysis; ‡rate ratios, 95% CI and p-values are based on a Poisson regression analysis

Roflumilast response is particularly evident in COPD patients with history >3 exacerbations or prior hospitalization.

Roflumilast Reduces Neutrophilic Inflammation

- The self-propagating acetyl-proline-glycine-proline (AcPGP) pathway is a novel means of neutrophilic inflammation that is pathologic in the development of COPD.
- AcPGP is produced by extracellular matrix collagen breakdown with prolyl endopeptidase and leukotriene A4 hydrolase serving as the enzymes responsible for its production and degradation, respectively.
- Roflumilast reduces pulmonary inflammation through decreasing prolyl endopeptidase activity and AcPGP.

Wells, et al. AJRCCM 2015;192(8).
Roflumilast blocks inflammation and COPD-like lung remodelling in secretory IgA deficient mice

Secretory deficient IgA mice develop increased bacterial invasion into small airways and persistent activation of the innate immune response to lung microbiota resulting in epithelial cell NF-κB activation, leukocyte recruitment and upregulation of MMP-12 and neutrophil elastase expression and ultimately small airway remodelling and emphysema.

Targeted biological approaches to modify disease are under active investigation

Eosinophil

Epithelial cell

DCs

TGFβ
CTG
Il-6

Fibroblast

CD8 + lymphocyte

Neutrophil

Chemotactic factors
IL-8, CXC Chemokines
LTB₄

Oxidants

Neutrophil elastase
Cathepsins
MMPs
Il-6, Il-17

Mucous hypersecretion

Fibrosis

Emphysema

Proteases

“Th2 high” COPD

Blood Eosinophils and Exacerbations in COPD
The Copenhagen General Population Study

- 7,225 with COPD in the CGP study: recorded blood eosinophils at baseline and future AECOPD longitudinally
- Blood eos > vs < 0.34 x 10^9/l had adjusted incidence rate ratios of 1.76 (95% CI 1.56–1.99) for severe exacerbations and 1.15 (1.05–1.27) for moderate exacerbations

Vedel-Krogh et al AJRCCM 2016;193:965–974
# Eosinophillic COPD in SPIROMICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>BLOOD EOS&lt;200</th>
<th>BLOOD EOS&gt;200</th>
<th>P value</th>
<th>BLOOD EOS&lt;300</th>
<th>BLOOD EOS&gt;300</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1262</td>
<td>1237</td>
<td></td>
<td>1949</td>
<td>550</td>
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<tr>
<td>Exacerbation-total&gt;1 (%positive)</td>
<td>25</td>
<td>25</td>
<td>0.352</td>
<td>24</td>
<td>27</td>
<td>0.196</td>
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<tr>
<td>Exacerbation-With HCU &gt;1 (%positive)</td>
<td>23</td>
<td>24</td>
<td>0.356</td>
<td>23</td>
<td>26</td>
<td>0.234</td>
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<tr>
<td>Exacerbation—with antibiotic&gt;1 (%positive)</td>
<td>18</td>
<td>19</td>
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<td>18</td>
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<tr>
<td>Exacerbation-with corticosteroid&gt;1 (%positive)</td>
<td>16</td>
<td>17</td>
<td>0.266</td>
<td>16</td>
<td>19</td>
<td>0.086</td>
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<tr>
<td>Exacerbation-With drug&gt;1 (%positive)</td>
<td>21</td>
<td>22</td>
<td>0.287</td>
<td>21</td>
<td>24</td>
<td>0.173</td>
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<tr>
<td>Exacerbation-severe &gt;1 (%positive)</td>
<td>11</td>
<td>13</td>
<td>0.146</td>
<td>12</td>
<td>12</td>
<td>0.598</td>
</tr>
</tbody>
</table>

Hastie, et al. ATS 2016
# Eosinophilic COPD in SPIROMICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>SPUTUM EOS&lt;1.25%</th>
<th>SPUTUM EOS≥1.25%</th>
<th>P-value</th>
<th>SPUTUM EOS&lt;2%</th>
<th>SPUTUM EOS≥2%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N =656</td>
<td>N =171</td>
<td></td>
<td>N=715</td>
<td>N=112</td>
<td></td>
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<tr>
<td>Exacerbation total≥1 (%positive)</td>
<td>19</td>
<td>26</td>
<td>0.05</td>
<td>19</td>
<td>29</td>
<td>0.02</td>
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<tr>
<td>Exacerbation with HCU ≥1 (%positive)</td>
<td>19</td>
<td>25</td>
<td>0.07</td>
<td>19</td>
<td>29</td>
<td>0.02</td>
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<tr>
<td>Exacerbation with antibiotic≥1 (%positive)</td>
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<td>20</td>
<td>0.09</td>
<td>14</td>
<td>22</td>
<td>0.04</td>
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<tr>
<td>Exacerbation with corticosteroid≥1 (%positive)</td>
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<td>19</td>
<td>0.002</td>
<td>10</td>
<td>23</td>
<td>&lt;0.001</td>
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<tr>
<td>Exacerbation with drug≥1 (%positive)</td>
<td>16</td>
<td>23</td>
<td>0.033</td>
<td>16</td>
<td>26</td>
<td>0.01</td>
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<tr>
<td>Exacerbation severe≥1 (%positive)</td>
<td>8</td>
<td>13</td>
<td>0.04</td>
<td>8</td>
<td>15</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Hastie, et al. ATS 2016
Expanded 100 gene Th2 signature (T2 score) developed in asthma was applied to airway biopsies in COPD

**GLUCOLD Study**: RCT of ICS±LABA versus placebo in COPD
- Measured T2 score from airway biopsies prior to randomization
- Lung function measured out to 30 months

T2 score is associated with improvement in lung hyperinflation following corticosteroids

- Suggests an “asthma-like” COPD subgroup that is more responsive to ICS
- This group cannot be identified by clinical history of asthma

Benralizumab

- IL-5 monoclonal antibody depletes blood and sputum eosinophils
- 101 subjects with >3% sputum eos and ≥ 1 AECOPD in prior year randomized to benralizumab vs placebo
- Mean pre-bronchodilator FEV\textsubscript{1} change from baseline to week 56 was –6 mL with placebo, and 130 mL with benralizumab (p=0.014).
- No significant difference in AECOPD rates in treatment vs. placebo groups

Brightling, et al. LRM 2014(2).
Benralizumab in COPD

Benralizumab in COPD

Brightling, et al. LRM 2014(2).
Conclusions

- COPD is a systemic and heterogeneous disease
- Defining endotypes from phenotypes in COPD will be an iterative, longitudinal process
- Careful patient characterizations including clinical, physiologic, radiologic and biologic assessments will be required for understanding the inflammatory mechanism behind COPD and developing targeted therapies