Anti-IL-13 Prospects in Asthma

Sally Wenzel, MD
Professor of Medicine
UPMC Chair in Translational Airway Biology

The University of Pittsburgh
Asthma Institute
@UPMC and the University of Pittsburgh School of Medicine
Disclosures

• Dr. Wenzel has received consulting fees from Actelion, Amgen, Gilead, GSK, MedImmune, Merck and Teva
• UPMC/Wenzel have received money to support multicenter clinical trials from Amgen, Array, GSK, MedImmune, Merck and Sanofi
• Dr. Wenzel has not received any funds from tobacco related sources
Molecular markers identify a Type-2 cytokine associated asthma

3 signature genes expressed *in vitro* in epithelial cells in response to IL-13 applied to *ex vivo* epithelial cells----“cluster’ of mild asthmatics with:

- More atopy, eosinophils and BHR…
- More expression of canonical Type 2 cytokines IL-4, 5 and 13

Woodruff P, et al. AJRCCM 2009
“Th2 Hi” predicts responses to anti-inflammatory therapy

We think we are so smart....

Lancet Dec 13 1958!!
Pitrakinra is a 14 kDa IL-4 mutein that inhibits assembly of IL2R or IL13R into receptor complexes with IL-4R.

POC: MILD allergic asthma responds to IL-4/-13 antagonists.
IL4R alpha blockade decreased allergen induced exacerbation

3.7-fold reduction in average LAR FEV$_1$ %fall from pre-challenge baseline

95% CI on ratio of ANCOVA-adjusted means, placebo / AEROVANT = (2.1, 6.3)

$p < 0.001$

Mean ± SEM (n = 14 placebo, 15 AEROVANT)
Inhibition of IL-4R pathway also improves allergic inflammation

• IL-13 stimulates iNOS expression (FeNO source) in human airway epithelial cells
• Nebulized blockade of IL-4R decreases FeNO at baseline confirming inhibition of biologic pathway

Wenzel, the Lancet Oct 2007
Chibana Clin Exp Allergy 2008
Amgen Anti-IL-4R antibody: Traditional approach

- Study of non-phenotyped moderate asthma patients Corren et al Am J Resp Crit Care Med 2010
- Endpoints ACQ and FEV1
  - Neither impacted by Rx
  - However, significant decrease in systemic IgE
Is there subgroup that responds?

- Prespecified subgroup analysis of the lowest tertile of asthma control
- Improvements in FEV1, PEFR and in ACQ
- No biomarker phenotyping
- Drug was not taken forward
Targeting a Th2 gene signature with specific Th2 biologic approaches

- 200+ pts with moderate to severe asthma on mid to high dose ICS, most with LABA randomized to Rx with anti-IL-13 vs placebo
- Anti-IL-13 was modestly effective in improving FEV1 in all comers
- However, secondary analysis was to target “Th2 Hi vs LO”
- Using blood eosinophils in combination with total serum IgE did not identify a responder subset

Th2 biomarker periostin appears to identify Th2 Hi asthma responsive to Rx

- Patients divided by median split of serum periostin levels
- Those with hi periostin had largest increase in FEV1 and borderline reduction in exacerbations
  - But no effect on ACQ or symptoms
Can blood eosinophils define an Anti-IL-4/13 responsive population

Wenzel et al, Eur Resp Soc meeting 2010
No significant impact in all comers
However, significant improvement in pre-defined BLOOD eos group

Blood eos > 350 mm³ at randomization

*p < 0.004*
Prospective evaluation of eosinophilic phenotype

**Type I Receptor**
B cells, T cells, Monocytes, Eosinophils, Fibroblasts

**Type II Receptor**
Epithelial cells, Smooth muscle cells, Fibroblasts, Monocytes, Activated B cells

**Dupilumab**
- IL-4
- IL-13

- IL-4Ra
- γc

- JAK1
- JAK3
- STAT6

- IL-4Ra
- IL-13Ra1

- JAK1
- TYK2
- STAT6
- STAT3
<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 52)</th>
<th>Dupilumab 300 mg (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of asthma (yr), mean ± SD</td>
<td>26.9 ± 14.8</td>
<td>24.2 ± 12.6</td>
</tr>
<tr>
<td>No. asthma exacerbations in prior 2 yrs</td>
<td>1.4 ± 1.1</td>
<td>1.4 ± 1.0</td>
</tr>
<tr>
<td>High dose ICS/LABA use, no. (%)</td>
<td>41 (78.8)</td>
<td>42 (80.8)</td>
</tr>
<tr>
<td>FEV(_1) (L)</td>
<td>2.54 ± 0.66</td>
<td>2.47 ± 0.65</td>
</tr>
<tr>
<td>FEV(_1) (% of predicted value)</td>
<td>72.0 ± 12.7</td>
<td>72.0 ± 12.6</td>
</tr>
<tr>
<td>Blood eosinophils (x10(^{-9})/L)</td>
<td>0.47 ± 0.21</td>
<td>0.55 ± 0.19*</td>
</tr>
<tr>
<td>ACQ5 score</td>
<td>2.1 ± 0.5</td>
<td>2.1 ± 0.5</td>
</tr>
</tbody>
</table>

Data are mean ± SD unless noted otherwise.

*p = 0.04 for difference between groups. No other variables were significantly different at baseline.

Proof of concept study design

Efficacy: 87% reduction in *induced* asthma exacerbations

Hazard ratio 0.10 (95% CI 0.03, 0.34)  
P < 0.001
Improvement in lung function, on top of combination Rx

P < 0.001
Improvement in Asthma Control

P = 0.001
Proof of biologic mechanism: Change in FeNO correlated with change in FEV1

![Graph showing mean percent change in FEV1 from baseline across different treatment phases.]

- **Stable ICS/LABA**
- **LABA discontinuation**
- **ICS taper**
- **Dupilumab or placebo monotherapy**

**No. patients**
- Placebo: 52
- Dupilumab: 51
Pharmacogenetics: Will they influence response to targeted Rx?

- **IL-4, IL-13, STAT6, IL-4RΔ** polymorphisms long associated with asthma/atopy
- Associated with severe exacerbating asthma/low lung function AND African racial background, but not usual descriptions of “severity”
  - Wenzel AJRCCM 2007
- Will genetic receptor differences impact response to Rx?
Genetics and responses

- Pitrakinra response in exacerbation study dependent on IL-4R genotype
- Clear dose response
- Common genotypes which account for up to 50% of population
  - Haplotypes of 40% population reduced exacerbations by 70%
- ?biomarker

Slager R, J Allergy Clin Immunol In press
Conclusions

• Molecular phenotyping allowed identification of Type-2 cytokine Hi asthma
  ▪ Predicts response to IL-13 and IL-4/-13 targeted therapies
  ▪ Not yet clear whether blockade of both IL-4 and IL-13 will lead to better responses than either alone
  ▪ Similarly unclear with addition of IL-5 inhibition would add anything more

• Biomarker driven biologic therapies poised to have substantial impact in asthma