EOSINOPHIL DEPLETION BY ANTIBODY TREATMENT: Lessons Learned from Clinical Trials

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Potential Targets for Eosinophil Depletion

CD52 (alemtuzumab)
Common β chain
GM-CSF
IL-2R (daclizumab)
IL-4
IL-4R
IL-9
IL-13
IL-31
IgE (omalizumab)
TSLP

(Wechsler et al. 2012 JACI)
## Antibodies in development: IL-5/IL-5R

<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab (SB-240563)</th>
<th>Reslizumab (SCH55700)</th>
<th>Benralizumab (MEDI-563)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IL-5</td>
<td>IL-5</td>
<td>IL-5Rα</td>
</tr>
<tr>
<td><strong>Antibody (parent)</strong></td>
<td>Humanized IgG1κ (murine 2B6)</td>
<td>Humanized IgG4κ (rat 39D10)</td>
<td>Humanized afucosylated IgG1κ</td>
</tr>
<tr>
<td><strong>K_d</strong></td>
<td>4.2 pmol/L</td>
<td>20 pmol/L</td>
<td>26 pmol/L</td>
</tr>
<tr>
<td><strong>t_{1/2]</strong></td>
<td>20 days</td>
<td>30 days</td>
<td>16 days</td>
</tr>
<tr>
<td><strong>Max dose in human trials</strong></td>
<td>10 mg/kg iv 250 mg sc</td>
<td>3 mg/kg iv</td>
<td>3 mg/kg iv 200 mg sc</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Phase III ongoing</td>
<td>Phase III ongoing</td>
<td>Phase II completed</td>
</tr>
</tbody>
</table>
Assumptions

• Eosinophils are responsible for the clinical manifestations of the disorder
• Blood and tissue eosinophils are equivalent in their responses to antibody therapy
• The clinical efficacy endpoint is appropriate for the disorder being studied
Asthma and Eosinophils: 1990-2000

(Barnes JACI 1989)

(Busse NEJM 2000)
Asthma and anti-IL-5 antibody: early trials

  - Double-blind, placebo-controlled, single dose trial of mepolizumab (2.5 or 10 mg/kg iv)
  - Study population: mild allergic asthma (n=24)
  - Efficacy endpoints:
    - late asthmatic response (drop in FEV$_1$ at 4-10 hrs) to allergen challenge
    - blood eosinophilia
    - sputum eosinophilia

  - Double-blind, placebo-controlled, single dose escalation trial of reslizumab (0.03-1 mg/kg iv)
  - Study population: severe persistent asthma (n=32)
  - Efficacy endpoints:
    - FEV$_1$
    - blood eosinophilia
    - sputum eosinophilia
    - symptom severity
Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions

Buttner et al. 2003 Eur Resp J

Role of eos in asthma?

Eosinophil’s Role Remains Uncertain as Anti–Interleukin-5 only Partially Depletes Numbers in Asthmatic Airway

Flood-Page et al. 2003 Am J Resp Crit Care

Efficacy of anti-IL-5?

selection of patient population and outcome
## Asthma and anti-IL-5 antibody: today

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>mepolizumab</td>
<td>mepolizumab</td>
<td>reslizumab</td>
<td>mepolizumab</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>monthly x 5 (iv)</td>
<td>monthly x 12 (iv)</td>
<td>monthly x 3 (iv)</td>
<td>monthly x 13 (iv)</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>severe asthma + <strong>sputum eosinophilia</strong> on oral CS</td>
<td>refractory asthma + <strong>sputum eosinophilia &gt;3%</strong> on inhaled CS + ≥2 exacerb/yr</td>
<td>poorly controlled asthma + <strong>sputum eosinophilia &gt;3%</strong> on inhaled CS</td>
<td>severe asthma + ≥2 exacerb/yr + signs of <strong>eo inflammation</strong></td>
</tr>
<tr>
<td><strong>Significant outcomes</strong></td>
<td>asthma exacerbations, prednisone dose, sputum and blood eos</td>
<td>asthma exacerbations, sputum and blood eos</td>
<td>ACQ score, FEV$_1$, sputum and blood eos</td>
<td>asthma exacerbations, sputum and blood eos</td>
</tr>
</tbody>
</table>
Reduction in asthma exacerbations with anti-IL-5 therapy

(adapted from Haldar et al 2009)
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Eosinophilic esophagitis (EoE)

<table>
<thead>
<tr>
<th></th>
<th>Stein JACI 2006 (n=4)</th>
<th>Straumann Gut 2010 (n=11)</th>
<th>Spergel JACI 2012 (n=226)</th>
<th>Assa’ad Gastroent 2011 (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Open label, phase I/II</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>Multicenter, randomized, double-blind</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>adults with active EoE &gt;20 peak eos/hpf + sx</td>
<td>adults with active EoE &gt;20 peak eos/hpf + sx</td>
<td>children with active EoE &gt;24 peak eos/hpf + sx</td>
<td>children with active EoE &gt;20 peak eos/hpf +/- sx</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>mepolizumab</td>
<td>mepolizumab</td>
<td>reslizumab</td>
<td>mepolizumab</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>monthly x 3</td>
<td>weekly x 2 (+ monthly x 2 at higher dose if no response)</td>
<td>monthly x 4</td>
<td>monthly x 3</td>
</tr>
<tr>
<td><strong>Blood eos</strong></td>
<td>Suppressed</td>
<td>Suppressed</td>
<td>Not assessed</td>
<td>Suppressed</td>
</tr>
<tr>
<td><strong>Tissue eos</strong></td>
<td>Dramatic decrease, but max eos ≥20/hpf in all 4 subjects week 20</td>
<td>Dramatic decrease (66% compared to 7% in placebo), but max eos ≥15/hpf in all subjects at weeks 4 and 13</td>
<td>Dramatic decrease, but &gt;50% with more than 24 eos/hpf at study end</td>
<td>Dramatic decrease with 8.8% &lt;5/hpf and 32% &lt;20/hpf at 12 weeks</td>
</tr>
<tr>
<td><strong>Clinical sx</strong></td>
<td>Improved in 4/4</td>
<td>Improvement in 2 mepo and 2 placebo subjects</td>
<td>Improvement in all including placebo</td>
<td>No significant effect</td>
</tr>
</tbody>
</table>

**Issues:** incomplete depletion of tissue eosinophils, lack of effect on mast cells, definition of clinical success
Tissue eosinophils, anti-IL-5 and EoE

(Spergel JACI 2012)

(Stein JACI 2012)
Assumptions

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Hypereosinophilic syndrome

- A heterogeneous group of disorders characterized by peripheral eosinophilia ≥1500/mL and eosinophil-related end organ manifestations
- Diverse therapeutic interventions that decrease peripheral eosinophilia result in clinical improvement

(Ogbogu JACI 2009)
HES and mepolizumab: trial design

• Placebo-controlled, randomized, multicenter trial of mepolizumab treatment in 85 FIP1L1/PDGFRA-negative patients with stable HES on 20-50 mg prednisone daily
• Primary endpoint: prednisone dose ≤10 mg daily for ≥8 weeks
HES and mepolizumab: outcomes

A  Prednisone Dose of ≤10 mg/day for ≥8 Consecutive Wk

Mepolizumab  Placebo

P<0.001

B  Blood Eosinophil Count of <600/μl for ≥8 Consecutive Wk

Mepolizumab  Placebo

P<0.001

C  Median prednisone dose (mg)

Previous Placebo  Previous Mepolizumab

Week

D  Proportion of intention-to-treat population with treatment failure

Mepolizumab  Placebo

P<0.001

E  % subjects prednisone-free

Weeks on Study

(Rothenberg NEJM 2009)  (Roufosse JACI 2012)
Lessons learned

• An understanding of the role of eosinophils in disease pathogenesis is critical in determining whether anti-eosinophil therapy is likely to be effective
• Not all eosinophils are the same
• The choice of clinical trial endpoints is paramount
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INTERNATIONAL EOSINOPHIL SOCIETY, INC.

KEBLE COLLEGE
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