Monoclonal Antibody Therapies: A Review of What’s New Up and Coming

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Disclosures

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Nomenclature for monoclonal antibodies

- Suffix - *mab* - used for *mAb*
- Animal source of the *mAb*
  - Mouse - *omab*
  - Chimera - *ximab*
  - Humanized - *zumab*
  - Human - *umab*
- Disease or target class
  - Immune - *lim*(dac *li(m) zumab)*
  - Tumor - *tum-*(Ri tu(m) xi *mab*)
- Unique prefix -
  - Nata *li(m) zu mab*
  - Mepo *li(m) zu mab*
  - Oma *li(m) zu mab*

United States Adopted Name Council (USAN)

Mouse hybridoma

- Mouse
- Chimeric - *ximab*
- Humanized - *zumab*
- Human - *umab*

- Genetic engineering
- V gene cloning
- CDR grafting
- Eukaryotic expression
Biologics as therapeutic agents

- Tyrosine kinase inhibitors (imatinib)
  - Initially introduced for the therapy of chronic myelogenous leukemia for its ability to bind to Bcr-Abl to induce apoptosis
  - Bind to c-Kit
    - Subset of systemic mastocytosis patients with wild-type c-Kit
      - Patients with D816 V kit mutation do not respond
  - Idiopathic hypereosinophilic syndrome patients
    - Mutations in FIP1L1/PDGFRα
- IFN – γ therapy (Actimmune)
  - chronic granulomatous disease
  - IFNγ/L-12 pathway defects/mycobacterial diseases (MSMD)
- IFN – α2a/b (Intron A; Roferon A)
  - TLR 3 deficiency
- G-CSF (Neupogen)/Filgrastim
  - Congenital neutropenia syndromes

Anti-IgE therapy
Potential Points of Interruption of the Allergic Pathways

- Omalizumab
  - Humanized mAb against IgE
  - Binds circulating IgE regardless of specificity
    - binds to Cɛ3 domain of IgE
  - Forms small, biologically inert Omalizumab:IgE complexes
  - Does not activate complement

> Omalizumab

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*CDR = complementarity-determining region
The “anti-inflammatory” effects of omalizumab

Immunobiology of Asthma

• Allergic asthma – Th2 driven inflammatory process
  • 50-80% of asthma patients
  • Well recognized role of IgE
• Th2 driven cytokines
  • IL-5
    • Growth, maturation and activation of eosinophils
  • IL-4
    • Th2 cell differentiation
    • Isotype switching of B-cells to IgE synthesis
    • Eosinophil recruitment
    • Development of mast cells
    • Collagen and fibronectin production
  • IL-13
    • IgE synthesis
    • Recruitment of eosinophils and basophils
    • Airway remodeling
      • Proliferation of fibroblasts and airway smooth muscle cells
      • Goblet cell hyperplasia
Potential Points of Interruption of the Allergic Pathways

Targeting immunomodulatory cytokines – IL-5

- Monoclonal antibodies to IL-5 –
  - mepolizumab, and reslizumab
  - benralizumab (against the α chain of IL-5 receptor)
- Several early studies in mild to moderate persistent asthma – mepolizumab
  - Significant reduction in blood and sputum eosinophils; reduced exacerbation rates
  - No changes in any of the clinical endpoints (symptoms, FEV1 or airway hyper-responsiveness) in early studies
  - More recent study in severe asthmatics with eosinophilia, poorly controlled with ICS
    - Fewer exacerbations
    - Decrease in sputum eosinophils
    - Possible efficacy for nasal polyps (reslizumab)
- Asthma endotypes and biomarkers are important
  - eNO
  - Periostin
    - Chloride channel regulator 1
- May also be efficacious in:
  - Hypereosinophilic syndromes
  - Eosinophilic esophagitis

Leckie, MJ Lancet 2000
Flood-Page, P J Clin Invest 2003
Nair, P New Eng J Med 2009
Castro et al Am J Resp Crit Care Med 2011
Pavord, ID Lancet 2012
Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma


New Eng J Med 2009

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D., Melanie Kjærsgaard, R.R.T., Mark D. Inman, M.D., Ph.D., Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D., Frederick E. Hargreave, M.D., and Paul M. O’Byrne, M.B.

N Eng J Med 2009
Biologics that target IL-5

- **Summary:**
  - Reduction in asthma exacerbations
  - Responses limited to patients who are on corticosteroids and still have eosinophilia
    - sputum and peripheral blood
  - Recent FDA approval for mepolizumab, and reslizumab for the treatment of severe asthma poorly responsive to inhaled steroids
Targeting immunomodulatory cytokines – IL-4

- Several early studies with monoclonal antibodies to IL-4 (pascolizumab)
  - No clinical efficacy
- Soluble recombinant IL-4 receptor (IL-4Rα chain)- altrakincept
  - Preliminary studies showed promise
  - Later clinical trials showed no clinical improvements
- Recombinant IL-4 variant (pitrakinra)
  - Blocks both IL-4 and IL-13 by binding to the common IL-4Rα receptor component
    - Importance of targeting both IL-4 and IL-13
    - Inhibited allergen-induced late phase responses
    - Reduced F$_2$NO
    - Failed to modify airway hyper-responsiveness

Shames RS et al JACI 2001
Borish LC et al JACI 2001
Wenzel S et al Lancet 2007
Slager et al JACI 2012
### Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Siboniranda, M.D., Lin Wang, Ph.D., Stephane Kikesseli, M.D., Ross Becklin, M.D., Brian Bock, D.O., Jennifer Hamiltion, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neer Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

**A Exacerbations — Primary End Point**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=52)</th>
<th>Dupilumab (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Patients with exacerbation</td>
<td>44%</td>
<td>6%</td>
</tr>
<tr>
<td>87% reduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# humanized monoclonal antibody to IL-4Rα prevents binding of IL-4 and IL-13


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### Lebrikizumab Treatment in Adults with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hanania, M.D., Phillip E. Korenblat, M.D., Merdad V. Parsey, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Heleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mosesova, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohen, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.

**Table 1. Mean Relative Change from Baseline FEV₁ at 12 Weeks in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Lebrikizumab (%)</th>
<th>Placebo (%)</th>
<th>Percentage Point Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>218</td>
<td>9.8</td>
<td>4.3</td>
<td>5.5 (0.8 to 10.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Low FEV₁ and low FVC</td>
<td>62</td>
<td>2.6</td>
<td>1.5</td>
<td>1.1 (-4.5 to 6.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Low FEV₁ and high FVC</td>
<td>39</td>
<td>9.1</td>
<td>6.8</td>
<td>2.3 (-10.7 to 15.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>High FEV₁ and low FVC</td>
<td>42</td>
<td>8.6</td>
<td>6.3</td>
<td>2.3 (-9.5 to 13.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>High FEV₁ and high FVC</td>
<td>67</td>
<td>16.7</td>
<td>5.5</td>
<td>11.2 (3.9 to 20.5)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Patient subgroups were defined according to the median baseline levels of fraction of exhaled nitric oxide (FNO₂) or per cent for all patients who met the protocol-defined entry criteria; high indicates levels that were at the median value or higher, and low indicates levels that were less than the median value. CI denotes confidence interval, and FEV₁ forced expiratory volume in 1 second.

# Monoclonal (humanized) antibody to IL-13

Corren J et al NEJM 2011
IL-4 and IL-13 inhibition

• Summary:
  • IL-4 and IL-13 are integral components of the Th2 response. IL-13 works in concert with IL-4 to influence airway inflammation and remodeling, mucus production, IgE synthesis, and recruitment of eosinophils and basophils, proliferation of bronchial fibroblasts and airway smooth muscle cells
  • “Attacking” both IL-4 and IL-13 together with biologics seems like an effective strategy in selective asthma patients with persistent eosinophilia (and other markers of Th2 phenotype) despite ICS therapy.

Biologics Directed at the Th2 Pathway

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Disease</th>
<th>FDA approved</th>
<th>Secondary Immune Def.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Eosinophilic asthma</td>
<td>Yes</td>
<td>Increase in Zoster</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Eosinophilic asthma</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5Rα</td>
<td>Eosinophilic asthma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>IL-13</td>
<td>Eosinophilic asthma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>IL-13</td>
<td>Eosinophilic asthma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>Asthma Atopic Dermatitis</td>
<td>No Yes</td>
<td>No</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>IL-2Rα</td>
<td>Asthma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>IL-2Rα</td>
<td>Renal Tx</td>
<td>Yes</td>
<td>Cellulitis Wound infection</td>
</tr>
</tbody>
</table>

Personalized Medicine in Immunodeficiency

Innate Immunity
- DC-mediated T-cell activation ↓
- Endocytosis ↓
- Pro-inflammatory cytokine production ↓
- Anti-inflammatory cytokine production ↑
- DC differentiation ↓
- Expression of MHC class II and costimulatory molecules ↓
- Expression of CD1d ↑
- Expression of activating FcγRs ↓

Induce changes in NK-cell trafficking from blood to tissue
- NK-cell activation ↑
- Cytokine production and degranulation ↑
- Anti-tumor activity ↑

- Expression of inhibitory FcγRIIB ↑
- Blockade of activating FcγRs
- Macrophage activation ↓
- Production of proinflammatory cytokines ↓
- Production of IL1-Ra ↑
- Expression of activating FcγRs ↓
- Expression of IFNγR2 ↓

Neutrophil death via siglec ↑
- Neutrophil activation by IgG monomers blocking FcγRs ↓
- Neutrophil activation by IgG dimers binding FcγRs or by ANCA ↑
- Neutrophil adhesion to endothelium ↓

Adaptive Immunity
- T-cell activation and proliferation ↓
- IL-2 production ↓
- T-cell apoptosis ↑
- T-cell differentiation ↓

Expansion of Treg cells ↑
- Suppressive function of Treg cells ↑

B-cell apoptosis ↑
- Inhibitory FcγRIIB ↑
- Neutralization of B-cell survival factors
- Blockade of activating FcγR
- B-cell proliferation ↓
- Regulation of antibody production
FDA (USA) -approved indications for IVIG

- IVIG is recommended for a limited number of FDA approved indications:
  - Primary immunodeficiency
  - Idiopathic thrombocytopenic purpura
  - Kawasaki disease
  - B-cell chronic lymphocytic leukemia for recurrent bacterial infections
  - Pediatric HIV for recurrent bacterial infections
  - Bone marrow transplantation
    - Acute graft-versus-host disease
    - Interstitial CMV pneumonia
    - Infections
  - Chronic inflammatory polyneuropathy (CIDP)
  - Multifocal motor neuropathy

“Biological Trough Levels”

Titrate IgG trough level to clinical efficacy for an individual patient

Bonagura et al JACI, 2008
IgG Trough Levels and IVIG Dose

Orange et al Clin Immunol, 2010

IgG Trough Levels and Pneumonia

Orange et al Clin Immunol, 2010
IVIG Administration

**Advantages**
- Data on clinical use for over 30 years
- Ability to give large volumes per infusion allows intermittent dosing (every 21–28 days)

**Disadvantages**
- Requires venous access and trained personnel in most situations
- Large shift in IgG levels during dosing may cause adverse effects at or just after peak and during low troughs
- Home infusion is possible, but more technically demanding than SC administration


SCIG Administration

**Advantages**
- Data on clinical use for over 20 years internationally
- Facilitates self- or home-infusion
- Venous access not required
- Gradual absorption maintains more consistent IgG levels

**Disadvantages**
- Ability to self-infuse requires reliable and adherent patient
- Requires frequent dosing
- Multiple infusion sites may be required

Conventional SCIG Delivery: Infusion Issues

- Infusion sites
  - Most common sites are in areas of the body where you can pinch an inch of skin.
  - Abdomen, upper outer quadriceps, upper outer arm, buttocks in babies
  - One or more infusion sites can be used.

Rituximab in CVID

- Directed at CD20+ B cells.
- Used for treatment of B cell lymphoma.
- Used for treatment of GLILD in CVID.
Abatacept for CTLA4 deficiency

CTLA-4 deficiency
(Cytotoxic T Lymphocyte Associated Protein 4)

- Brain, GI, lung, lymphocytic infiltrates.
- Autoimmune thrombocytopenia and other cytopenias,
- Hypogammaglobulinemia
- Clonally expanded gd-CD8+ T cells
- CD4 T cell lymphopenia.
- Low circulating mature B cells
- Reduced expression of FOXP3 Treg cells

Lee et al. JACI. 2016
CTLA-4

- Inhibitory receptor expressed on activated T cells

Jakinibs in immunodysregulatory diseases

- Ruxolitinib JAK-STAT inhibitor used in GOF-STAT3 and GOF-STAT1
- Improvement in clinical manifestations.
- Resolution of CMC.

Weinacht K et al. JACI. 2017
Mosner. CID. 2016.
Higgins E. JACI. 2015.
Tocilizumab for GOF-STAT3

Anti IL-1 therapy

• Anakinra
• Periodic fever syndromes
  • CAPS