

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



Jennifer Leiding, MD
Associate Professor
Division of Allergy and Immunology
Department of Pediatrics
University of South Florida
jleiding@health.usf.edu



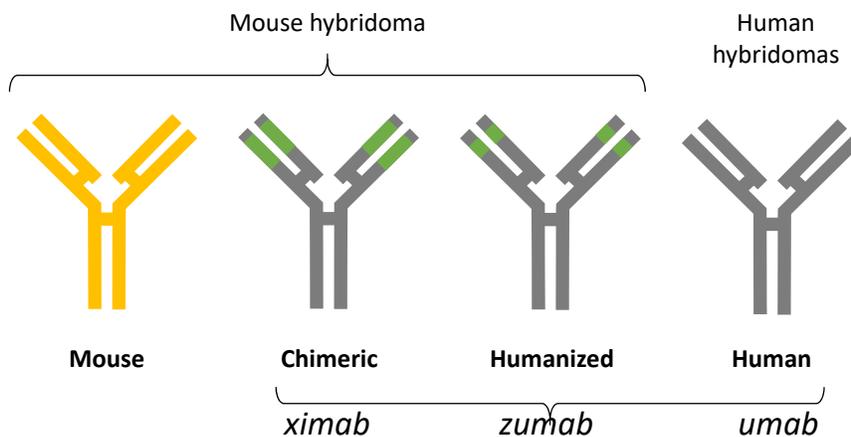
Disclosures

- Horizon Pharma – Speaker and Consultant
- CSL-Behring – Speaker and Consultant
- All Children's Foundation – Grant support
- USF – grant support

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)



- Genetic engineering
- V gene cloning
- CDR grafting
- Eukaryotic expression

Biologics as therapeutic agents

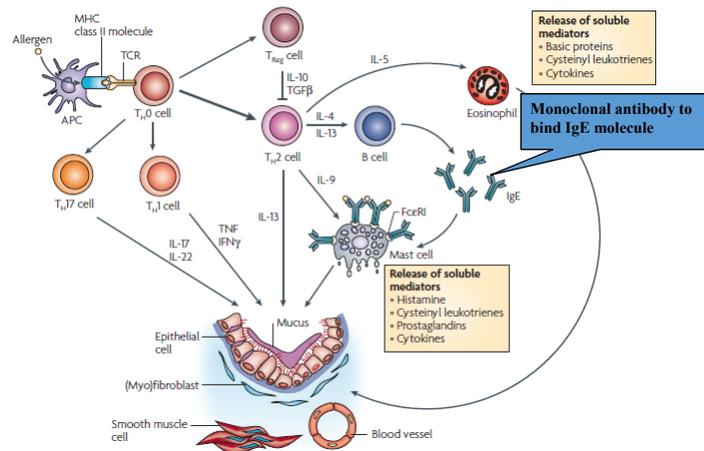
- Tyrosine kinase inhibitors (imatinib)
 - Initially introduced for the therapy of chronic myelogenous leukemia for its ability to bind to Bcr-Abl to induce apoptosis
 - Bind to c-Kit
 - Subset of systemic mastocytosis patients with wild-type c-Kit
 - Patients with D816 V kit mutation do not respond
 - Idiopathic hypereosinophilic syndrome patients
 - Mutations in FIP1L1/PDGFR α
- IFN γ therapy (Actimmune)
 - chronic granulomatous disease
 - IFN γ /IL-12 pathway defects/ mycobacterial diseases (MSMD)
- IFN α 2a/b (Intron A; Roferon A)
 - TLR 3 deficiency
- G-CSF (Neupogen)/ Filgrastim
 - Congenital neutropenia syndromes

MSMD – Mendelian susceptibility to mycobacterial diseases

CGD Study Gp New Eng J Med 1991
Ogbogu et al JACI 2009
Moi et al J Biol Chem 2004
Al-Muhsen and Casanova JACI 2008

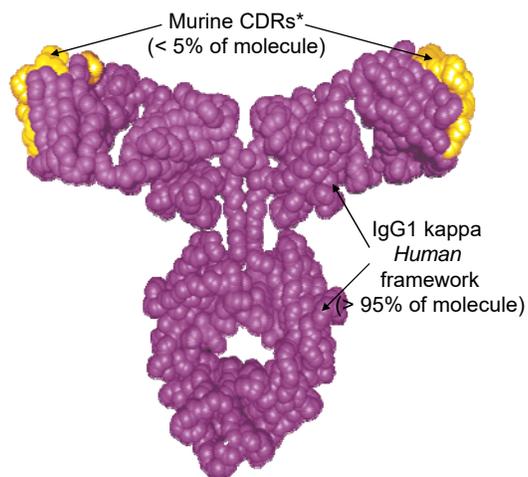
Anti-IgE therapy

Potential Points of Interruption of the Allergic Pathways



Omalizumab

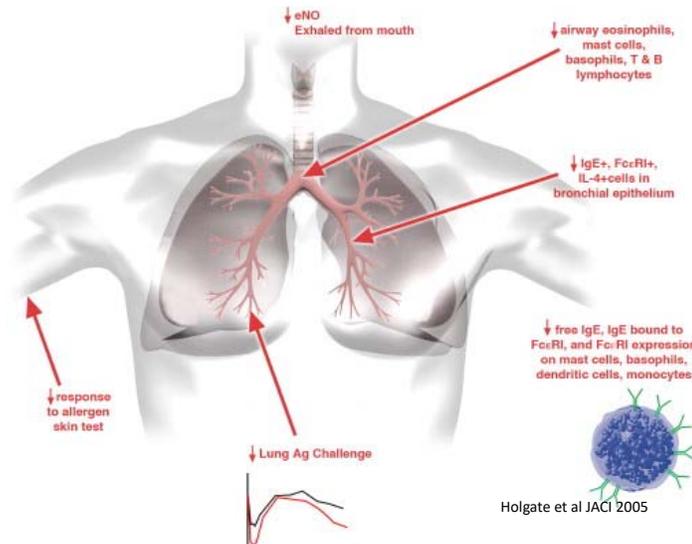
- Humanized mAb against IgE
- Binds circulating IgE regardless of specificity
 - binds to Cε3 domain of IgE
- Forms small, biologically inert Omalizumab:IgE complexes
- Does not activate complement



*CDR = complementarity-determining region

Adapted with permission from Boushey H. *J Allergy Clin Immunol.* 2001;108:S77-S83.

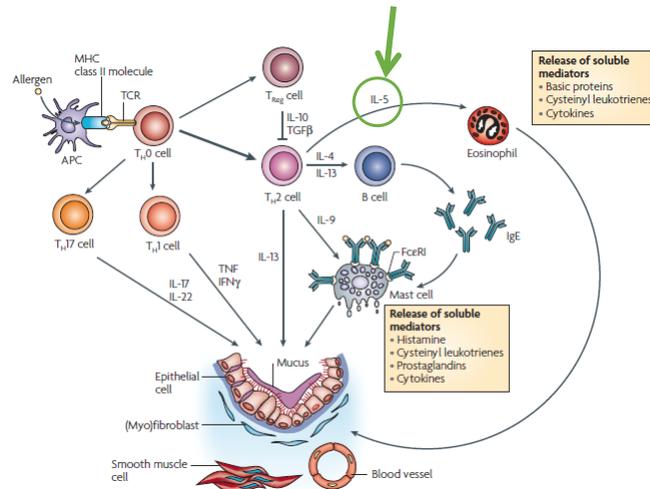
The “anti-inflammatory” effects of omalizumab



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

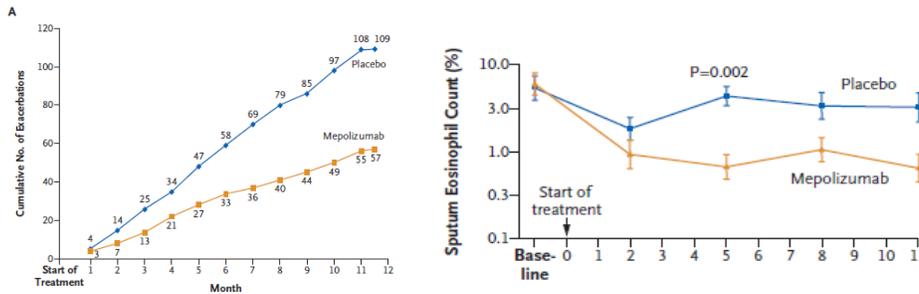
- Monoclonal antibodies to IL-5 –
 - mepolizumab, and reslizumab
 - benralizumab (against the α chain of IL-5 receptor)
- Several early studies in mild to moderate persistent asthma – mepolizumab
 - Significant reduction in blood and sputum eosinophils; reduced exacerbation rates
 - **No changes** in 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
 Flood-Page, P J Am J Resp Crit Care Med 2007
 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

Pranabashis Haldar, M.R.C.P., Christopher E. Brightling, Ph.D., F.R.C.P.,
 Beverley Hargadon, R.G.N., Sumit Gupta, M.R.C.P., William Monteiro, M.Sc.,
 Ana Sousa, Ph.D., Richard P. Marshall, Ph.D., M.R.C.P.,
 Peter Bradding, D.M., F.R.C.P., Ruth H. Green, M.D., F.R.C.P.,
 Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.

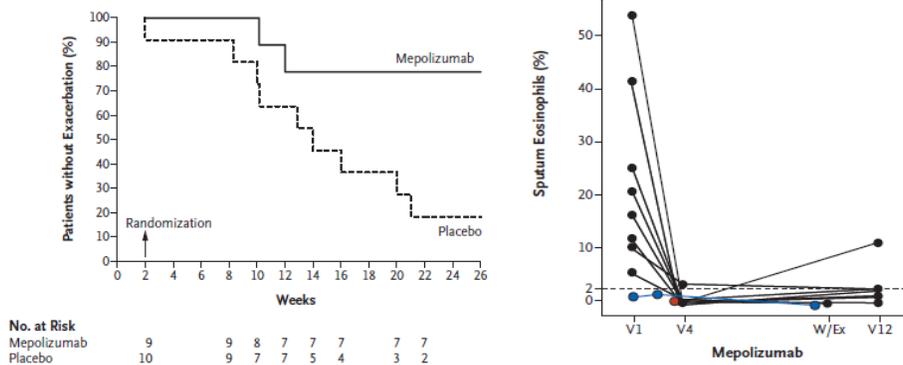
New Eng J Med 2009



Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D.,
 Melanie Kjarsgaard, 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.

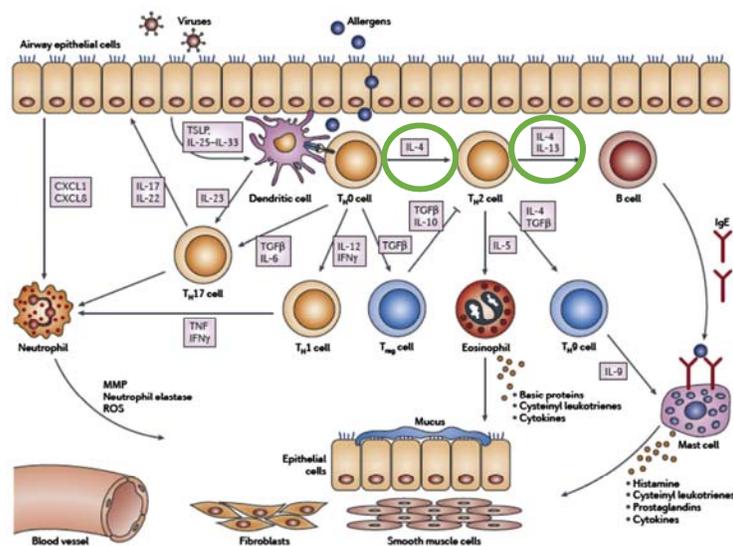
N Eng J Med 2009

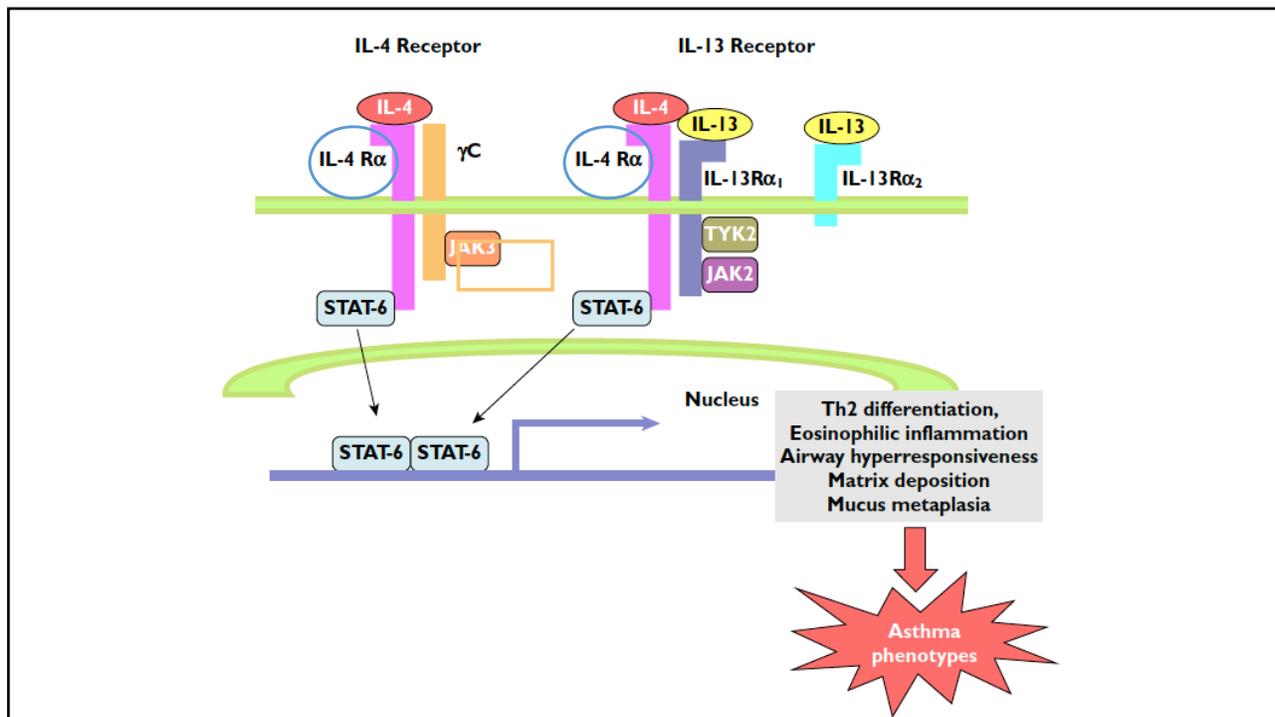


Biologics that target IL-5

- 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

Pathobiology of Asthma





Targeting immunomodulatory cytokines – IL-4

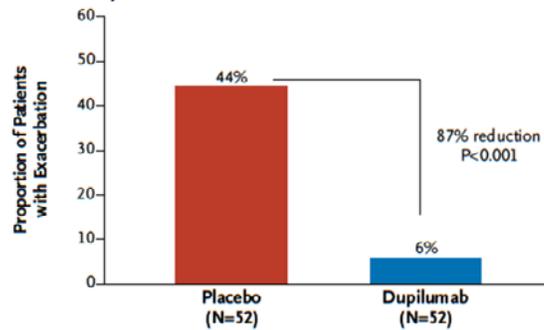
- Several early studies with monoclonal antibodies to IL-4 (pascolizumab)
 - No clinical efficacy
- Soluble recombinant IL-4 receptor (IL-4R α chain)- altrakincept
 - Preliminary studies showed promise
 - Later clinical trials showed no clinical improvements
- Recombinant IL-4 variant (pitrakinra)
 - Blocks both IL-4 and IL-13 by binding to the common IL-4R α receptor component
 - Importance of targeting both IL-4 and IL-13
 - Inhibited allergen-induced late phase responses
 - Reduced F_ENO
 - 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 Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil 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



[#] humanized monoclonal antibody to IL-4R α prevents binding of IL-4 and IL-13

Wenzel S et al New Eng J Med 2013

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. Bohlen, 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.*

Group	No. of Patients	Lebrikizumab (%)	Placebo (%)	Percentage Point Difference (95% CI)	P Value
All subjects	218	9.8	4.3	5.5 (0.8 to 10.2)	0.02
Low periostin and low FE _N O	62	2.6	1.5	1.1 (-4.5 to 6.6)	0.71
Low periostin and high FE _N O	39	9.1	6.8	2.3 (-10.7 to 15.2)	0.73
High periostin and low FE _N O	42	8.6	6.3	2.3 (-9.3 to 13.9)	0.70
High periostin and high FE _N O	67	16.7	5.5	11.2 (1.9 to 20.5)	0.02

* Patient subgroups were defined according to the median baseline levels of fraction of exhaled nitric oxide (FE_NO) or periostin 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:**

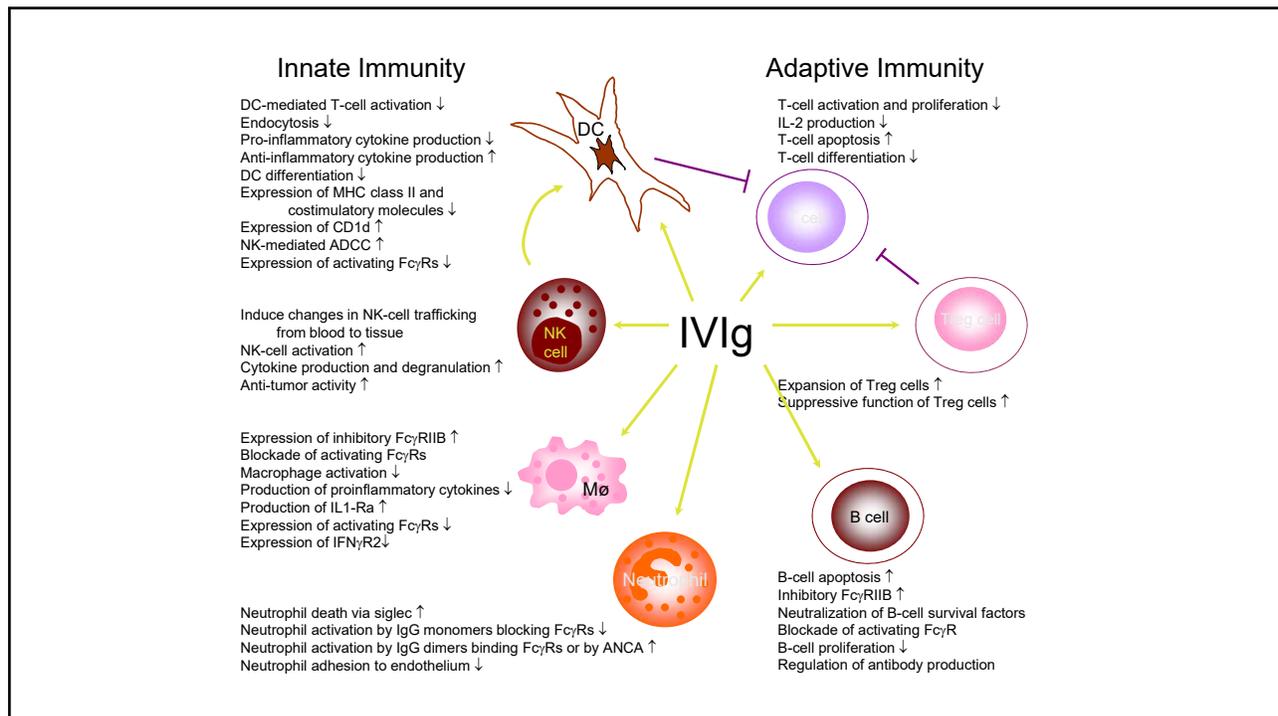
- IL-4 and IL-13 are integral components of the Th2 response. IL-13 works in concert with IL-4 to influence airway inflammation and remodeling, mucus production, IgE synthesis, and recruitment of eosinophils and basophils, proliferation of bronchial fibroblasts and airway smooth muscle cells
- “Attacking” 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

Name	Target	Disease	FDA approved	Secondary Immune Def.
Mepolizumab	IL-5	Eosinophilic asthma	Yes	Increase in Zoster
Reslizumab	IL-5	Eosinophilic asthma	Yes	No
Benralizumab	IL-5R α	Eosinophilic asthma	No	No
Lebrikizumab Tralokinumab	IL-13	Eosinophilic asthma	No	No
Dupilumab	IL-4R α	Asthma Atopic Dermatitis	No Yes	No
Daclizumab	IL-2R α	Asthma	No	No
Daclizumab	IL-2R α	Renal Tx	Yes	Cellulitis Wound infection

Corren et al NEJM, 2011; Busse et al Am J Respir Crit Care Med, 2008
 Flood-Page Am J Respir Crit Care Med, 2007; Haldar et al NEJM, 2009
 Nair et al NEJM, 2009; Thaci et al The Lancet, 2015

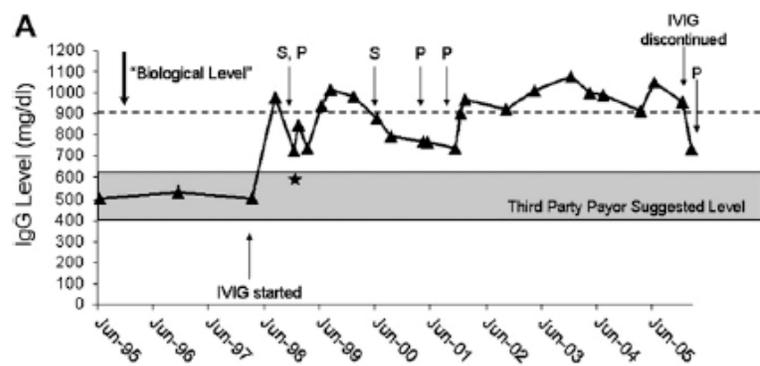
Personalized Medicine in Immunodeficiency



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

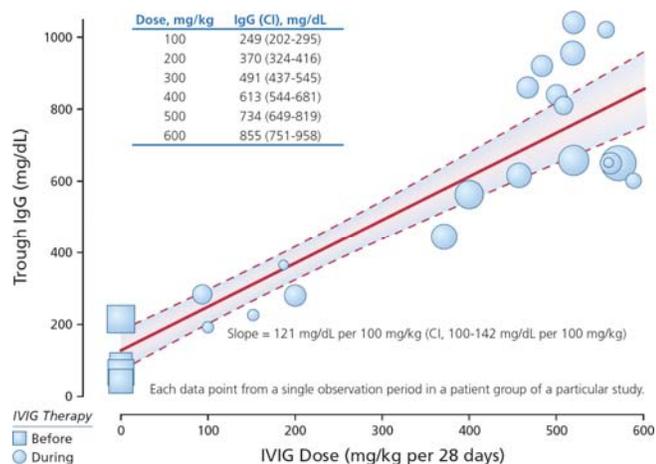
“Biological Trough Levels”



Titrate IgG trough level to clinical efficacy for an individual patient

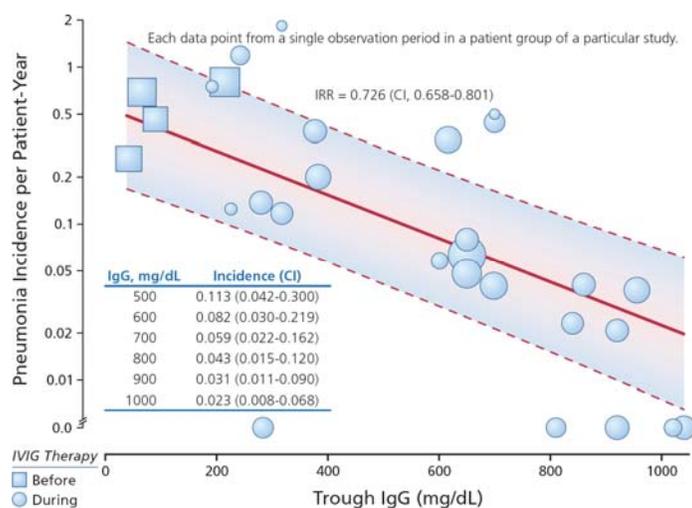
Bonagura et al JACI, 2008

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

Berger M. *Clin Immunol.* 2004;112:1-7.

29

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

30

Berger M. *Clin Immunol.* 2004;112:1-7.

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.

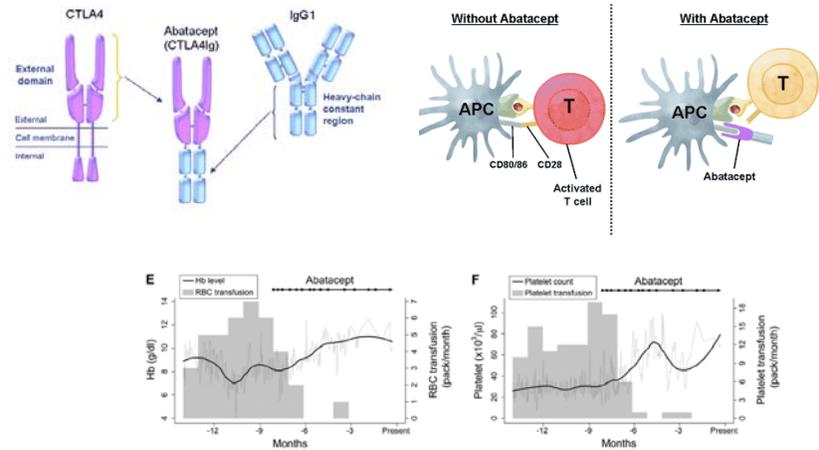


Rituximab in CVID

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

Abatacept for CTLA4 deficiency

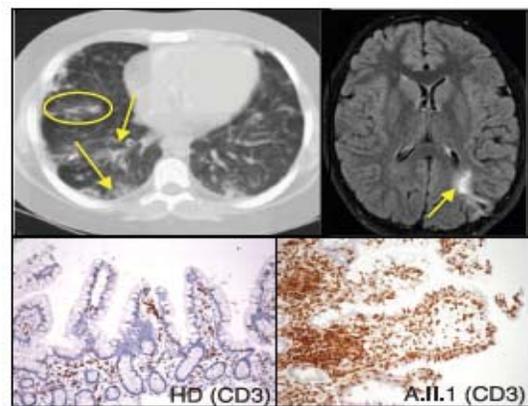
Abatacept alleviates severe autoimmune symptoms in a patient carrying a *de novo* variant in *CTLA-4*



Lee et al. *JACI*. 2016

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

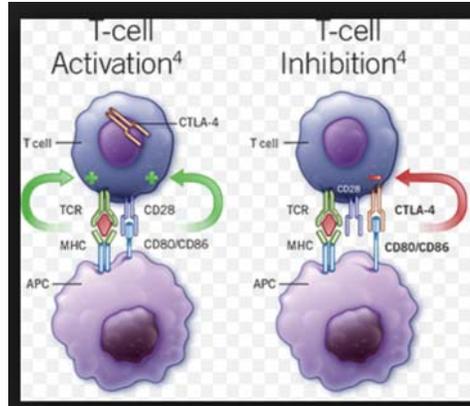
- Brain, GI, lung, lymphocytic infiltrates.
- Autoimmune thrombocytopenia and other cytopenias,
- Hypogammaglobulinemia
- Clonally expanded gd-CD8+ T cells
- CD4 T cell lymphopenia.
- Low circulating mature B cells
- Reduced expression of FOXP3 Treg cells



Kuehn HS et al. *Science*. 2015.

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

Castro-Wagner J and Leiding JW. CIS
2016.

Anti IL-1 therapy

- Anakinra
- Periodic fever syndromes
 - CAPS