Biologic Asthma Therapies and Individualized Medicine

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Disclosures

Advisory boards
Merck (advisor, honorarium)
Shire (advisor, honorarium)

Editorial boards
Allergy & Asthma Proceedings
American Journal of Rhinology & Allergy
Clinical Reviews in Allergy & Immunology
Journal of Angioedema

Learning Objective

To better understand the use of biologic modifiers in individualized asthma treatment.

Biological therapies

- May fill unmet needs, potentially in subpopulations or phenotypes of patients with more severe asthma.
- May provide insight into mechanisms of asthma

Sheharyar, Durrani, Busse. Biological Therapy for Asthma. ACCP PCCSU Article | 03.15.11

Omalizumab (Anti-IgE)

- Biologic mechanism: Mab against IgE; decreases IgE levels; results in down-regulation of IgE receptor
- Patient subsets: persistent asthma selected for specific IgE to perennial allergen, total serum IgE in specified range
- Benefits: 8 trials (n=3429) Rodrigo. Chest 2011 139:28
  - decreases in exacerbations, dose of inhaled and oral corticosteroids, hospitalizations
  - improvement in QOL when used as add-on Rx
  - no improvement in lung function.

Biologics with action against

- IgE (omalizumab)
- Cytokines
  - IL-4 and/or IL-13
  - IL-5
- Chemokine Receptors
  - CCR3
  - CXCR2
- Transcription Factors
  - PPARs (peroxisome proliferator-activated receptors)
- Prostaglandin Receptors
  - CRTH2

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IL-4 Modifiers

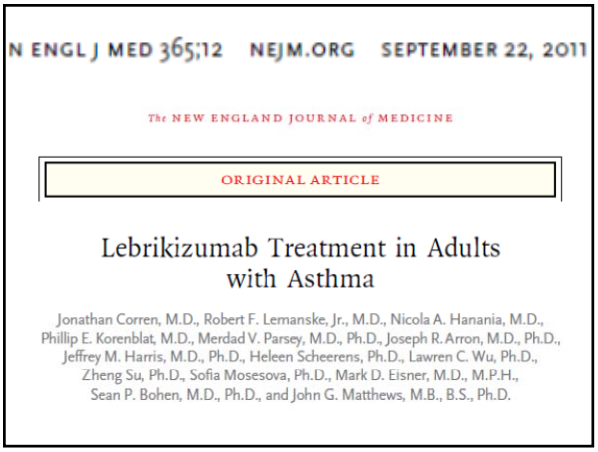
Altrakincept	Solubilized IL-4 receptor fragment, neutralizes IL-4	Failed to show efficacy in large phase 3 trial. Adcock et al (2008)
Pascolizumab	Monoclonal Ab against IL- 4	Phase 2 study of pascolizumab discontinued because of inefficacy. Hart et al (2002)
Pitrakinra	IL-4 mutant protein. Binds to α subunit of IL-4 receptor, antagonizes both IL-4 & IL-13/ STAT-6	Inhaled form improved pulmonary function & decreased exhaled nitric oxide, genetic basis for response Wenzel et al. Lancet 2007;370:1422 Slager RE et al. AJRCCM 2011; 183:A6178 Slager RE et al. JACI 2010; 126:875

IL-13

- Pleiotropic cytokine of Th2 cells, promotes IgE production
- May contribute to key features of asthma
- IL-13 production inhibited by inhaled glucocorticoids [GC] (although they have many other effects on airways)
- Despite use of systemic and inhaled GCs, some patients with uncontrolled asthma have persistently elevated IL-13 levels in sputum
- Hypothesis: IL-13 contributes to GC resistance

IL-13

- Induces bronchial epithelial cells to secrete periostin, a matricellular protein.
- Activated airway epithelial cells secrete large quantities of *periostin* basally into underlying matrix, where it has autocrine effects on epithelial cell function and paracrine effects on fibroblasts – potentially contributing to mechanisms of airway remodeling in asthma


N ENGL J MED 365;12 NEJM.ORG SEPTEMBER 22, 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

Methods

Corren et al. NEJM 2011;365:12

- 219 adults with asthma inadequately controlled by inhaled glucocorticoids
- 12% increase FEV1 after SABA
- Prebronchodilator FEV1 between 40-80% of predicted

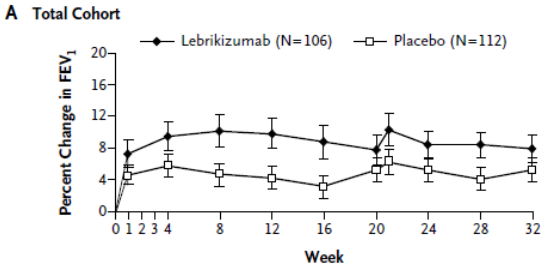
Methods

Corren et al. NEJM 2011;365:12

- Before randomization, patients assessed for IL-13 signature surrogate, "Th2 status", combination of total serum IgE and peripheral-blood eosinophil count
  - **High Th2**: total IgE > 100 IU/ml AND eos count > 0.14×109 cells/Liter
  - **Low Th2**: either/both threshold (s) not met
- Dynamic randomization to receive lebrikizumab or placebo, balanced through stratification according to hierarchy of 1) Th2 status (high vs. low), 2) use or no use of LABA, 3) study site

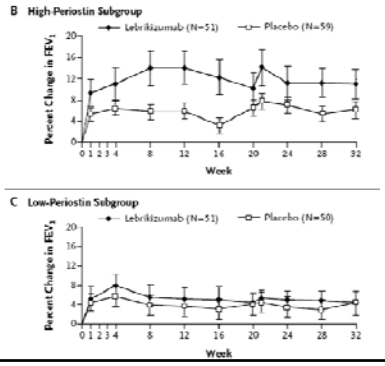
Corren et al. NEJM 2011;365:12

Total cohort: % change FEV1 (treatment weeks 0-20)



Corren et al. NEJM 2011;365:12

% Change FEV1 by Periostin Subgroup



Corren et al. NEJM 2011;365:12

Results & Discussion

- Lebrikizumab caused reductions in serum Th2 chemokines (CCL13 and CCL17) and IgE - support a biologic effect that underlies the clinical effect in the airway.

Corren et al. NEJM 2011;365:12

Results & Discussion

- Periostin level not only predictor of response to lebrikizumab – also FeNO
- In post hoc analysis, high FeNO, but not high Th2, also identified patients who had greater improvements in FEV1

From online appendix for Corren et al. NEJM 2011;365:12

% Change in FEV1 at 12 Weeks

Treatment Group	Lebrikizumab n=106	Placebo n=112	Lebrikizumab–Placebo
All patients	9.8%	4.3%	5.5% (0.8%,10.2%) P=0.02
Th2-high	9.5%	3.1%	6.4% (0.3%, 12.6%) P=0.04
Th2-low	10.1%	5.4%	4.7% (-2.6%,12.1%) P= 0.21
Periostin-high (≥median)	14.0%	5.8%	8.2% (1.0%,15.4%) P=0.03
Periostin-low (<median)	5.1%	3.5%	1.6% (-4.5%,7.7%) P=0.61
FeNO-high (≥ median)	14.2%	5.6%	8.6% (1.3%,15.9%) P=0.02
FeNO-low (<median)	4.8%	2.9%	1.9% (-3.8%, 7.5%) P=0.52

Corren et al. NEJM 2011;365:12

Results & Discussion

- Lebrikizumab decreased FeNO, consistent with either
  - modifying eosinophilic inflammation, or
  - by indirectly inhibiting the expression of nitric oxide synthase through IL-13

RE: Corren et al. NEJM 2011;365:12

Lebrikizumab

- NEJM Editorial: "one step further towards personalized immunomodulatory treatment for asthma"

Kraft M. Asthma Phenotypes and Interleukin-13 — Moving Closer to Personalized Medicine. NEJM 2011; 365:1141

IL-5 Modifiers

Mepolizumab
Resilizumab

IL-5 and eosinophils

- IL-5 is proinflammatory mediator involved in eosinophil
  - maturation
  - recruitment
  - activation
  - survival

Eosinophils in asthma

- Elevated levels of eosinophils in lung & sputum can be used to phenotype asthma
- Numbers of eosinophils in blood and bronchial fluid can correlate with asthma severity

  Bousquet. NEJM 1990;323:1033
- Eosinophils involved in lung tissue remodeling, including airway thickening and fibrosis, and angiogenesis, which promotes further tissue growth and remodeling

Anti-IL 5 treatment

- Reduces blood and sputum eosinophils in asthma patients.
- Not effective at reducing signs and symptoms of asthma in studies of patients who were not selected according to their asthma phenotype

Leckie MJ. Lancet 2000;356:2144
Kips JC. AJRCCM 2003;167:1655
Flood-Page P. AJRCCM 2007;176:1062

Anti-IL 5 treatment

- But, in patients with severe refractory, prednisone-dependent asthma and increased sputum eosinophils,
  - prednisone-sparing
  - decreased asthma exacerbations
  - increased QOL

Nair P. NEJM 2009;360:985
Haldar P NEJM 2009;360:973

Am J Respir Crit Care Med Vol 184. pp 1125–1132, 2011

Reslizumab for Poorly Controlled, Eosinophilic Asthma

A Randomized, Placebo-controlled Study

Mario Castro[1], Sameer Mathur[2], Frederick Hargreave[3†], Louis-Philippe Boulet[4], Fang Xie[5], James Young[6], H. Jeffrey Wilkins[5], Timothy Henkel[5], and Parameswaran Nair[2]; for the Res-5-0010 Study Group

Castro et al. AJRCCM 2011;184:1125-1132

Methods

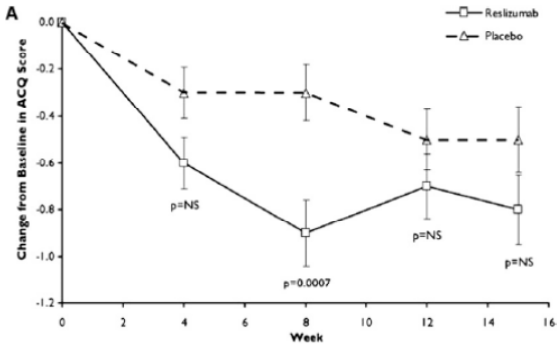
- Induced sputum eosinophils of ≥ 3%
- Poor baseline score by Asthma Control Questionnaire, ACQ (>1.5)
- High dose ICS
- Either airway hyperreactivity or reversibility of obstruction
- Randomization with infusions at weeks 4, 8, 12

Castro et al. AJRCCM 2011;184:1125-1132

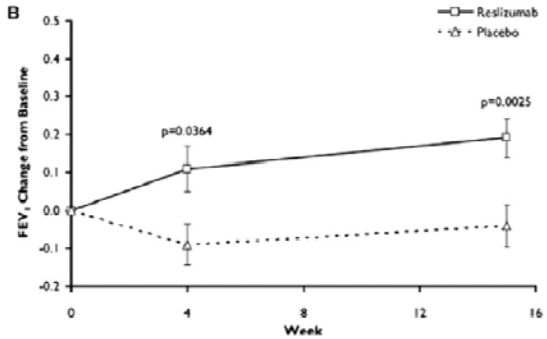
Results

- Reduction in sputum and blood eosinophils counts
- Statistically significant yet modest improvement in FEV1 when compared with placebo after 15 weeks
- Failed to improve asthma control (ACQ) in the population as a whole.

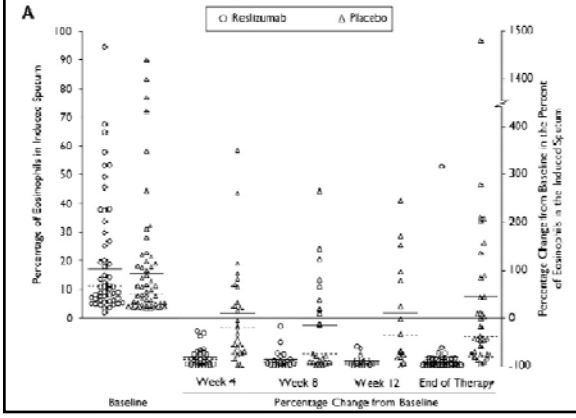
Castro et al. AJRCCM 2011;184:1125-1132



Castro et al. AJRCCM 2011;184:1125-1132



Castro et al. AJRCCM 2011;184:1125-1132



Castro et al. AJRCCM 2011;184:1125-1132

Nasal polyps +/- in phenotyping responders?

- In subgroup analyses, nasal polyps associated with greater improvement in ACQ, although not with pulmonary function
- Presence of nasal polyps may help identify patients who may benefit most from anti–IL-5
- Small sample size (of 53, 22 with nasal polyps), no standardized confirmation method, no objective scoring systems for polyps
- Possible confounding factors, e.g. AERD or use of LTRAs in nasal polyp group, not considered

(Results) "add to the growing body of evidence that suggests that the accurate definition of asthma phenotypes is critical in selecting targets for investigational therapies, ultimately providing the basis for targeted treatment and phenotype-specific asthma care."

McCallister JW. Reslizumab and Eosinophilic Asthma: One Step Closer to Phenotype-directed Therapy? AJRCCM 2011;184:1096

- "As evidence continues to grow in support of customizing treatment approaches for particular patient populations, we must continue to challenge ourselves to generate new classifications of asthma phenotypes that will not only guide our clinical decision making, but also help increase our understanding of disease pathogenesis and progression."

McCallister JW. Reslizumab and Eosinophilic Asthma: One Step Closer to Phenotype-directed Therapy? AJRCCM 2011;184:1096

Ultimately, define role of *Biologic Asthma Therapies in Individualized Medicine*