BIOLOGICS & BIOMARKERS: EMERGING APPROACHES TO EFFECTIVE ASTHMA TREATMENTS

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Disclosures

• Speaker/Advisory/Honorarium/Research
  – AstraZeneca, Circassia, Genentech, MEDA, Merck, Mylan, Teva, Kaleo, Pfizer

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Objectives

- Discuss different biomarkers used to identify specific asthma endotypes
- Discuss how to use biomarkers to personalize asthma care with current medications
- Discuss current biologics and those being developed to target specific asthma endotypes
Background

- Asthma is a heterogeneous disease associated with significant impairment and risk

- Therapeutic responses that is highly variable

- Current treatments are usually effective for patients with mild to moderate disease

- Patients with more severe asthma are often unresponsive to medication
  - “One size fits all” approach often unsuccessful
Current Guidelines

STEPWISE APPROACH FOR MANAGING ASTHMA LONG TERM
The stepwise approach tailors the selection of medication to the level of asthma severity (see page 5) or asthma control (see page 6). The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.

ASSESS CONTROL:

STEP UP IF NEEDED (first, check medication adherence, inhaler technique, environmental control, and comorbidities)

STEP DOWN IF POSSIBLE (and asthma is well controlled for at least 3 months)

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Inhaler Technique

- https://www.youtube.com/watch?v=bDHEEV0M62Y
Background

- As we learn more about the mechanisms involved asthmatic airway inflammation, several key components have been identified
  - These can offer potential therapeutic targets

- However, the inflammatory process is complex, interactive, and redundant
  - Variable between patients

- How do we decide who is going to respond to different therapeutic agents?
Biomarkers in General

• Traceable substances used to examine organ function or other aspects of health\(^1\)
  • HgbA1c in diabetes
  • CD4 T-cell count for AIDS patients
  • Troponins in MI

• At their best, biomarkers are used to determine presence or absence of disease, disease severity and progression, targets for therapy and response to therapy, and guidance about the affected subject’s survival

1. Lapraz JC. Glob Adv Health Med 2013
Biomarkers in Asthma

- Spirometry – diagnosis, severity, response to treatment
  - Do not tell us about underlying cause of disease

- Several biomarkers have been identified that can help define asthma endotypes

- To be most useful, biomarkers in asthma must\(^1\)
  - Be vetted in large numbers of patients
  - Be able to be measured by standard methods to ensure widespread and accurate use
  - Display strong sensitivity, specificity, accuracy and reproducibility.

Asthma Syndrome
Characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and inflammation

Spirometry

Allergy, exercise, infection

Phenotypes
Observable characteristics including clinical presentation, triggers, and treatment response

IgE, \( F_E\)NO, Eosinophilia

Endotypes
Condition subtype defined by a distinct functional or pathophysiological mechanism (links clinical characteristic with a molecular pathway)
IgE as a Biomarker

• Allergic sensitization is present in the majority of asthmatic patients\(^1\)
  • Allergy is known to contribute to asthmatic inflammation
  • Activated mast cells release histamine and produce prostaglandins, leukotrienes, and cytokines\(^2\)

• IgE levels correlate with asthma severity in both children and adults\(^3\)

• This made IgE a natural target for asthma therapy

1. Darveau J. JACI, In practice 2015
2. Fahy JV. Am J Respir Crit Care Med 1997
Omalizumab

- Monoclonal antibody targeted at the Fc portion of IgE
- Prevents IgE from binding to its receptor
- Reduces symptoms, prevent exacerbations, allowed for a reduction in ICS use without a loss of asthma control

- Omalizumab is approved for use ages 6 and above
  - Requires sensitization to a perennial allergen and sufficient IgE level
  - Dose/frequency of administration is based on weight and IgE level
Efficacy of Omalizumab

- Omalizumab reduced:
  - Mean number of days during which participants had symptoms by 24.5% (from 1.96 to 1.48; p<0.001)
  - Exacerbations by 18.5% (48.8% in the placebo group vs. 30.3% in the omalizumab group; p<0.001)
  - Inhaled Glucocorticoid dose by 109 mcg/day (p<0.001)
Efficacy of Omalizumab

Choosing the Right Biomarker

Eosinophils

- Lung histology in asthmatic patients is often characterized by eosinophilic infiltration
- Boost the allergic response
  - Recruit inflammatory cells
  - Promote IgE production through secretion of other interleukins
- Can be elevated both peripherally and in sputum
  - Blood eosinophilia seems to be the best marker to identify sputum eosinophilia
- Reductions in eosinophils linked to clinical improvement

- Berry A. J Allergy Clin Immunol 2016
- Seys SF. Curr Opin Pulm Med 2016
- Miranda C. J Allergy Clin Immunol. 2004
Eosinophil

Green, R.H. Lancet, 2002
Targeting Eosinophils

• Early studies with anti-IL5 therapy were disappointing
  • Studied in moderate to severe asthmatics
  • Reductions in sputum and peripheral eosinophil counts were seen, but no effects on clinical features of asthma

• Later studies requiring peripheral eosinophilia as inclusion criteria were much more successful

• Highlights the need to select appropriate patients based on biomarkers, in this case peripheral eosinophils
Effect of Targeting Eosinophils

- Consistent feature of medications targeting eosinophils is reduction in exacerbations
- Atopic status has no impact on response to mepolizumab
- Most impressive responses are in patients with high peripheral eosinophilia

Darveau J. JACI, In Practice 2015
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Darveaux J. JACI, In Practice 2015
Fractional Exhaled Nitric Oxide - $F_{E}NO$

- Nitric Oxide is produced by respiratory epithelium
  - Increased with allergic type inflammation
  - Highly correlates with sputum eosinophilia
- Like eosinophils, high levels correlate with increased risk of exacerbation
$F_{ENo}$

- Although eNO levels correlate with eosinophilia, these are thought to be 2 separate biomarkers
  - Patients treated with mepolizumab have reductions in eosinophils without change in eNO

Patients with high eNO are likely to benefit from ICS

- Upper limit of normal is 25 ppb
- High eNO despite ICS therapy may reflect a subtype unresponsive to ICS

Levels rise quickly once ICS is stopped, so can be used to monitor adherence
IL-4 and IL-13
IL-4 and IL-13

• IL-4 and IL-13 work in concert and produces many of the same effects.

• Two receptor types
  • One binds IL-4 alone, the other binds both IL-4 and IL-13.
IL4 & IL13 Targeted Therapies

• Approaches to reduce IL-4 activity have included
  • Anti-IL-4 antibody
  • Soluble IL-4 receptor
  • IL-4 transcription inhibitors
  • IL-4/IL-13 receptor antagonists

• These have met mixed results as far as efficacy in asthma

• The overlapping actions of these cytokines brings into question the potential effectiveness of blocking of either of them individually.
Periostin

- Extracellular matrix protein produced by epithelial cells
  - Induced by IL-13
  - High periostin levels are thought to reflect a high Th2 endotype

- Periostin has effects on epithelial cell function and effects on fibroblasts
  - May contribute to the mechanisms of airway remodeling in asthma
Utilizing Periostin

- Lebrikizumab is an anti-IL-13 monoclonal antibody
- Improved FEV-1 in asthmatics, but showed a greater improvement in “high Th2” patients

IL4 & IL13 Targeted Therapies

• Dupilumab – IL4R blocker

• Inhibits interaction with BOTH IL-4 and IL-13

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Unmet Needs

- Although much has been learned about the pathophysiologic mechanisms involved in different asthma endotypes, practical application of biomarkers in clinical practice is still being developed
  - Invasiveness of tests, accessibility, cost

- The vast majority of research has been directed at T2 predominant asthma phenotypes
  - Other phenotypes, specifically T2 low or neutrophilic asthma do not typically respond to either standard therapy or current biologics
  - Further research is needed to identify biomarkers and potential therapeutic agents for this phenotype
Who should see a specialist?

• Current recommendations are that any patient requiring **Step 4** treatment or higher should be evaluated by an asthma specialist
  • Step 4 = Medium dose ICS + LABA
Summary

• A significant portion of asthmatics do not achieve control with current inhaler treatments

• Several biologic agents have been developed, and others are currently being explored targeting key components of asthma pathophysiology

• Biomarkers can help provide information to strategically select biologic agents for specific asthma endotypes

   personalized therapy