Advances in Drug Therapy for Asthma and COPD

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Overview

• Biologic therapy for asthma
  ▫ IgE
  ▫ IL-5
  ▫ Therapeutic positioning
  ▫ What’s in the pipeline

• COPD therapy
  ▫ Impact of new GOLD guidelines on therapy
  ▫ New twists on old players
  ▫ Combination therapy
  ▫ Future directions
Asthma affects 25 million in USA (Maybe) 2 Million have Severe** Asthma and it’s Costly

** Although consensus definition is lacking
LABA
Long acting beta agonist

LAMA
Long acting muscarinic

ICS
Inhaled corticosteroid

Tonight’s English as a second language class has been cancelled.
Current Treatment Paradigm

Step 1
- SABA PRN

Step 2
- Low-dose ICS
  - Alternative: cromolyn, LTRA, nedocromil, or theophylline

Step 3
- Low-dose ICS + LABA or medium-dose ICS
  - Alternative: low-dose ICS + LTRA, theophylline, or zileuton

Step 4
- Medium-dose ICS + LABA
  - Alternative: medium-dose ICS + LTRA, theophylline, or zileuton

Step 5
- High-dose ICS + LABA and consider omalizumab if allergies are present

Step 6
- High-dose ICS + LABA + oral corticosteroids and consider omalizumab if allergies are present
Omalizumab: The original biologic

- Xolair
- Approved 2003
- SC q 2 or 4 weeks
- Dose based upon IgE & weights
- ≥ 6 years
- Blocks IgE
- Positive skin test for perennial allergens and elevated IgE
- Recommended** before IL-5 based therapy in allergic patients with elevated IgE
Neutralizing IgE attenuates allergic manifestations
The year of the Eosinophil

• Peripheral eosinophilia is present in about 15% ¹
• Defined as > 400 cells/uL
• Associated with increased cost of care²
• More severe exacerbations¹
• More common in asthma onset age 35-50

¹ Price, DB. Lancet 2015; 3 (11): 849
² Casciano J.
J Manag Care Spec Pharm. 2017;23:85e91.
Eosinophil Refresher

- 5-7% of circulating WBCs
- Bilobed nucleus
- Granules containing > 200 proteins and enzymes
  - Major basic protein
  - Eosinophil peroxidase
  - Eosinophil cationic protein
IL-5 Key Cytokine in Eosinophil Function

- Enhanced bone marrow differentiation and maturation
- Increased cell migration
- Increased release of granule proteins
- Increased respiratory burst

Eosinophil responsiveness to mediators:

- LYN
- Highened responsiveness to mediators

Mediators:
- IL-5
- IL-3
- GM-CSF
- ADCC
- Fc receptors
- Benralizumab
- Reslizumab
- Mepolizumab

Granule proteins:
- ECP
- MBP
- EPX
- EDN

Respiratory burst:
- $O_2^-$
- $O_2^-$
IL-5 and IL5 Receptor Blockade

Figure 2 Anti-IL-5/IL-5R biologic therapies.
Notes: Monoclonal antibodies aimed to inhibit eosinophil functions include mepolizumab and reslizumab, which bind to and neutralize IL-5, as well as benralizumab, which targets and blocks IL-5Rα.
<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab</th>
<th>Reslizumab</th>
<th>Benrlalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Nucala</td>
<td>Cinqair</td>
<td>Faserna</td>
</tr>
<tr>
<td><strong>Method of Delivery</strong></td>
<td>100 mg SC q. 4 weeks</td>
<td>3 mg/kg IV over 0-50 mins q 4 weeks</td>
<td>30 mg SC q 4 weeks * 3 then q 8 weeks</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>&gt; 12 years</td>
<td>&gt; 18 years</td>
<td>&gt; 12 years</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Blocks IL-5</td>
<td>Blocks IL-5</td>
<td>Blocks IL-5 receptor alpha</td>
</tr>
<tr>
<td><strong>Indications/ Miscellaneous</strong></td>
<td>Add on therapy for severe asthma with eosinophilia</td>
<td>Add on therapy Eosinophils &gt; 400 **Black box warning for anaphylaxis</td>
<td>For those who have failed standard therapy; or if IgE elevated and omalizumab unhelpful</td>
</tr>
</tbody>
</table>
Clinical Efficacy: Mepolizumab

- **DREAM Study**
  - Reduced severe exacerbations
  - Rate of reduction tied to eosinophil level

- **MENSA Study**
  - Reduced exacerbation rate about 50%
  - Improved QOL

- **SIRIUS Study**
  - Reduced steroid use AND fewer exacerbations
Reduction in Exacerbations with Mepolizumab

Asthma Exacerbations

Cumulative No.

Week

Placebo
Mepolizumab 75 mg, intravenously
Mepolizumab 100 mg, subcutaneously

Ortega H, MENS A Trial NEJM, 2014
Eosinophil Count as Marker of Efficacy

Reslizumab Clinical Trials

• With elevated eosinophils, improved lung function, QOL, and asthma control

• Population included all levels of eosinophils (n=492)
  ▫ Only subgroup with eosinophil count > 400 showed meaningful improvement
  ▫ Corren J Chest 150 (4):799-810
Predictors of response to Benralizumab

- Analysis of SIROCCO and CALIMA trials
- N= 2295 (combined trials)
- Eosinophil count 0-494
- Greatest effects seen with
  - Higher eosinophil count
  - Greater number of exacerbations

Fitzgerald JM The Lancet Resp Med 2018; 6:51-64
Greater Effect with Higher Eosinophilia

A. Eosinophils ≥300 cells per μL

- Placebo (n=267)
- Benralizumab 30 mg Q4W (n=275)
- Benralizumab 30 mg Q8W (n=267)

Percentage reduction relative to placebo:
- (1.12–1.58)
- ~45%
- ~51%

B. Eosinophils <300 cells per μL

- Placebo (n=140)
- Benralizumab 30 mg Q4W (n=124)
- Benralizumab 30 mg Q8W (n=131)

Percentage reduction relative to placebo:
- (0.96–1.52)
- ~30%
- ~17%

Annual asthma exacerbation rate ratio (95% CI)
Blaiss MS. Ann Allergy Asthma Immun 2017 119(6):533
The Future: Targeting IL-4 and IL-13

- Produced by T cells, mast cells and innate lymphoid cells
- Tralokinumab and Lebrikizumab
  - Targets IL-13
  - Mucous hypersecretion & bronchial hyperresponsiveness
- Dupilumab and Pitrakinra
  - Targets both IL-4 and IL-13
  - T-lymphocyte differentiation, upregulation of IgE, mucous hypersecretion
The Future: Targeting IL-17A and IL-17RA

- Associated with neutrophilic asthma
  - Common in sudden fatal asthma
- Secukinumab (IL-17A)
  - Clinical trial results pending
- Brodalumab (IL-17RA)
  - Improved bronchodilator response but not QOL
Take Home Messages: Asthma

• Meaningful advances in personalized therapy for asthma
  ▫ Measure IgE and eosinophils
    • At least in the difficult to control patient
• Targeting eosinophilic inflammation is efficacious
• Choose wisely
• Don’t overlook the basics
  ▫ Incorrect diagnosis
  ▫ Inhaler technique
  ▫ Compliance
  ▫ Controllable triggers
### Treatment by Class

<table>
<thead>
<tr>
<th>Exacerbations</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td><strong>A</strong></td>
<td>Short acting bronchodilator</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>LAMA or LAMA/LABA</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>LAMA/LABA, LABA/ICS + LAMA</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>LAMA or LABA, Regular Use</td>
</tr>
</tbody>
</table>

- **A**: Short acting bronchodilator
- **B**: LAMA or LABA, Regular Use
- **C**: LAMA or LAMA/LABA, LABA/ICS less preferable
- **D**: LAMA/LABA, LABA/ICS + LAMA
### The New Comers

<table>
<thead>
<tr>
<th></th>
<th>Long Acting beta agonist (LABA)</th>
<th>Long-Acting Muscarinic (LAMA)</th>
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<tbody>
<tr>
<td>Old</td>
<td>Formoterol</td>
<td>Tiotropium</td>
</tr>
<tr>
<td></td>
<td>Salmeterol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>Indacaterol</td>
<td>Umeclidium</td>
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<tr>
<td></td>
<td>Vilanterol</td>
<td>Glycopyrronium</td>
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</table>
"Whatever."

"I'll take that as a 'yes.'"
COPD Drug Therapy: The Age of the Combo and once daily dosing

• ICS/LABA
  ▫ Fluticasone and vilanterol

• LABA/LAMA
  ▫ Tiotropium/Olodaterol
  ▫ Umeclidium/Vilanterol
  ▫ Glycopyrronium/Indacterol

• Triple Threat
  ▫ Fluticasone
  ▫ Umeclidium
  ▫ Vilanterol
Indacaterol-Glycopyrronium v Salmeterol-Fluticasone

- RCT
- 1600 per group
- Mostly Group D
- All had at least 1 exacerbation in prior year
- Longer time to first exacerbation
- Lower rate of exacerbation

Wedzicha, JA New Eng J Med 2016; 374
Drug Therapy in COPD: General Caveats

• Progressive “Step Up” Therapy
  ▫ Single long acting bronchodilator (LABA or LAMA)
  ▫ Add second long acting bronchodilator (LABA + LAMA)
  ▫ Triple therapy

• Inhaled corticosteroid alone NOT indicated
  ▫ Added as third line therapy
    • Personalization needed

• Mortality benefit of drug therapy remains elusive
Nebulized LAMA: Glycopyrrolate

- Only one available nebulized LAMA on market
- Dose 25 mcg BID
- Lonhala Magnair (Sunovion)
  - Portable, closed unit nebulizer
  - 2-3 minute delivery
- Pipeline: Revefenacin
  - Once daily
  - New drug application to FDA in Feb 2018
Mepolizumab: Role in Eosinophilic COPD?

- Two phase 3 trials
  - METREX (n=836)
    - With (462) or without eosinophilia
  - METREO (n=674)
    - All had eosinophilia
    - Two doses studied
- All patients were on LAMA/LABA/ICS
- Endpoint: Exacerbations
  - Overall negative trial
  - About 20% lower rate of moderate to severe exacerbations in those with eosinophilia treated with lower dose
- Greater effect in those with higher eosinophils at baseline

Pavord ID New Eng J Med 2017; 377:1613-1629
Mepolizumab: Role in Eosinophilic COPD?

- GSK seeking FDA approval for patients with COPD and eosinophilia
- $32,500/annually
- Proof of concept study...
Don’t forget the “Forgotten Therapies”

- Smoking cessation...DUH!
- Pulmonary rehabilitation
- Vaccination
- Evaluation of and treatment of concomitant disease (s)
  - Cardiac disease
  - Depression
  - Sleep disordered breathing
- Oxygen
- Transplant or lung volume reduction (surgical or valves)
Take Home Messages: COPD

- Drug therapy for COPD is guided by severity of symptoms and frequency of exacerbations
- Primary treatment includes bronchodilators
- Unlike asthma, ICS are not initially indicated
- Although combination therapy is attractive, single agent use often adequate
See, I told you my doctor could help you quit smoking.