Biologic Agents in the treatment of Severe Asthma

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Paradise
MidMichigan Health
UNIVERSITY OF MICHIGAN HEALTH SYSTEM
Michigan
Hell

Disclosures

- 3 Dogs
  - 2 Bulldogs
  - 1 Dogue de Bordeaux
- Like British TV
- GSK Speaker Bureau (2002 – 2015)

Objectives

- Review Physiology and Impact of Severe Asthma
- Review Conventional Treatment of Severe Asthma
- Introduce Concept of Phenotypically Driven Therapy
- Review Novel Biologic Agents for Treatment of Severe Asthma
  - Physiology
  - Indications
  - Benefits
  - Expense
- Discuss Choice of Agents

Asthma

- **G**lobal **IN**itiative for **A**sthma (**GINA**)
  - Heterogenous disease characterized by chronic airway inflammation
  - Recurrent respiratory symptoms including:
    - Wheeze
    - Dyspnea
    - Chest Tightness
    - Cough
  - Variable expiratory airflow limitation

Asthma

- Burden (USA)
  - 25.5 million patients
    - 20.4 million adults
    - 6.1 million children/adolescents
  - 14.2 million office visits
  - 1.8 million Emergency Department visits
  - 440,000 hospital admissions
  - $50,000,000 direct cost
    - Severe Asthma 5 – 10% of cases
    - 50% of direct care costs

Goals of Treatment

Symptom Control

- Normal activity levels
  - patient defined

Risk reduction

- Minimize exacerbation risk
- Limit fixed airflow obstruction
  - normal intercurrent spirometry

Minimize Side Effects

- Minimal medication to achieve goals

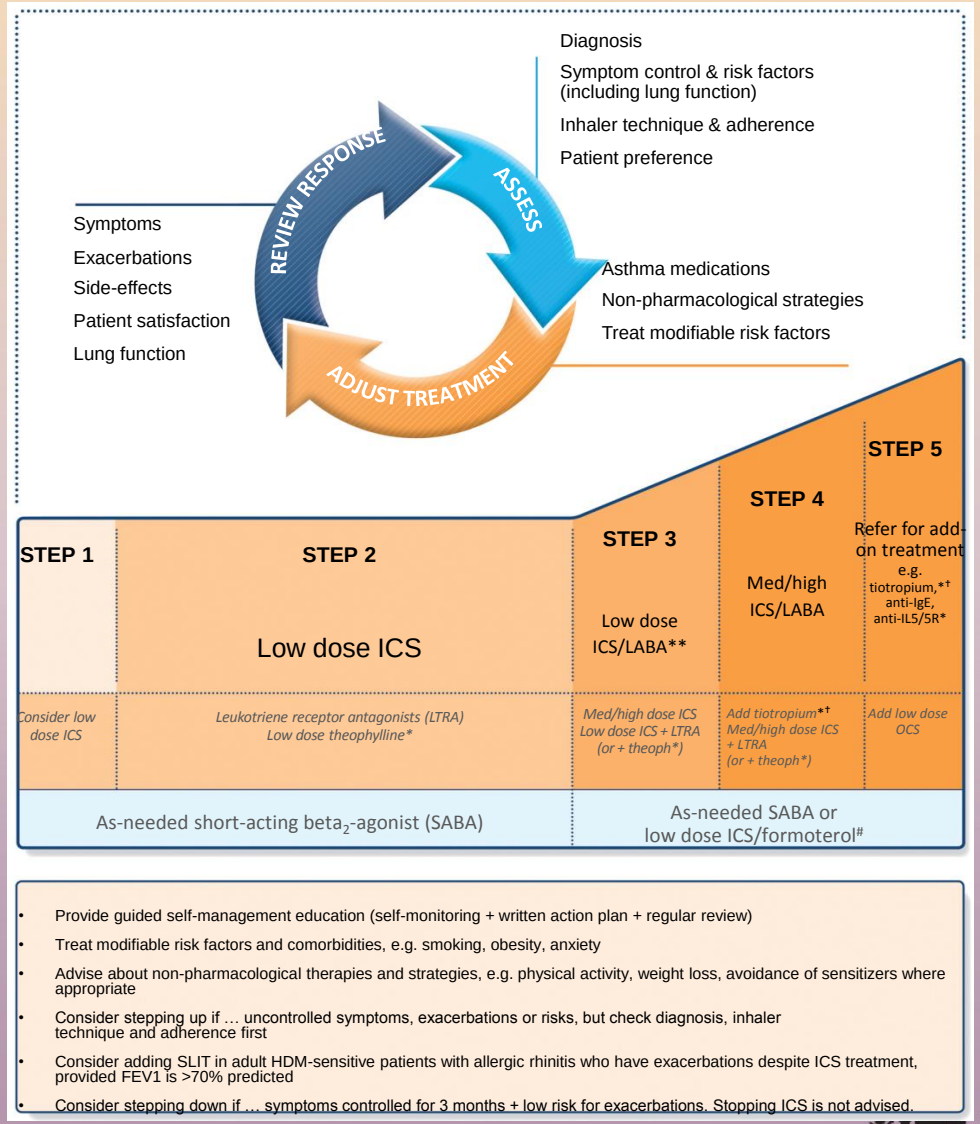
Treatment

- Nonpharmacologic
  - Individualized
  - **SMOKING CESSATION**
    - Including avoidance of second-hand exposure
  - Environmental Manipulation
    - Identified allergens
      - Environmental
      - Food
    - Nonspecific irritants
    - Occupational
  - Physical Activity
  - Avoidance of Medications That May Worsen Asthma
  - Asthma Action Plan
  - OMT

Treatment

- Pharmacologic
  - Individualized
  - Inhaled preferred
  - MDI/DPI preferred
    - Training and observation in inhaler use
  - Systemic therapy
    - Required for more severe disease
  - Stepwise
    - Also used to define level of severity

Stepwise approach to control asthma symptoms and reduce risk



Asthma

- Severity
  - Assessed retrospectively
    - Based on treatment required to achieve control
  - Not Static
    - Changes over time with treatment

Mild: well-controlled Step 1 or 2

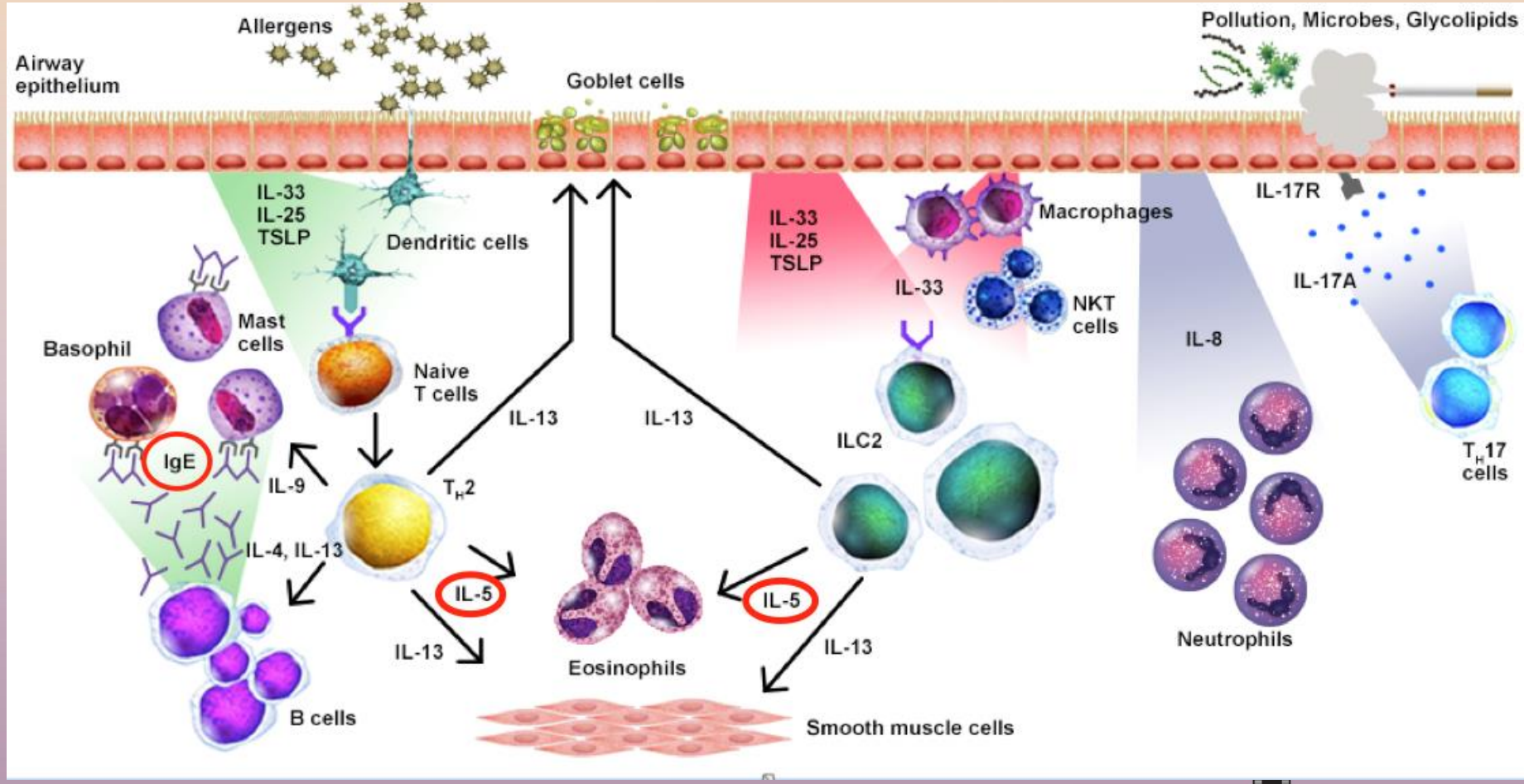
Moderate: well controlled Step 3

Severe: requires Step 4 or 5 treatments for control
uncontrolled
systemic steroid dependent

Treatment

- Step 5 / Severe Asthma
  - Medium to High Dose LABA/ICS
    - Trial of increased dose ICS
  - LAMA
  - AntiLeukotriene (LTRA)
    - Montelukast
    - Zafirlukast
    - Zileuton
  - Systemic Corticosteroids
  - Phenotype-Guided Treatment
    - Biologics
  - Bronchial Thermoplasty
    - Controversial

Inflammation



Phenotype Guided Treatment

- Allergic
  - Increased IgE
  - Hypereosinophilic
  - Identified allergen(s)
- Non-allergic
  - Hypereosinophilic
- Aspirin Exacerbated

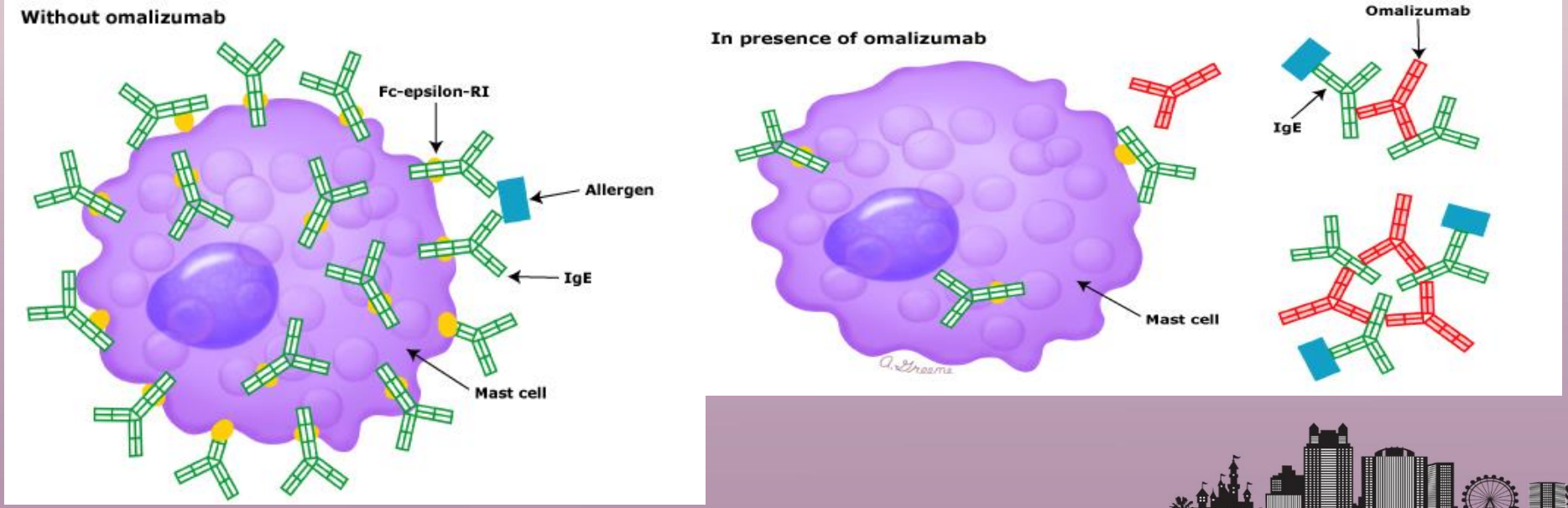
- Late Onset
- Asthma with Obesity
- COPD Crossover

Biologic Treatments

- Anti-IgE
  - Omalizumab (XOLAIR)
- Anti IL-5
  - Mepolizumab (NUCALA)
  - Reslizumab (CINQAIR)
  - Benralizumab (FASENRA)

Omalizumab (XOLAIR)

- Recombinant humanized IgG1 monoclonal antibody
  - High affinity for IgE (specific)
  - Binds to IgE at the same site which binds to IgE receptors
  - Omalizumab-IgE complex cleared hepatic RE system



Omalizumab (XOLAIR)

- Decreased Free IgE
- Downregulation of Fc-epsilon-RI
  - Basophils
  - Mast Cells
- Decreased allergen responsiveness
- Minimal (if any) improvement in FEV_1
- Minimal (if any) change in bronchial hyperreactivity

- Decreased airway inflammation
- Total IgE levels increase
- Blood Eosinophils decrease
- Skin test responses and allergen specific IgE assays blunted

Omalizumab (XOLAIR)

- Indications
  - Age > 5 years
  - Moderate to Severe Asthma
  - Incompletely controlled with ICS
  - Total IgE 30 – 700 IU/mL
    - 30 – 1300 IU/mL children 6 – 11 years old
  - Positive response to perennial aeroallergen(s)
- Improved response with Eosinophil Count >300
- Dosage based on IgE level and patient weight

Omalizumab (XOLAIR)

- Clinical Benefits
  - Decreased incidence of exacerbation
  - Decreased ICS dose
  - Decreased systemic corticosteroid requirement
  - Improved QOL scores
  - Improved ACT scores
- Approved 2003
- Cost $12,000 - $ 70,000 annually
- Black Box Warning
  - Anaphylaxis (<1%)

Omalizumab (XOLAIR)

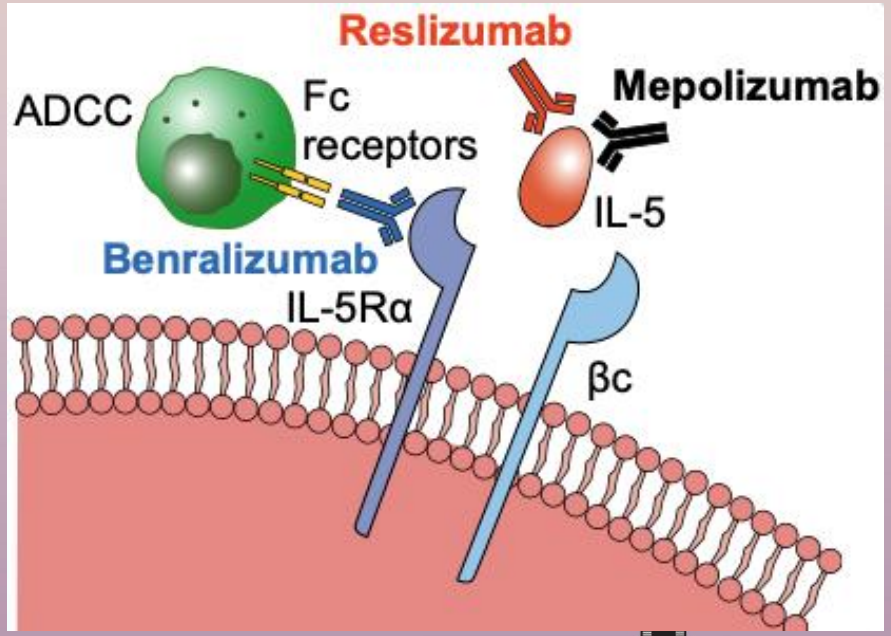
- Adverse Effects
  - Anaphylaxis
    - Majority 1st – 2nd dose
    - < 1 hour
  - Local Site Reactions
  - Headache
  - Fever / Arthralgia / Rash
  - ? Increased Risk of Helminthic Infections
- Not Indicated for Acute Exacerbation

Anti IL-5 Treatments

- IL-5 major cytokine regulating differentiation, recruitment , activation and survival of eosinophils

- IL-5 Receptor Antibody
  - Benralizumab (FASENRA)

- Direct IL–5 Antibody
  - Mepolizumab (NUCALA)
  - Reslizumab (CINQAIR)



Mepolizumab (NUCALA)
Reslizumab (CINQAIR)

- Humanized IgG1 monoclonal antibody
- Binds IL-5
  - Blocks attachment to IL-5 receptor (alpha)
  - Inhibits IL-5 activity and signaling
  - Decreases production and survival of eosinophils
  - Mechanism of action not definitively established
- Degraded by widely distributed proteolytic enzymes

Mepolizumab (NUCALA)
Reslizumab (CINQAIR)

- Decreased eosinophil count
- Improved airway structure
  - Decreased reticular basement membrane thickening
- Clinically significant improvement in FEV1
  - Degree of improvement dependent on pretreatment eosinophil count
  - Not evident in early studies
- Clinically significant improvement in QOL
  - St George's Respiratory Questionnaire
  - Degree of improvement NOT dependent on pretreatment eosinophil count
- Minimal (if any) improvement in bronchial hyperreactivity

Mepolizumab (NUCALA)

- Indications
  - Age > 11 years
  - Severe Asthma
    - Incompletely controlled on Step 4 Therapy
    - Recurrent exacerbations
    - Chronic systemic corticosteroids
  - Eosinophilic Phenotype
    - > 150 / microL
- Dosage: 100 mcg SQ every 4 weeks

Reslizumab (CINQAIR)

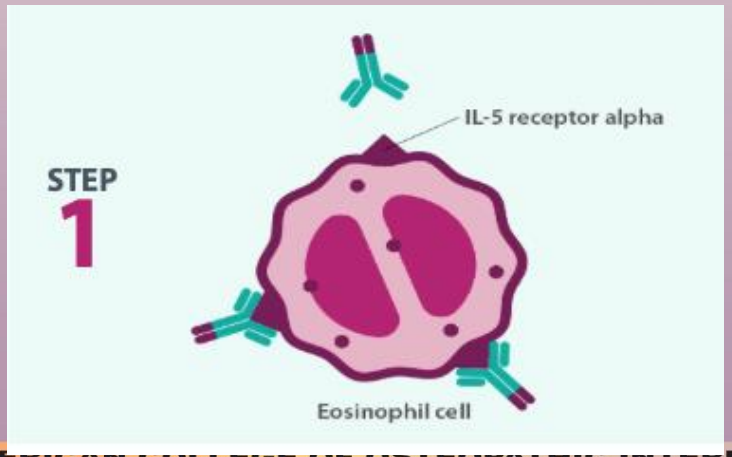
- Indications
  - Age > 17 years
  - Severe Asthma
    - Incompletely controlled on Step 4 Therapy
    - Recurrent exacerbations
    - Chronic systemic corticosteroids
  - Eosinophilic Phenotype
    - > 400 / microL
- Dosage 3mg/kg IV (20 – 50min.) every 4 weeks
- Black Box Warning:
  - Anaphylaxis 0.3%
  - Second (+) dose

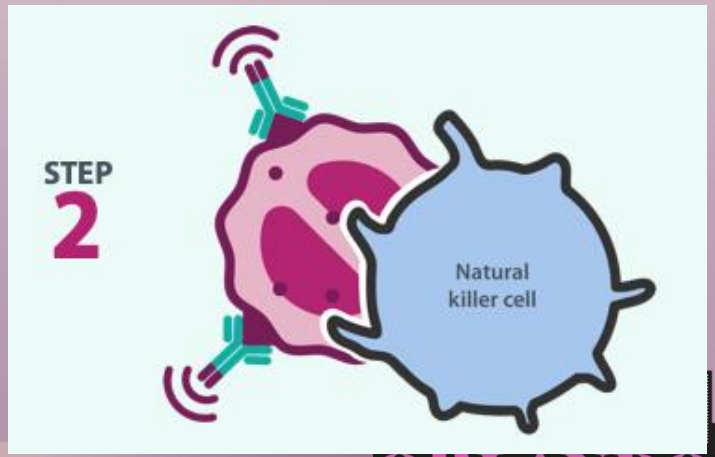
Mepolizumab (NUCALA)
Reslizumab (CINQAIR)

- Clinical Benefits
  - Decreased incidence of exacerbation
  - Improved QOL scores
  - Decreased systemic corticosteroid requirement
    - mepolizumab
- Mepolizumab
  - Approved 2015
  - Cost $ 32,500 annually
- Reslizumab
  - Approved 2016
  - Cost $ 20,040 - $ 40,080 annually
    (+administration costs)

Benralizumab (FASENRA)

- Humanized IgG1 monoclonal antibody
- Binds IL-5 (alpha subunit) receptor
  - Blocks IL-5 attachment
  - Induces apotosis of eosinophils (and basophils)
    - Enhanced antibody dependent cytotoxicity
  - Mechanism of action not definitively established
- Degraded by widely distributed proteolytic enzymes





Benralizumab (FASENRA)

- Dramatic (near 100%) and rapid reduction in Eosinophil Count
  - Sustained x 12 weeks
  - Decreased recruitment, activation, mobilization
  - Antibody dependent cytotoxic properties
    - Depletion / apoptosis circulating and tissue eosinophils
- Clinically significant improvement in FEV1
- Improvement in QOL

Benralizumab (FASENRA)

- Indications
  - Age > 11 years
  - Severe Asthma
    - Incompletely controlled on Step 4 Therapy
    - Recurrent exacerbations
  - Eosinophilic Phenotype
    - > 300 /microL
- Dosage
  - 30 mg every 4 weeks x 3 then
  - 30 mg every 8 weeks
- Warnings
    - Helminthic infections

Benralizumab (FASENRA)

- Clinical Benefits
  - Decreased incidence of exacerbations
    - Single dose use in ER setting
  - Improved FEV1
  - Improved QOL scores
  - Decreased systemic corticosteroid requirement
- Approved 2017
  - Cost $ 60,000 first year then $ 30,000 annually

IL-5 Inhibitors

- Adverse Effects
  - Anaphylaxis (reslizumab) 0.3%
  - Local Site Reaction
  - Headache
  - Shingles (mepolizumab)
  - Neutralizing antibodies (benralizumab)
  - ? Risk for helminthic infection
- Not Indicated for Acute Exacerbation

Conclusions

- Conventional treatment of Severe Asthma is inadequate
  - Incomplete resolution of symptoms
  - Oral corticosteroids
- Novel Biologic Agents provide safe and effective treatment of Severe Asthma
  - Improved symptomatology
  - Improved Quality of Life
  - Improved physiologic parameters
    - Eosinophil Count
    - Airway Inflammation
    - FEV1
  - Decreased (if not eliminated) systemic corticosteroids
- Extremely Expensive

- How do we choose when to use biologic agents?
- If we're going to use a biologic agent, which one?

When to Use Biologic Agents

- Severe Persistent Asthma
  - Corticosteroid dependent
  - Recurrent exacerbations (> annually)
  - Maximal Conventional Therapy
    - ICS/LABA
    - LAMA
    - LTRA
  - Proper use of inhalers
  - Documented compliance
- Add-on-Therapy

Which Agent to Use?

- Phenotypically Driven
  - Atopic (IgE)
    - omalizumab
  - Hypereosinophilic
    - IL-5 / IL-5 RA
  - Atopic / Hypereosinophilic
    - No direct comparison studies
    - Indirect studies
      - Comparing response to placebo

IL-5 / IL5-RA

- No Direct Comparative Studies
  - Route of Administration
  - Risks
  - Cost
  - Experience

Atopic / Hypereosinophilic Phenotype

- Eligible for either anti IL-5 or anti IgE therapy
  - Indirect Studies comparing omalizumab and mepolizumab
    - Reductions in exacerbations compared to placebo of similar magnitudes (47% vs 50%)
    - No significant difference in FEV1 improvement vs placebo
    - No significant difference in QOL scores vs placebo

Atopic / Hypereosinophilic Phenotype

- Recommendation
  - Trial of omalizumab x 16 weeks
    - If good response continue
    - If inadequate response trial of IL-5 / IL-5RA
  - Based on cost, experience, effect of omalizumab on eosinophil count and potential long term effect
  - May change
- No trials of combination therapy

Summary

- Monoclonal Antibodies provide a safe and effective addition to the therapeutic armamentarium
- Expensive
  - Cost offset by decreased hospitalizations, ER visits, and unplanned office visits
  - Effect on mortality?
- Limited Applicability
  - Severe Asthma (5 – 10%)
  - Uncontrolled with conventional therapy