Biologic Agents in the treatment of Severe Asthma

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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

• Global INitiative for Asthma (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

**Diagnosis**
- Symptom control & risk factors (including lung function)
- Inhaler technique & adherence
- Patient preference

**Asthma medications**
- Non-pharmacological strategies
- Treat modifiable risk factors

**Symptoms**
- Exacerbations
- Side-effects
- Patient satisfaction
- Lung function

**Step 1**
- Consider low dose ICS

**Step 2**
- Low dose ICS

**Step 3**
- Low dose ICS + LTRA
- Med/high dose ICS + LTRA (or + theoph*)

**Step 4**
- Med/high ICS/LABA
- Add tiotropium**
- Add anti-IgE
- Add anti-IL5/5R*

**Step 5**
- Refer for add on treatment
  - e.g. tiotropium,**
  - anti-IgE,
  - anti-IL5/5R*

**Preferred Controller Choice**

**Other controller options**

**Reliever**
- As-needed short-acting beta2-agonist (SABA)
- As-needed SABA or low dose ICS/formoterol#

**Remember To…**
- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Stopping ICS is not advised.
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 apoptosis 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