Disclosures

I have no conflicts and nothing to disclose.
Asthma Treatment Update: 2018

- Asthma pathophysiology
- Asthma care guidelines
- Newer uses of medications for asthma treatment
- Biological agents for severe asthma
- Bronchial Thermoplasty
Implications of Uncontrolled Asthma (U.S.)¹

13.9 million
People experience asthma attacks

10.6 million
Asthma physician office visits

2.1 million
Emergency department visits

479,300
Hospitalizations

3,388
Asthma-related deaths

Higher Cost of Severe Asthma (U.S.)

Higher healthcare costs with asthma severity

Severe Asthma:

“Asthma that, despite patient adherence, requires high-dose ICS plus LABA and/or additional controller medication or requires oral corticosteroids (OCSs) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.”

Asthma Definition

Asthma is a chronic disease of the airways, with the following features:

- Airway obstruction that is reversible (although not always completely)
- Airway inflammation
- Airway hyperreactivity (i.e. increased responsiveness to various stimuli)
Airway Inflammation

Bronchial lining is infiltrated with:
  - Eosinophils
  - Mast cells
  - Lymphocytes

Inflammation is variable across patients and within the same patient at different times

BAL of asthmatic airway showing abundant inflammation, especially with eosinophils.
Asthma Pathology

Ref. #5

Report of an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP), coordinated by the NHLBI.


Monitoring asthma control as the goal for asthma therapy:

› Severity: the intrinsic intensity of the disease process.
› Control: the degree to which the manifestations of asthma are minimized by therapy.

Impairment and Risk:

› Impairment: the frequency and intensity of symptoms and functional limitations.
› Risk: the likelihood of asthma exacerbations, progressive decline in lung function or adverse effects from medication.

Modifications to the stepwise approach to managing asthma long term.
Asthma patient: Severity?

45 y.o. male with 3 year history of asthma. 
He has been treated with albuterol as needed to control symptoms. 
He has asthma symptoms most days and uses his albuterol 6 times per week. 
He has had 3 exacerbations that required prednisone over the last year. 
He has rare nocturnal asthma episodes, but has stopped exercising, since this often worsens his asthma. 
Baseline FEV1 is 70% predicted.

What is the severity of this patient’s asthma?
Asthma patient: Severity?

1. Intermittent.
2. Mild Persistent.
3. Moderate Persistent.
4. Severe Persistent.
Asthma patient: Severity?

1. Intermittent.
2. Mild Persistent.
3. Moderate Persistent.
4. Severe Persistent.
Classification of Asthma Severity and Initiating Therapy

Remember the rule of “2s.”
Use the highest impairment and risk findings to categorize the patient.
Asthma Severity (12 and Older)
NHLBI EPR-3 Panel Report

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (Youths ≥12 years of age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
</tr>
<tr>
<td>Normal FEV/FVC:</td>
<td></td>
</tr>
<tr>
<td>8-19 yr 85%</td>
<td>&lt;2 days/week</td>
</tr>
<tr>
<td>20-39 yr 80%</td>
<td>≤2 days/month</td>
</tr>
<tr>
<td>40-59 yr 75%</td>
<td>&lt;2 days/week</td>
</tr>
<tr>
<td>60-69 yr 70%</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>Normal FEV, between exacerbations</td>
<td>FEV &lt;80% predicted</td>
</tr>
<tr>
<td>FEV/FVC normal</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0-1/year</td>
</tr>
<tr>
<td>requiring oral</td>
<td>Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.</td>
</tr>
<tr>
<td>systemic corticosteroids</td>
<td>Relative annual risk of exacerbations may be related to FEV₁</td>
</tr>
</tbody>
</table>
Asthma Management (12 and Older)
NHLBI EPR-3 Panel Report

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-relief medication for all patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Peak Expiratory Flow (PEF, Day-to-Day Mean) in the Morning and Evening.
Twice Daily Budesonide vs. Terbutaline
Effects of Inhaled Steroids on Airway Inflammation

Airway cells before and after 3 months of Budesonide treatment

### Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children: Symptom-free Days

**Cochrane Database of Systematic Reviews**

16 MAY 2012 DOI: 10.1002/14651858.CD002314.pub3


<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Anti-leukotriene</th>
<th>Inhaled steroids</th>
<th>Mean Difference (95% CI)</th>
<th>Weight</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediactrics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'connor 2005</td>
<td>167</td>
<td>31.3 (43.94)</td>
<td>168</td>
<td>37.7 (46.67)</td>
<td>103 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>167</td>
<td>168</td>
<td>10.3 %</td>
<td></td>
<td>-6.40 [-15.82, 3.02]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordson 2000</td>
<td>215</td>
<td>15.6 (34.11)</td>
<td>225</td>
<td>26.5 (39.52)</td>
<td>18.3 %</td>
</tr>
<tr>
<td>Recently 2005</td>
<td>278</td>
<td>46.1 (34.1)</td>
<td>354</td>
<td>49.5 (67)</td>
<td>25.1 %</td>
</tr>
<tr>
<td>Davies 2001</td>
<td>111</td>
<td>61.7 (34.1)</td>
<td>113</td>
<td>21.2 (45.2)</td>
<td>5.1 %</td>
</tr>
<tr>
<td>FDLH4301</td>
<td>168</td>
<td>9.4 (34.3)</td>
<td>101</td>
<td>22.2 (45.2)</td>
<td>8.6 %</td>
</tr>
<tr>
<td>FDLH4301</td>
<td>113</td>
<td>11.7 (37.21)</td>
<td>111</td>
<td>23.4 (61.61)</td>
<td>11.2 %</td>
</tr>
<tr>
<td>Hoang 2008</td>
<td>164</td>
<td>-10 (24.58)</td>
<td>159</td>
<td>-9.5 (48.65)</td>
<td>16.4 %</td>
</tr>
<tr>
<td>Sheth 2001</td>
<td>55</td>
<td>17.6 (88)</td>
<td>51</td>
<td>28.1 (79)</td>
<td>Not estim</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1044</td>
<td>1044</td>
<td>99.7 %</td>
<td></td>
<td>-9.18 [-12.38, -5.98]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1211</td>
<td>1212</td>
<td>100.0 %</td>
<td></td>
<td>-8.89 [-11.97, -5.87]</td>
</tr>
</tbody>
</table>

**Heterogeneity:** $I^2 = 5.45$, $Q = 6.36$, $P = 0.5$; $I^2 = 5.63$, $Q = 0.00001$

**Test for overall effect:** $Z = 2.57$, $P = 0.01$

**Test for subgroup differences:** $Z = 2.57$, $P = 0.01$

**Note:** Not estimatable.
Effect of Inhaled Formoterol and Budesonide on Exacerbations of Asthma
Romain A. Pauwels, M.D., Claes-Göran Löfdahl, M.D., Dirkje S. Postma, M.D., Anne E. Tattersfield, M.D., Paul O’Byrne, M.B., Peter J. Barnes, D.M., and Anders Ullman, M.D. for the Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group
Combination of ICS/LABA Improves Asthma Control
Mometasone/formoterol vs. components and asthma control

Asthma Control

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ICS+LABA Mean (SD)</th>
<th>N</th>
<th>ICS Mean (SD)</th>
<th>SMD (Random) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning PEF (l/min) change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyd ICS1675</td>
<td>17</td>
<td>54.00 (41.60)</td>
<td>20</td>
<td>28.0 (50.10)</td>
<td></td>
</tr>
<tr>
<td>Kawara FP400</td>
<td>29</td>
<td>52.50 (49.46)</td>
<td>28</td>
<td>17.3 (40.57)</td>
<td></td>
</tr>
<tr>
<td>Kemp ICNSN</td>
<td>84</td>
<td>47.00 (38.73)</td>
<td>85</td>
<td>14.0 (52.59)</td>
<td></td>
</tr>
<tr>
<td>Shapiro FP1000</td>
<td>27</td>
<td>53.50 (50.40)</td>
<td>27</td>
<td>15.2 (41.40)</td>
<td></td>
</tr>
<tr>
<td>Reduction Rescue Beta-agonist 24 hr use (puffs/absolute) from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyd ICS1675</td>
<td>18</td>
<td>3.10 (4.70)</td>
<td>21</td>
<td>2.50 (4.00)</td>
<td></td>
</tr>
<tr>
<td>Kawara FP400</td>
<td>29</td>
<td>1.90 (2.43)</td>
<td>28</td>
<td>0.40 (1.94)</td>
<td></td>
</tr>
<tr>
<td>Kemp ICNSN</td>
<td>84</td>
<td>3.48 (3.02)</td>
<td>83</td>
<td>1.25 (2.25)</td>
<td></td>
</tr>
<tr>
<td>Shapiro FP1000</td>
<td>27</td>
<td>2.30 (3.60)</td>
<td>27</td>
<td>0.90 (1.80)</td>
<td></td>
</tr>
<tr>
<td>% Symptom Free days change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyd ICS1675</td>
<td>18</td>
<td>22.00 (30.0)</td>
<td>21</td>
<td>13.00 (22.00)</td>
<td></td>
</tr>
<tr>
<td>Kawara FP400</td>
<td>29</td>
<td>22.60 (42.81)</td>
<td>29</td>
<td>7.20 (37.70)</td>
<td></td>
</tr>
<tr>
<td>Kemp ICNSN</td>
<td>84</td>
<td>38.10 (36.5)</td>
<td>84</td>
<td>13.60 (28.69)</td>
<td></td>
</tr>
<tr>
<td>Shapiro FP1000</td>
<td>27</td>
<td>33.80 (41.4)</td>
<td>27</td>
<td>15.40 (37.80)</td>
<td></td>
</tr>
</tbody>
</table>

Total N = 473
Test for heterogeneity: p = 0.94
Test for overall effect: p < 0.0001
Should Patients with Controlled Asthma on ICS/LABA be Switched to Inhaled Steroids Alone?

First Serious Asthma-Related Event (Death, ET intubation, Hospitalization)
Budesonide-Formoterol in Combination Reduces the Risk of Asthma Exacerbation by 16.5%

Time to First Asthma Exacerbation

Hazard ratio, 0.84 (95% CI, 0.74–0.94)
Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids

Review: Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids
Comparison: 1 Stopped LABA vs continued LABA+ICS
Outcome: 1 Exacerbation: systemic corticosteroids

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>LABA stopped</th>
<th>LABA continued</th>
<th>Odds Ratio M-H,Random, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger 2010 (1)</td>
<td>2/144</td>
<td>1/152</td>
<td></td>
<td>9.5%</td>
<td>2.13 [0.19, 23.71]</td>
</tr>
<tr>
<td>Godard 2008 (2)</td>
<td>16/154</td>
<td>9/154</td>
<td></td>
<td>76.3%</td>
<td>1.87 [0.80, 4.37]</td>
</tr>
<tr>
<td>GSK SAS40037 (3)</td>
<td>1/161</td>
<td>1/161</td>
<td></td>
<td>7.1%</td>
<td>1.00 [0.06, 16.13]</td>
</tr>
<tr>
<td>Koenig 2008 (4)</td>
<td>1/159</td>
<td>1/172</td>
<td></td>
<td>7.1%</td>
<td>1.08 [0.07, 17.45]</td>
</tr>
</tbody>
</table>

Total (95% CI) 618 639 100.0% 1.74 [0.83, 3.65]

Total events: 20 (LABA stopped), 12 (LABA continued)
Heterogeneity: Tau² = 0.0; Chi² = 0.32, df = 3 (P = 0.96); I² = 0.0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

(1) "A clinical exacerbation was defined as an exacerbation requiring emergency treatment, hospitalization, or use of an asthma medication not allowed by the protocol" (assumed to
(2) Requiring oral corticosteroids
(3) "Any use of systemic corticosteroids" (From Brozek 2012. obtained from study sponsor)
(4) Data for Koenig 2008 and SAS40037 have been incorporated with permission from Brozek et al (provided to them by the study sponsor)
Is Adding An Anticholinergic Helpful?

What Is the Role of Tiotropium in Asthma?:
A Systematic Review With Meta-analysis
Gustavo J. Rodrigo, MD; José A. Castro-Rodríguez, MD, PhD
Lung Function and Severe Exacerbations.

A FEV₁ Change in Trial 1

C Severe Exacerbation

No. at Risk
Placebo 454 435 412 338 379 367 356 339 332 319 303 290 282 272
Tiotropium 453 430 409 401 389 378 363 353 348 339 331 319 308 298
Why Not Prednisone?
Costs Per Patient Year of Oral Corticosteroids

Figure 2. Cost per Patient Year of OCS Related AEs.

Stephanie C. Manson, Ruth E. Brown, Annamaria Cerulli, Carlos Fernandez Vidaurre

The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use
Respiratory Medicine, Volume 103, Issue 7, 2009, 975–994
http://dx.doi.org/10.1016/j.rmed.2009.01.003
Short-acting Beta2-agonists

Low-dose Inhaled Corticosteroids (ICS)

Low-dose ICS + Long-acting Beta2-agonists (LABA) or Medium-dose ICS

Medium-dose ICS + LABA

High-dose ICS + LABA and Consider Omalizumab

High-dose ICS + LABA + Oral Corticosteroids and Consider Omalizumab

41 y.o. female with a history of asthma since the age of 2.
• Worsening symptoms of wheezing, cough and shortness of breath.
• Had required increasing medications for worsening asthma
  • Treated with mometasone/formoterol, beclomethasone dipropionate, tiotropium, intermittent azithromycin.
• 25 ER visits or hospitalizations in the last 2 years.
• On daily prednisone 10-20 mg.
Asthma Patient

- FEV1 is 1.41 L - 26% predicted.
- History of severe reflux-improved after Nissen fundoplication.
- Prior allergy testing (RAST) positive for tree pollens, grass pollens and molds.
- IgE level 26 IU/L (normal 20-158).
- Eosinophil count 1,220 /cumm.
- RAST to Aspergillus is negative.
- Serum Aspergillus antigen is negative.
- Aspergillus antibodies by CF is negative.
- Bronchial culture is negative for bacterial, AFB or fungal organisms.
What other treatments might you consider for this patient?
1. Omalizumab
2. Mepolizumab
3. Daily prednisone
4. Bronchial Thermoplasty
Asthma Patient

What other treatments might you consider for this patient?
1. Omalizumab
2. Mepolizumab
3. Daily prednisone
4. Bronchial Thermoplasty
IgE Production

**Nature Reviews | Drug Discovery**

**IgE Production**

**a** IgM → TCR → Naive B cell → Peptide-MHC class II → T<sub>1,2</sub> cell → IL-4, IL-13 → IgE-positive memory B cell expansion → IgE production by plasma cells

**b** IgE production → IgE-positive memory B cell

**c** Type 1 hypersensitivity

- Antigen → FcεRI → Degranulation → Mast cell
- Vasoactive amines (histamine)
- Lipid mediators (PGD<sub>2</sub>, PAF, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>)
- Cytokines (IL-3, IL-4, IL-5, IL-13)
- Chemokines
IgE Structure
Olmalizumab Binding to IgE
Anti-IgE Treatment for Severe Asthma

Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. William Busse, MDa, Jonathan Corren, MD, Bobby Quentin Lanier, MDc, Margaret McAlary, MSd, Angel Fowler-Taylor, RPh, Giovanni Della Cioppa, MD, Andre van As, MD, PhD, Niroo Gupta, MD, PhD


- Double-blinded, placebo-controlled trial, 525 subjects with severe allergic asthma requiring daily inhaled corticosteroids.
- Randomized to receive placebo or omalizumab subcutaneously every 2 or 4 weeks.
- Inhaled corticosteroid doses were kept stable over the initial 16 weeks of treatment and tapered during a further 12-week treatment period.
Omalizumab Treatment: Asthma Symptom Scores and Medication Use
Omalizumab (Xolair): When to Use

- Patients 12 years and older with moderate to severe asthma, not well controlled on Inhaled corticosteroids or ICS/LABA combination.
- IgE levels 30-700 IU/L.
- Evidence of sensitivity to inhalant allergens (ideally perennial) by skin test or RAST.
- History of worsening asthma symptoms with exposure to allergens.
- Consider as add on therapy for allergic bronchopulmonary aspergillosis.
The Role of Eosinophils in Allergic Inflammation

Diagram showing the interaction between mast cells, eosinophils, and the immune system, highlighting the role of eosinophils in allergic inflammation.
Mepolizumab: A fully humanized anti-IL-5 monoclonal IgG(1) antibody that binds to free IL-5 with high affinity and specificity to prevent IL-5 from associating with the IL-5 receptor complex alpha-chain on the surface of eosinophils.
Mepolizumab

Haldar et al. NEJM 2009.

• Asthmatics with refractory symptoms, despite usual care and sputum eosinophils > 3%.
• History of at least 2 exacerbations requiring rescue prednisolone in the previous 12 months (mean of 5 for each group).
• 29 treated with Mepolizumab 750 mg IV monthly vs 32 placebo
• Mean eosinophil count in blood was 320 in the Mepolizumab group.
• 57% of the treated group were on daily prednisone.
Mepolizumab effects on exacerbations

Hader et al. NEJM 2009.
Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma


135 patients (69 active vs 66 placebo) with severe eosinophilic asthma

- All patients had a 6 month history of daily prednisolone (5-35 mg/d)
- 300 eos/cc microliter before study or 150 eos/cc microliter during optimization.
- All patients were on high dose inhaled corticosteroids and LABA or other controller.

Mepolizumab 100 mg SQ monthly for 20 weeks vs placebo.

Primary outcome was reduction in steroid use.

Secondary outcomes: Rate of asthma exacerbations, asthma control and safety.
A. Reduction in Oral steroid dose
B. Asthma exacerbations
C. Asthma quality of life scores
Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma


576 patients with recurrent exacerbations

- At least 2 exacerbations in the prior year that required corticosteroids, despite high dose inhaled steroids and a second controller.
- Eosinophilia of 300 eos/cu microliter in the prior year or 150 eos/cu microliter at study entry.
- 25% of patients were on daily prednisone

Assigned to monthly Mepolizumab 75 mg IV, 100 mg SQ or placebo.
Primary outcome was frequency of exacerbations.
Asthma exacerbations and FEV1 at 32 weeks.
Mepolizumab in patients who have been treated with Omalizumab

Post hoc analysis of patients from 2 prior randomized trials of Mepolizumab.

Mepolizumab: When to use it:

- Patients 12 years and older with severe asthma, not controlled on current medical therapy.
  - High dose inhaled steroids with a second controller (LABA, Leukotriene blocker, theophylline).
  - High dose inhaled steroids and oral corticosteroids.
- Evidence of eosinophilic asthma: >150 cells/μl within 6 weeks of starting therapy, or >300 cells/μl within 12 months of starting therapy.
Reslizumab for Inadequately Controlled Asthma: Castro et al. 2015.

Two Phase III studies of 953 patients with eosinophilic asthma (>400 cell/ccmm). Monthly Reslizumab 3.0 mg/kg monthly vs. Placebo. Followed for 1 year.
Figure 3. Time to first exacerbation in two Phase IIIb clinical trials of reslizumab on eosinophilic asthma reported by Castro et al. The addition of reslizumab to usual asthma controller therapy significantly reduced the time to first CAE in both trials (A and B). Subgroup analysis showed that the greatest effect occurred in participants using OCS at baseline (C).

Published in: Juan Carlos Cardet; Elliot Israel; Expert Opinion on Biological Therapy. 2015, 15, 1531-1539. DOI: 10.1517/14712598.2015.1099372
Copyright © 2015 Informa UK, Ltd.
Reslizumab (Cinqair): When to use it

- Severe asthma patients 18 and older not controlled on inhaled steroids.
- Experiencing significant exacerbations.
- Evidence of eosinophilic asthma with more than 400 cells/microliter within 12 months of starting therapy.
Benralizumab: IL-5 Receptor Inhibitor: Binds to IL-5 Receptor and Results in Eosinophil Death by Natural Killer Cell-Mediated Cytotoxicity
Benralizumab Treatment Allows for Reduction in the Oral Glucocorticoid Dose

A Change from Baseline in Oral Glucocorticoid Dose

No. at Risk
- Benralizumab 30 mg, every 4 wk: 72, 70, 70, 69, 69, 68, 66, 68
- Benralizumab 30 mg, every 8 wk: 70, 72, 67, 69, 69, 66, 69, 68
- Placebo: 74, 75, 73, 74, 74, 73, 73, 72

Benralizumab Treatment Results in Fewer Asthma Exacerbations

![Graph showing time to first asthma exacerbation with different treatment groups.]

IL-4 and IL-13 in Eosinophilic Asthma
IL-13 and IL-4 Signaling
Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

- Patients receiving a long-acting beta-agonist (LABA) and inhaled glucocorticoid for asthma were given dupilumab, a monoclonal antibody to part of the IL-4 receptor, with the LABA and inhaled glucocorticoid withdrawn.
- There were fewer exacerbations with dupilumab than with placebo.
Dupilumab Treatment Significantly Reduces Asthma Exacerbations

A. Exacerbations — Primary End Point

<table>
<thead>
<tr>
<th></th>
<th>Proportion of Patients with Exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=52)</td>
<td>44%</td>
</tr>
<tr>
<td>Dupilumab (N=52)</td>
<td>6%</td>
</tr>
</tbody>
</table>

87% reduction
P<0.001
Note: Although chronic OCS is an accepted therapy in the NAEPP and GINA guidelines, the panel recommends that all other therapies be considered prior to employing maintenance OCS.
Role of Airway Smooth Muscle on Asthma

Normal Airway

Asthma Attack
BT Reduces Excess Airway Smooth Muscle

Effect of methacholine on canine asthmatic airways.

Untreated airway (arrow-right) and airway treated with bronchial thermoplasty (left)
Bronchial Thermoplasty
Asthma Intervention Research 2 (AIR2) Trial

Pivotal U.S. study to evaluate safety and effectiveness of BT with the Alair™ System in adult patients with severe asthma.

† Study Population: patients with severe persistent asthma symptomatic despite high dose ICS (>1,000 mg/d beclomethasone or equivalent) + LABA (>100 mg/d salmeterol or equivalent).²

2. Severe asthma classification based on treatment in Steps 5 or 6 per the NAEPP 2007 guidelines.
Improved Asthma-Related Quality of Life (AQLQ Score)\(^1\)

BT group demonstrated a clinical treatment effect over the sham group.

AQLQ score for patients treated with BT increased 1.35 over baseline through 12 months (integrated AQLQ).

<table>
<thead>
<tr>
<th></th>
<th>BT (N=190)</th>
<th>Sham (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>1.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Difference in AQLQ score between groups was 0.21 (PPS=96.0%).

Clinical treatment effect persistent across 6, 9, and 12 months.

## AIR2 Respiratory Adverse Events\(^1,2\)

Selected AEs with >3% incidence and difference between groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Period (~12 weeks)</th>
<th>Post-Treatment Period (~46 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BT (N=190) %</td>
<td>Sham (N=98) %</td>
</tr>
<tr>
<td>Asthma (Multiple Symptom)</td>
<td>52.1</td>
<td>38.8 *</td>
</tr>
<tr>
<td>Wheezing</td>
<td>15.3</td>
<td>6.1 *</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>4.7</td>
<td>0 *</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>3.2</td>
<td>0 *</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>7.9</td>
<td>2.0 *</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>20.0</td>
<td>11.2 *</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>4.7*</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*Posterior Probability of Superiority (PPS) >95.0%

AIR2 Extension Study

Objective:
Durability of effect

Primary Endpoint:
% of patients with severe exacerbation* at Years 2, 3, 4 and 5 is non-inferior to Year 1

Secondary Endpoints:
Severe exacerbations, ER visits for respiratory symptoms, Lung function (Pre-BD FEV₁), Respiratory adverse events

Retention rate (from n=190) = 85.2%


* Exacerbations requiring treatment with systemic corticosteroids or a doubling of ICS
Reduction in Severe Exacerbations Maintained out to 5 years

The reduction in severe exacerbations requiring systemic corticosteroids at Year 1 was maintained out to at least 5 years.

Compared with 1 year prior to BT treatment (baseline):
- **44%** average decrease in percentage of patients having severe exacerbations
- **48%** average decrease in severe exacerbation event rates

Reduction in ER Visits Maintained out to 5 years

The reduction in ER visits for respiratory symptoms at Year 1 was maintained out to at least 5 years.

Compared with 1 year prior to BT treatment (baseline):
- 78% average decrease in percentage of patients having ER visits
- 88% average decrease in ER visit event rates

Take home points:

• Evaluate your asthma patients based on their disease impairment and risk.
• Evaluate your asthma patients in follow up exams to assess their asthma control.
  • Reinforce compliance and inhaler technique.
  • Evaluate for environmental triggers that can be avoided (cigarette smoke, allergens, irritants).
Take home points:

• Patients with severe asthma may require additional evaluation and referral.
• Patients with allergic asthma, not well controlled with high dose inhaled steroids and an additional controller can be considered for treatment with omalizumab.
• Patients with severe eosinophilic asthma not controlled with ICS/LABA may benefit from an inhibitor of Interleukin 5 (mepolizumab, reslizumab, or benralizumab).
• Patients with severe asthma not well controlled with ICS/LABA and frequent exacerbations may benefit from Bronchial Thermoplasty.