Asthma Year in Review

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Grant support – GSK

I will not be discussing off-label use for any drugs or devices
Objectives

- Review findings from, and strengths/limitations of recent significant publications in asthma
- Discuss how these findings may impact daily clinical practice when caring for patients with asthma
• Are LABAs safe in asthma?
• Is as-needed ICS/LABA an effective strategy for mild asthma?
• Can escalation of ICS dose early in ‘yellow zone’ of asthma action plan abort exacerbations?
• New treatment for severe asthma
Background: LABA safety concerns

1993: Serevent nationwide surveillance study (SNS)
- A 16-week RCT in the UK, evaluating Salmeterol vs. Salbutamol in ~25,000 participants, found a small, not statistically significant, increase in asthma-related deaths in Salmeterol group

2006: Salmeterol Multicenter Asthma Research Trial (SMART)
- 28-week RCT in ~26,000 participants evaluated Salmeterol vs. placebo added-on to usual therapy
- Interim analysis revealed a small but statistically significant increase in serious asthma related events in African American subjects

Castle et al. BMJ 1993; 306:1034-1037
Nelson et al. Chest 2006; 129: 15-26
Background

• 2005: FDA required black-box warning regarding increased asthma related deaths for all LABAs

• 2011-2016: FDA mandated LABA safety studies

• 2016: 4 parallel trials with 41,297 patients (3 studies > age 12, & 1 age 4-11)
  – No significant increase in risk of serious asthma events with LABA used in combination with ICS (Hazard ration 1.10; 95% CI 0.85-1.44)
  – Significant reduction in exacerbations (Hazard ratio 0.79-0.89)

• 2017: ‘black box warning’ removed!
Combined Analysis of Asthma Safety Trials of Long-Acting $\beta_2$-Agonists

William W. Busse, M.D., Eric D. Bateman, M.B., Ch.B., M.D.,
Arthur L. Caplan, Ph.D., H. William Kelly, Pharm.D., Paul M. O’Byrne, M.B.,
Klaus F. Rabe, M.D., Ph.D., and Vernon M. Chinchilli, Ph.D.
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O’Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O’Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszná, M.D., and J. Mark FitzGerald, M.D.
Mild asthma occurs in 50-75% of patients with asthma
Symptoms may not be burdensome but airway inflammation is often present
These patients are at risk of exacerbations and event asthma related death
Guidelines recommend regular use of inhaled steroids as maintenance but poor adherence is a major problem, leading to undertreatment of airway inflammation
At the same time, patients rely heavily on SABAs for symptom relief.
52 week double blind RCT, age > 12 years
GINA Step 2 (either uncontrolled on SABA alone, or controlled on Step 2)
Primary outcome: electronically recorded weeks with well controlled asthma (electronic diary and digital inhaler) with as needed ICS/Formoterol compared to terbutaline alone
Secondary outcome: non inferiority of ICS/Formoterol to fixed dose ICS

SYGMA 1: Budesonide/Formoterol given as needed in mild asthma

O’Byrne PM et al. NEJM 2018; 378: 1865
SYGMA 1: Budesonide/Formoterol given as needed in mild asthma

In terms of weeks of well controlled asthma, budesonide-formoterol was:
Superior to as needed terbutaline
Inferior to Budesonide maintenance
In terms of exacerbations:
As-needed budesonide/formoterol was non-inferior to maintenance ICS with 1/5th of the ICS dose (57 ug vs. 340 ug)

SYGMA 1: Budesonide/Formoterol given as needed in mild asthma

P values were not controlled for multiple comparisons. Insets show the same data on an enlarged y axis.
SYGMA 2: Budesonide/Formoterol given as needed in mild asthma

Parallel study to SYGMA 1 but Pragmatic design:
- no daily reminders to use maintenance inhalers
- only 2 mid-trial visits
- no diary, no PEF monitoring

Remote digital monitoring of inhaler use
- BFC non-inferior to fixed dose ICS and ICS lower similar to SYGMA 1
- Higher than anticipated adherence

Bateman ED et al. NEJM 2018; 378: 1877
Can exacerbations be prevented with early escalation in ICS dose?
Background

Acute exacerbations of asthma cause considerable illness and costs related to asthma

Asthma action plans have been shown to improve asthma control

Limited guidance for change in asthma medications for early loss of asthma control ‘yellow zone’ = Zone 2

2016 Cochrane review concluded that doubling ICS dose not efficacious

Quadrupling the dose of ICS identified as potentially efficacious in a single study previously
Quadrupling ICS dose to abort exacerbations

Pragmatic unblinded randomized trial in adults and adolescents
N = 1922, age > 16, > 1 exacerbation in past 12 months
Primary outcome: Time to first severe exacerbation (OCS or urgent medical visit)
Quadrupling ICS dose to abort exacerbations

58% of participants had a zone 2 event

45% in intervention vs. 52% in control group

RR 0.81

Increased laryngeal adverse effects
Quintupling ICS dose to prevent exacerbation in children

Randomized, blinded study
Children ages 5-11 years
Mild-to-moderate doctor diagnosed asthma
Step 2 therapy of NAEPP-EPR3
Quintupling ICS dose to prevent exacerbation in children

No difference in number of exacerbations, ED visits, hospitalization, treatment failure

Systemic levels of steroids in high dose group and possible decreased linear growth in children < 7

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma


Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D., Jennifer D. Hamilton, Ph.D., Brian N. Swanson, Ph.D., Asif Khan, M.B., B.S., M.P.H., Jingdong Chao, Ph.D., Heribert Staudinger, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Christian Antoni, M.D., Ph.D., Nikhil Amin, M.D., Marcella Ruddy, M.D., Bolanle Akinlade, M.D., Neil M.H. Graham, M.B., B.S., M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Ariel Teper, M.D.
Background - Dupilumab

- IL-4 and IL-13 bind to a shared subunit, IL-4Rα.
- Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4Rα, blocking both IL-4 and IL-13 signaling.
- IL-4 and IL-13 pathways have unique and overlapping function.
Dupilumab & OCS-dependent Asthma

- 210 patients with OCS dependent asthma
- Dupilumab vs. placebo after an OCS optimization run-in period
- Tapering week 4-20 then stable for 4 weeks
- Primary endpoint: % reduction in OCS at week 24

Rabe et al NEJM 2018; 378:2486
### Table 2. Overview of Adverse Events during 24-Week Intervention Period and Injection-Site Reactions (Safety Population).%

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo Group (N = 107)</th>
<th>Dupilumab Group (N = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>69 (64)</td>
<td>64 (62)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>6 (6)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Any adverse event leading to death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any adverse event leading to permanent discontinuation of trial regimen</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Adverse event occurring in ≥5% of patients in either group†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>19 (18)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (6)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4 (4)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Eosinophilia‡</td>
<td>1 (1)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Injection-site reaction§</td>
<td>4 (4)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>≥1 measurement of blood eosinophil count &gt;3000 cells/mm³</td>
<td>1 (1)</td>
<td>13 (13)</td>
</tr>
</tbody>
</table>

Register now at [congress.chestnet.org](http://congress.chestnet.org)
Dupilumab & mod-severe uncontrolled asthma

1902 patients
Adolescents & adults
200 vs 300 mg dupilumab SC q 2 weeks

Adjusted Annual Severe Exacerbation Rate over 52 weeks

Castro et al NEJM 2018; 378:2486
Effect of dupilumab by baseline Eos and FeNO

Castro et al. NEJM 2018; 378:2486
• Reassuring data on safety of LABA in asthma when used in combination with ICS
• More evidence for formoterol containing ICS/LABA as ‘SMART’ strategy
• Escalation of ICS dose during ‘yellow’ zone
  • Not effective in children
  • Small benefit in adults
• New class of biologic – dupilumab – effective in reducing exacerbation and OCS dependence. Effect size larger in patients with elevated FeNO or blood eos
Honorable mentions

- Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy. Results from a systematic literature review and modelling study. European Respiratory Journal 2019; DOI: 10.1183/13993003.02161-2018
- Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. JACI 2019; 143: 104.
- Managing Asthma in Pregnancy (MAP) trial: FENO levels and childhood asthma. JACI 2018; 142: 1765
- Asthma Is a Risk Factor for Respiratory Exacerbations Without Increased Rate of Lung Function Decline. CHEST 2018; 153: 368
- Associations of Asthma and Asthma Control With Atrial Fibrillation Risk. Results From the Nord-Trøndelag Health Study (HUNT). JAMA 2018; 3: 721