Do We Need Biologics in Pediatric Asthma Management?

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Department of Paediatrics
The Chinese University of Hong Kong
Asthma and Allergy by ISAAC

Table 1. Trends in self-reported symptoms of asthma and allergic rhinoconjunctivitis in 13-14-year-old Asian children from ISAAC Phases 1 and 3 results: average annual change in prevalence

<table>
<thead>
<tr>
<th>Cities/Countries</th>
<th>Asthma Ever</th>
<th>Current Wheeze</th>
<th>Rhinoconjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alor Setar</td>
<td>10.8 (+0.09%)</td>
<td>9.3 (+0.05%)</td>
<td>16.3 (-0.06%)</td>
</tr>
<tr>
<td>Bangkok</td>
<td>15.9 (+0.30%)</td>
<td>13.9 (+0.06%)</td>
<td>23.9 (+1.41%)</td>
</tr>
<tr>
<td>Beijing</td>
<td>6.3 (-0.08%)</td>
<td>7.2 (+0.30%)</td>
<td>10.2 (+0.33%)</td>
</tr>
<tr>
<td>Philippines</td>
<td>20.9 (+0.47%)</td>
<td>8.4 (-0.55%)</td>
<td>11.0 (-0.61%)</td>
</tr>
<tr>
<td>Chiang Mai</td>
<td>9.9 (+0.10%)</td>
<td>8.7 (-0.55%)</td>
<td>17.2 (+0.26%)</td>
</tr>
<tr>
<td>Guangzhou</td>
<td>4.6 (+0.09%)</td>
<td>4.8 (+0.20%)</td>
<td>10.7 (+0.33%)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>10.1 (-0.15%)</td>
<td>8.6 (-0.55%)</td>
<td>22.6 (-0.21%)</td>
</tr>
<tr>
<td>Indonesia</td>
<td>12.4 (+1.80%)</td>
<td>5.2 (+0.52%)</td>
<td>4.8 (-0.08%)</td>
</tr>
<tr>
<td>Japan</td>
<td>19.9 (+0.12%)</td>
<td>13.0 (-0.05%)</td>
<td>17.6 (+0.34%)</td>
</tr>
<tr>
<td>Klang Valley</td>
<td>16.1 (+0.37%)</td>
<td>11.6 (-0.11%)</td>
<td>19.8 (+0.87%)</td>
</tr>
<tr>
<td>Kota Bharu</td>
<td>9.0 (+0.04%)</td>
<td>5.8 (-0.20%)</td>
<td>12.5 (+0.46%)</td>
</tr>
<tr>
<td>Seoul</td>
<td>5.0 (+0.44%)</td>
<td>9.1 (+0.16%)</td>
<td>11.9 (+0.24%)</td>
</tr>
<tr>
<td>Singapore</td>
<td>26.5 (+0.73%)</td>
<td>11.4 (+0.24%)</td>
<td>18.5 (+0.20%)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>17.0 (+1.28%)</td>
<td>7.0 (+0.26%)</td>
<td>17.8 (+1.02%)</td>
</tr>
<tr>
<td>Mean</td>
<td>12.6 (+0.39%)</td>
<td>8.8 (+0.07%)</td>
<td>15.1 (+0.32%)</td>
</tr>
</tbody>
</table>
# Levels of Asthma Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (All of the following)</th>
<th>Partly controlled (Any present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (2 or less / week)</td>
<td>More than twice / week</td>
<td></td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td>3 or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Nocturnal symptoms / awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for rescue / “reliever” treatment</td>
<td>None (2 or less / week)</td>
<td>More than twice / week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV₁)</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best (if known) on any day</td>
<td></td>
</tr>
<tr>
<td>Exacerbation</td>
<td>None</td>
<td>One or more / year</td>
<td>1 in any week</td>
</tr>
</tbody>
</table>
Inefficient Asthma Control Worldwide

<table>
<thead>
<tr>
<th>Region</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
<th>Intermittent</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>25.0</td>
<td>13.0</td>
<td>19.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Western Europe</td>
<td>34.5</td>
<td>18.2</td>
<td>21.2</td>
<td>36.1</td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>28.0</td>
<td>8.0</td>
<td>12.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Japan</td>
<td>27.0</td>
<td>7.0</td>
<td>2.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Central and Eastern Europe</td>
<td>28.9</td>
<td>15.3</td>
<td>21.3</td>
<td>38.0</td>
</tr>
</tbody>
</table>

Severity of reported symptoms in the past 4 weeks

Rabe et al. JACI 2004
AIRIAP2 in Asian Children

**GINA-defined Asthma Control**

- A
  - Overall
  - Hong Kong
  - India
  - Indonesia
  - Mainland China
  - Malaysia
  - Philippines
  - Singapore
  - South Korea
  - Sri Lanka
  - Taiwan
  - Thailand
  - Vietnam

<table>
<thead>
<tr>
<th>% of Participants</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>Partly controlled</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Use of Urgent Healthcare Services**

- A
  - Total
  - Hosp.
  - ER
  - Other

**Use of Anti-asthma Medications**

- B
  - Total
  - SABA
  - ICS

Wong GW et al. Allergy 2013
Control-based Asthma Management Cycle

**Assess:**
diagnosis, symptom control and risk factors, spirometry, inhaler technique and adherence, patient preference

**Review response:**
symptoms, exacerbations, side effects, patient satisfaction, spirometry

**Adjust treatment:**
asthma medications, non-pharmacological strategies, treat modifiable factors
Assessment of Uncontrolled Asthma

1. Watch patient using the inhaler; discuss adherence and barriers to use
   • Correct errors and recheck frequently

2. Confirm the diagnosis of asthma
   • May repeat spirometry after 2-3 wks of ICS

3. Remove potential risk factors and manage comorbidities
   • Tobacco smoke, allergen exposure, NSAIDs; rhinitis, obesity, depression/anxiety

4. Consider treatment Step-up
   • Balance potential benefits and risks

5. Refer to specialist or severe asthma clinic
   • Refer early if severe asthma despite step 4 treatments for 3-6 mo, or doubts about diagnosis
# Stepwise Asthma Management

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma Education</strong> <em>(self monitoring, written action plan, regular review)</em></td>
<td><strong>Treat modifiable factors</strong> <em>(tobacco smoke, obesity, anxiety)</em></td>
<td><strong>Advise non-pharmacological strategies</strong> <em>(physical activity, weight loss, avoidance of sensitizers)</em></td>
<td><strong>As-needed short-acting $\beta_2$-agonist (SABA)</strong></td>
<td><em><em>As-needed SABA or low-dose ICS/formoterol</em>#</em>*</td>
</tr>
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<tr>
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<th>Add one or more</th>
<th>Add one or both</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Low-dose ICS</td>
<td>Low-dose ICS <em>plus</em> LABA**</td>
<td>Medium/high-dose ICS <em>plus</em> LABA</td>
<td>Refer for add-on treatments: Tiotropium*, omalizumab, or mepolizumab*</td>
</tr>
<tr>
<td>Consider low-dose ICS</td>
<td>Leukotriene receptor antagonist (LTRA)</td>
<td>Medium/high-dose ICS</td>
<td>Add tiotropium*</td>
<td>Add low-dose oral corticosteroid</td>
</tr>
<tr>
<td>Low-dose theophylline*</td>
<td>Low-dose ICS <em>plus</em> LTRA (or theophylline*)</td>
<td>Low-dose ICS <em>plus</em> LTRA (or theophylline*)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Not for children < 12 yrs; ** preferred step 3 treatment is medium-dose ICS for children aged 6-11 yrs; # as maintenance and reliever by SMART approach
Correlations among steroid fear, acceptability, usage frequency, quality of life and disease severity in childhood eczema

Kam Lun Hon¹, Yin Ching K. Tsang¹, Nga Hin Pong¹, David C. K. Luk², Vivian W. Lee³, Wing Man Woo⁴, Chak Yiu Justin Lam⁴, Yun Ting Eunice Yeung⁴, Yiu Shing Sunny Chau⁴, Ka Kam Kenneth Chui⁴, Ka Hin Gabriel Li⁴, and Ting Fan Leung¹

¹Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China, ²Department of Paediatrics & Adolescent Medicine, United Christian Hospital, Kwun Tong, Hong Kong SAR, China, ³School of Pharmacy, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China, and ⁴Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China
No Long-term Effectiveness of ICS

- Symptomatic relief but no long-term benefit after fluticasone in preschool kids

Total Asthma Control

Total Control was achieved at a lower steroid dose with Seretide

% patients achieving Total Control

- Steroid naïve (S1)
- Low dose ICS (S2)
- Moderate dose ICS (S3)

Seretide 500
Seretide 250
Seretide 100
FP 500
FP 250

Bateman ED et al. AJRCCM 2004
Precision Medicine: From Treating Phenotypes to Endotyping to Genotyping

CLINICAL PHENOTYPE

E.g. severe asthma, early vs late onset, atopic, fixed airflow obstruction

ENDOTYPE (mechanisms or pathways)

E.g. eosinophilic asthma, Th2-type, high IgE

GENOTYPE
Molecular Phenotyping for Severe Asthma

Severe Asthma

Symptoms

Exacerbations

FEV$_1$

Type 2 Inflammation

- Early-onset/allergic

No/less Type 2 Inflammation

- Late-onset/eosinophilic
- Obese
- Neutrophilic
Stepping Up Asthma Treatment

1. Achieve and maintain best possible clinical control
   - Current control
     - Symptoms
     - Reliever use
     - Activity
     - Lung function

2. Target: Reduction of risk
   - Future risk
     - Instability / worsened symptoms
     - Exacerbations
     - Loss of lung function
     - Adverse effects of medications

2a. Treatments not requiring specific biomarker criteria
2b. Treatments requiring specific biomarker criteria
Omalizumab (Xolair) is the first of a new class of agent that specifically target human IgE; the first biologic approved for treating asthma.
Omalizumab for Asthma in US Inner City Children

- 419 children, adolescents and adults aged 6-20 years
- symptoms of persistent asthma or evidence of uncontrolled disease (e.g. hospitalization or unscheduled urgent care within 12 months)
- ≥ one positive skin test for a perennial allergen, weigh 20-150 kg, and total serum IgE levels between 30 and 1300 kIU/L

Figure 4.1 Study Design for Participants Receiving Injections Every 4 Weeks

<table>
<thead>
<tr>
<th>Screening Period</th>
<th>Double-Blind Treatment Period</th>
<th>Dose: 0.016 mg/kg/IgE (kIU/L) q4w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment, Pre-screening and Screening</td>
<td>Randomization</td>
<td></td>
</tr>
<tr>
<td>Week -9 to Day -1</td>
<td>Day 0</td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>Visit 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatments 3-16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weeks: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visits 3-16*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Open-Label Treatment Period</th>
<th>One Month Follow-Up</th>
<th>Final Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments 17-22</td>
<td>Week 84</td>
<td>End of study</td>
</tr>
<tr>
<td>Weeks: 60, 64, 68, 72, 76, 80</td>
<td>Visit 23</td>
<td>Week 96</td>
</tr>
<tr>
<td>Visits 17-22*</td>
<td></td>
<td>Visit 24</td>
</tr>
</tbody>
</table>

Prevent Fall Asthma Exacerbations by Omalizumab vs ICS Boost

318 Treatment Steps 2 to 4
- 133 Omalizumab
  - 12 excluded
    - 5 lost to follow-up
    - 4 missed first injection
    - 2 anaphylaxis (grade 1)
    - 1 exclusionary condition
- 47 Placebo
  - 4 excluded
    - 3 lost to follow-up
    - 1 other (school calendar)
- 138 ICS Boost
  - 8 excluded
    - 3 withdrew consent
    - 2 lost to follow-up
    - 1 anaphylaxis (grade 1)
    - 1 missed first injection
    - 1 other (scheduling)

195 Treatment Step 5
- 145 Omalizumab
  - 1 excluded
    - 1 anaphylaxis (grade 1)
- 50 Placebo
  - 4 excluded
    - 1 lost to follow-up
    - 1 missed first injection

294 mITT

Teach SJ et al. JACI 2015
Treatment Effects in Relation to Patients with Exacerbation Phenotype
Time to First Asthma Exacerbation

FeNO

Eosinophil Count

Periostin Level

Hanania NA et al. AJRCCM 2013
Mepolizumab (Bosatria) is a humanized murine IgG₁ mAb against free IL-5; inhibits binding of IL-5 to IL-5Rα on eos. FDA-approved for ≥ 12 yrs with severe “eos” asthma in Nov 2015; 100 mg SC q4w.

Reslizumab (Cinquil) is a humanized IgG₄ anti-IL-5 mAb; binds to and neutralizes circulating IL-5 by preventing its binding to eosinophils (given by IV route).

Benralizumab, a fully human afucosylated mAb to IL-5Rα that blocks the effects of IL-5.
Mepolizumab for Severe Asthma ("DREAM")

- 621 patients aged 12-74 years with a history of recurrent severe asthma exacerbations
- Eosinophilic inflammation: sputum eos ≥ 3%; FeNO ≥ 50 ppb; or blood eos ≥ 300 cells/µl
- Taking fluticasone propionate ≥ 880 µg and additional controller; ± maintenance oral CS
- Randomly assigned to IV mepolizumab (75 mg, 250 mg, or 750 mg) or placebo (normal saline)

Clinically Significant Exacerbations

Pavord ID et al. Lancet 2012
Blood Eosinophil Count

Sputum Eosinophil Count

Prebronchodilator FEV₁

ACQ Score
Mepolizumab in Severe Eosinophilic Asthma ("MENSA")

- 576 patients aged 12-82 yrs with asthma and two or more exacerbations in past 12 months
- Received fluticasone propionate $\geq 880 \, \mu g$/day with additional controller
- $FEV_1 < 90\%$ of predicted or $FEV_1/FVC < 0.8$ (12-17 yrs) OR $FEV_1 < 80\%$ of predicted ($\geq 18$ yrs)
- Blood eos level of $\geq 300$ cells/$\mu l$ within the previous year

Asthma Exacerbations

Placebo

Mepolizumab 75 mg, intravenously

Mepolizumab 100 mg, subcutaneously

$P < 0.001$
$P = 0.02$ for IV; $P = 0.03$ for SC
Steroid-sparing Effect of Mepolizumab ("SIRIUS")

- 135 patients aged ≥ 12 yrs (and ≥ 45 kg) with asthma
- 6-mo history of maintenance treatment with systemic glucocorticoids (5 to 35 mg/day of prednisone); all patients received high-dose ICS and an additional controller
- Blood eos level of ≥ 300 cells/µl
Change from Baseline in Steroid Dose

- Placebo (N=66)
- Mepolizumab (N=69)

Median Change (%) vs Week

- Optimized dose
- Maintenance dose
Asthma Exacerbation

Week

Cumulative No.

Placebo

Mepolizumab
# Stepwise Asthma Management

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Conclusions

- Asthma is a major health problem in Asian children.
- The pathogenesis of asthma is heterogeneous (endotypes).
- Although generally controlled, asthma can be severe and difficult to treat in a small group of children.
- A number of biologics capable of blocking specific endogenous molecules are either approved (omalizumab, mepolizumab) or undergoing clinical trials in asthmatic children who are poorly controlled despite adherence to guideline therapies.
- Only a subset of meticulously selected patients would benefit from biologics, i.e. “targeted therapy”.
- Offers an opportunity for precision medicine in asthma.