Engineered therapeutic antibodies for childhood asthma

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Therapeutic Ab for childhood asthma
• children with asthma in the US
• complexity of asthma
• therapy of asthma with inhaled corticosteroids
• therapy with antibodies
• therapy of asthma with anti-IgE
• therapies of asthma with antibodies under investigation
• conclusions

Asthma is the leading serious chronic illness of children in the US
• 6.8 million under age 18
• 1.2 million under age 5
• many others have undiagnosed asthma
• rate in those under 18 (92.8 per 1,000)
• rate in those over 18 (72.4 per 1,000)
• asthma is the third leading cause of hospitalization among children under the age of 15
• asthma is one of the most common causes of school absenteeism

Asthma prevalence in children: years 1980-2005

Data Source: CDC/NCHS: National Health Interview Survey

Children’s hospitalizations for asthma: 1980-2004

Data Source: CDC/NCHS: National Hospital Discharge Survey
Pediatric patients require more health care resources than adults

**Graph:**
- **Outpatient Visits**
  - Adults (≥18 y): 687
  - Children (≤17 y): 181
- **Emergency Department Visits**
  - Adults (≥18 y): 100
  - Children (≤17 y): 24
- **Hospitalizations**
  - Adults (≥18 y): 13
  - Children (≤17 y): 27

*CDC. National Center for Health Statistics Web site. Asthma Prevalence, Health Care Use and Mortality, 2002*

**Asthma treatment guidelines**

**Graph:**
- **Steps 1-5:**
  - Step 1: Asthma education
  - Step 2: Environmental control
  - Step 3: As needed rapid-acting β2-agonist
  - Step 4: Controller options
  - Step 5: Oral corticosteroid (lowest dose)

*GINA Workshop Report 2006*

**Stepwise approach for managing asthma in children 5-11 years of age**

**Key:**
- Low-dose ICS: Inhaled corticosteroids
- LABA: Long-acting β2-agonists
- Anti-IgE: Immunotherapy

**Therapeutic Ab for childhood asthma**

- children with asthma in the US
- complexity of asthma
Interaction of genes and environment and the risk of allergic sensitization


Effects on airways

Inflammatory cells
- mast cells
- eosinophils
- TH2 cells
- basophils
- neutrophils
- platelets

Structural cells
- epithelial cells
- smooth muscle cells
- endothelial cells
- fibroblast
- nerves

Mediators
- histamine
- leukotrienes
- prostanoids
- PAF
- kinins
- adenosine
- endothelins
- nitric oxide
- cytokines
- chemokines

Effects
- bronchospasm
- plasma exudation
- mucus secretion
- AHR
- structural changes

Allergic mechanisms

Holgate. Nat Rev Immunol 2008;8:218

A central role for inflammatory TH2 cells in asthma


Mast cells in allergic inflammation

Effect of mast cells on IgE responses (and *vice versa*)


Inflammatory and remodelling responses in asthma

Holgate. *Nat Rev Immunol* 2008;8:218

Escher: Path of Life

Therapeutic Ab for childhood asthma

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- therapy of asthma with inhaled corticosteroids

Asthma is a heterogeneous disease

- age of onset: childhood vs adulthood
- atopy: present or absent
- predominant inflam cell: neutrophil or eosinophil
- predominant trigger: viral allergic exercise-related ASA
- therapeutic response: to steroids to LTRA’s to β-agonists

Variability of response to fluticasone and montelukast

Variability in response to ICS

- Approximately 1/3 of patients failed to achieve improvement in FEV1 despite high dose ICS tx
- Approximately 1/3 failed to reduce AH despite high dose ICS tx
- Improvement in FEV1 did not correlate with the reduction in AH

Szefer. JACI 2002;109:410

Adherence to ICS by children

120
110
100
90
80
70
60
50
40
30
20
10
0
%

Diary report
Chronolog record

Doses taken at correct times

Highest
Median
Lowest

Milgrom. JACI 1996;98:1051

Days without ICS

% Days

Pts not requiring steroid bursts
Pts requiring steroid bursts

Milgrom. JACI 1996;98:1051

Comparing ICSs to placebo


Childhood Asthma Management Program: study design

N=1,041
Aged 5–12 yr
FEV1 >93 % of predicted (prebronchodilator)

budesonide (BUD) 200 mg bid n=311
Budesonide (BUD) 200 mg bid n=311
nedocromil 8 mg bid n=312
Placebo n=418

Inhaled beclomethasone dipropionate, albuterol, or oral corticosteroids allowed as necessary

Childhood Asthma Management Program Research Group. NEJM. 2000;343:1054

Steroid dose-response relationships for various outcome measures

A child who had a significant reduction in post-BD FEV$_1$ % predicted/year

Definition of a significant reduction in lung function

- A regression slope $\leq$ -1% post-BD FEV$_1$ % predicted per year, $P$ value of $< 0.1$ and an $R^2 \geq 0.14$
- at least 4 points to define the line
- SRP: participants with a significant reduction in post-BD FEV$_1$ % predicted/year
- NSRP: participants without a significant reduction in post-BD FEV$_1$ % predicted/year.

SRP across treatment groups

The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma

Busse, Pedersen, Pauwels, Tan, Chen, Lamm, O’Byrne
JACI 2008;121:1167
START: study design

<table>
<thead>
<tr>
<th>Years</th>
<th>Double-blind phase</th>
<th>Open-label phase</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Busse, JACI 2008;121:1167

Mean percentage of symptom-free days

Busse, JACI 2008;121:1167

Long-term ICS in preschool children at high risk for asthma

NEJM 2006;354:1985

Schedule of procedures and enrollment

456 enrolled
285 randomized

143 assigned to fluticasone
142 assigned to placebo

11 dropped out in yr 1 and 2
12 dropped out in year 1 and 2
1 dropped out in year 3
5 dropped out in year 3

Gulibert. NEJM 2006;354:1985

Proportion of episode-free days

Guilbert. NEJM 2006;354:1985

Therapeutic Ab for childhood asthma

- children with asthma in the US
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- therapy of asthma with inhaled corticosteroids
- therapy with antibodies
Classical immunology
- each antibody binds to a specific antigen
- the interaction is similar to a lock and key

Passive immunity
- 1888 Roux and Yersin isolate diphtheria toxin
- 1890 von Behring and Kitasato discover an antitoxin-based immunity to diphtheria and tetanus
- antitoxin becomes the first major success of modern therapeutic immunology

Clemens Peter Freiherr von Pirquet (1874–1929)
- Austrian pediatrician
- in 1906 noticed that patients who had previously received injections of horse serum or smallpox vaccine had quicker, more severe reactions to a second injection.
- along with Bela Schick, coined the word allergy (from the Greek allos meaning “other” and ergon meaning “reaction”) to describe this hypersensitivity reaction

Diseases still treated by passive immunization
- botulism
- CMV
- diphtheria
- hepatitis A
- hepatitis B
- measles
- rabies
- tetanus
- vaccinia
- Varicella
- ITP
- Kawasaki disease

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Monoclonal antibody production
Anti-IgE (omalizumab) biological characteristics

- Humanized monoclonal antibody against IgE
- Binds circulating IgE regardless of specificity
- Forms small, biologically inert complexes
- Does not activate complement

CDR = complementarity-determining region


IgE binds to mast cells at the high affinity receptor (FcεRI)

Mast cell

FcεRI binding site

IgE molecule bound to mast cell

FcεRI receptor

IgE molecule


Anti-IgE blocks IgE binding to mast cells

IgE molecule

anti-IgE

FcεRI receptor

Mast cell

Interaction of IgE with high-affinity IgE receptors (FcεRI)

Epithelial cell

Airway smooth muscle?

Eosinophil

Lymphocyte

Macrophage/monocyte

IgE

Effect of mast cells on IgE responses (and vice versa)

Expression of high-affinity IgE receptors on peripheral blood basophils from 15 subjects before and after 90 days of treatment with anti-IgE

Median Receptor density (per basophil)

Controls

P = 0.0022

Pretreatment 90 days


Down-regulation of IgE receptors

The effects of targeting IgE on allergic responses

- **Omalizumab**
  - Binds to free IgE, decreasing cell-bound IgE
  - Decreases expression of high-affinity receptors
  - Decreases mediator release
  - Decreases allergic inflammation
  - Prevents exacerbation of asthma and reduces symptoms

Release of soluble mediator

B cell
Plasma cell
IgE class-switching
Release of IgE FcεRI
IgE antibodies
Mast cell, basophil, or eosinophil
Release of soluble mediator

Mean corticosteroid dose reduction

<table>
<thead>
<tr>
<th>% Change from baseline</th>
<th>Inhaled corticosteroid (total n=282)</th>
<th>Oral corticosteroid (total n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>25%</td>
<td>0.006 mg/kg/IU/mL</td>
<td>0.014 mg/kg/IU/mL</td>
</tr>
<tr>
<td>42%</td>
<td>0.014 mg/kg/IU/mL</td>
<td>0.014 mg/kg/IU/mL</td>
</tr>
<tr>
<td>50%</td>
<td>0.014 mg/kg/IU/mL</td>
<td>0.014 mg/kg/IU/mL</td>
</tr>
<tr>
<td>65%</td>
<td>0.014 mg/kg/IU/mL</td>
<td>0.014 mg/kg/IU/mL</td>
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</table>

Anti-IgE reduced the mean number of exacerbations in children

<table>
<thead>
<tr>
<th>Mean exacerbations per patient</th>
<th>Placebo</th>
<th>Anti-IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable steroid phase</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Steroid reduction phase</td>
<td>0.72</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Anti-IgE reduced ICS use

<table>
<thead>
<tr>
<th>Reduction of ICS dose (%)</th>
<th>Placebo</th>
<th>Anti-IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-25</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>25-50</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>50-75</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>75-100</td>
<td>17%</td>
<td>14%</td>
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</tbody>
</table>

Anti-IgE pediatric trial extensions

- 24-week open-label extension
- 3-year open-label extension
- Primary outcomes
  - Long-term safety and tolerability

Anti-IgE reduced exhaled nitric oxide

<table>
<thead>
<tr>
<th>Time (wk)</th>
<th>Steroid stable</th>
<th>Steroid reduction</th>
<th>Open label</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3.0</td>
<td>2.5</td>
<td>2.5</td>
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<tr>
<td>8</td>
<td>2.5</td>
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<tr>
<td>12</td>
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<tr>
<td>16</td>
<td>1.5</td>
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</tr>
<tr>
<td>20</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
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2. Milgrom. Poster G46 ATS Meeting 2005; San Diego, CA

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Therapeutic antibodies
• as blocking or neutralizing agents
• used to neutralize or block harmful substances
• used as cytotoxic mediators
• acting as delivery agents
• used to interfere with signaling pathways, binding ligands or receptors and disrupting their interactions

Therapeutic antibodies
• the use of antibodies offers target specificity
• unparalleled in conventional treatments and therapies
• antibodies possess the ability to generate an unlimited diversity of specificity
• antibody-based therapies can be used to target many different aspects of disease

Potential targets for new asthma drugs
Adcock. Lancet 2008;372:1073
Cytokine-based therapies in asthma

Mepolizumab and exacerbations of refractory eosinophilic asthma

- double-blind, placebo-controlled, parallel-group study of 61 subjects with refractory eosinophilic asthma and a history of recurrent severe exacerbations
- subjects received infusions of either mepolizumab, an anti-interleukin-5 monoclonal antibody, or placebo at monthly intervals for 1 year
- primary outcome measure was number of severe exacerbations during the 50-week treatment phase

The effects of a MAb directed against TNF-α in asthma

- double-blind, placebo-controlled, parallel-group study of 61 subjects with refractory eosinophilic asthma and a history of recurrent severe exacerbations
- subjects received infusions of either mepolizumab, an anti-interleukin-5 monoclonal antibody, or placebo at monthly intervals for 1 year
- primary outcome measure was number of severe exacerbations during the 50-week treatment phase

Effect of an IL-4 variant on asthmatic LPR to allergen challenge

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- subjects received infusions of either mepolizumab, an anti-interleukin-5 monoclonal antibody, or placebo at monthly intervals for 1 year
- primary outcome measure was number of severe exacerbations during the 50-week treatment phase

FENO at screening and after 4 wks’ tx

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- subjects received infusions of either mepolizumab, an anti-interleukin-5 monoclonal antibody, or placebo at monthly intervals for 1 year
- primary outcome measure was number of severe exacerbations during the 50-week treatment phase

Reversal of IL-4 and IL-13 inhibition of cathelicidin by neutralizing antibodies
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Current state

• residual symptoms
• exacerbations
• life threatening disease
• patients remain dependent on continuing medication
• cessation of treatment causes full recurrence of the phenotype

Goals for therapy of childhood asthma

• individualized therapy
• preventive therapy
• new treatments based on recognition of asthma phenotypes
• understanding of associated risk factors

Thank you very much!