World Allergy Forum Symposium:
The Future Use of Biologicals in Allergy and Asthma

XXVIII Congress of the European Academy of Allergology and Clinical Immunology
Sunday, June 7, 2009
15:30 – 17:00

Palace of Culture and Science, London (Sklodowska) room
Warsaw, Poland

Chairpersons:
G. Walter Canonica, Italy
Roy Gerth van Wijk, The Netherlands

Future Use of Biologicals in Allergy and Asthma – Pro
Andrew Wardlaw, United Kingdom

Future Use of Biologicals in Allergy and Asthma – Con
Klaus Rabe, The Netherlands

Anti-IgE – Beyond the Current Indications
William W. Busse, United States

The World Allergy Organization (WAO) is an international organization of 77 regional and national allergy and clinical immunology societies. WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care, education, research and training through a world-wide alliance of allergy and clinical immunology societies.

WAF is an educational program of the World Allergy Organization.
“The Future Use of Biologicals in Allergy and Asthma”

Program

Moderators:
G. Walter Canonica
Italy
Roy Gerth van Wijk
The Netherlands

1. Welcome to the World Allergy Forum Symposium and Introduction to “The Future Use of Biologicals in Allergy and Asthma”
   G. Walter Canonica and Roy Gerth van Wijk

2. Future Use of Biologicals in Allergy and Asthma – Pro
   Andrew Wardlaw, United Kingdom

3. Future Use of Biologicals in Allergy and Asthma – Con
   Klaus Rabe, The Netherlands

4. Anti-IgE – Beyond the Current Indications
   William W. Busse, United States

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About the World Allergy Organization

World Allergy Organization (WAO)
The World Allergy Organization (WAO) is an international umbrella organization of 77 regional and national allergy and clinical immunology societies. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to WAO individual members around the globe.

The World Allergy Organization Mission
To be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

Programs of the World Allergy Organization

GLORIA Global Resources in Allergy™
www.worldallergy.org/gloria
The GLORIA program promotes good practice in the management of allergic diseases through programs developed by panels of world experts. GLORIA educates medical professionals worldwide through regional and national presentations and local training initiatives. GLORIA educational modules promote the World Allergy Organization’s (WAO) mission – to optimize allergy care worldwide.

GLORIA Modules
Module 1: Allergic Rhinitis
Module 2: Allergic Conjunctivitis
Module 3: Allergic Emergencies
Module 4: Immunotherapy
Module 5: Treatment of Severe Asthma
Module 6: Food Allergy
Module 7: Angioedema
Module 8: Anaphylaxis
Module 9: Diagnosis of IgE Sensitization
Module 10: Chronic Rhinosinusitis and Nasal Polyposis
Module 11: Drug Allergy
Module 12: Urticaria

WAO Seminars & Conferences
www.worldallergy.org/sc
The Seminars & Conferences program invites member societies to apply to host a WAO Invited Lecturer. Complementing WAO’s existing programs, Seminars & Conferences gives Member Societies the opportunity to bid for an international speaker to give a plenary lecture in the scientific program of the Society’s annual meeting, on a topic of the Society’s choice.

World Allergy Forum (WAF)
www.worldallergy.org/waf
WAF symposia are held at major international allergy meetings. Developed by international expert advisory panels, the symposia provide up-to-the-minute presentations on scientific and clinical developments in the field of allergic disease.

Emerging Societies Program
www.worldallergy.org/esp
WAO offers advice on initiating and developing allergy societies throughout the world. This proactive initiative aims to expand and improve the specialty of allergy by supporting colleagues working in the field of allergy worldwide. Through sharing practical experiences and alerting new societies to the criteria required for WAO membership, ESM creates relationships with future World Allergy Organization member societies, and educates WAO’s leadership about the challenges and opportunities faced by colleagues in developing countries.

World Allergy Organization Journal
www.waojournal.org
World Allergy Organization Journal is the official publication of the World Allergy Organization. An international online-only journal, World Allergy Organization Journal underscores WAO’s commitment to raising awareness and advancing excellence in clinical care, education, research and training in the field of allergy.
### WAO Member Societies

<table>
<thead>
<tr>
<th>Society/Association</th>
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<tbody>
<tr>
<td>Albanian Society of Allergology and Clinical Immunology</td>
<td>Italian Association of Territorial and Hospital Allergists</td>
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<tr>
<td>American Academy of Allergy, Asthma and Immunology</td>
<td>Italian Society for Allergology and Clinical Immunology</td>
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<td>American College of Allergy, Asthma and Immunology</td>
<td>Japanese Society of Allergology</td>
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<td>Argentine Association of Allergy and Immunology</td>
<td>Korean Academy of Allergy, Asthma and Clinical Immunology</td>
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<td>Argentine Society of Allergy and Immunopathology</td>
<td>Latvian Association of Allergists</td>
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<td>Australasian Society of Clinical Immunology and Allergy</td>
<td>Lebanese Society of Allergy and Immunology</td>
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<td>Mexican College of Allergy, Asthma and Clinical Immunology</td>
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<td>Bangladesh Society of Allergy and Immunology</td>
<td>Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology</td>
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<td>Mongolian Society of Allergology</td>
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<td>Brazilian Society of Allergy and Immunopathology</td>
<td>Netherlands Society of Allergology</td>
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<td>Philippine Society of Allergy, Asthma and Immunology</td>
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<td>(Chinese) Hong Kong Institute of Allergy</td>
<td>Polish Society of Allergology</td>
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### Associate Member Societies

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<tr>
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<tr>
<td>Ecuadorian Society of Allergology and Affiliated Sciences</td>
<td>Slovenian Association for Allergology and Clinical Immunology</td>
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<tr>
<td>Ecuadorian Society of Allergy and Immunology</td>
<td>Allergy &amp; Immunology Society of Sri Lanka</td>
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<tr>
<td>Honduran Society of Allergy and Clinical Immunology</td>
<td>Swedish Association for Allergology</td>
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### Regional Organizations

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<tr>
<td>The Asia Pacific Association of Allergology and Clinical Immunology</td>
<td>International Association of Asthmology</td>
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<td>Commonwealth of Independent States (CIS Society)</td>
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<td>European Academy of Allergology and Clinical Immunology</td>
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<tr>
<td>Latin American Society of Allergy and Immunology</td>
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For WAO membership information please contact the Secretariat
World Allergy Organization (WAO)
555 East Wells Street, Suite 1100 • Milwaukee, WI 53202-3823 USA
Tel: +1 414 276 1791 • Fax: +1 414 276 3349
E-mail: info@worldallergy.org
Web site: www.worldallergy.org
Dear Colleagues,

Welcome to the 34th symposium of the World Allergy Forum, “The Future Use of Biologicals in Allergy and Asthma”. World Allergy Forum is the longest running educational program of the World Allergy Organization, and it is a great pleasure to bring the latest symposium in this series to the 2009 EAACI Congress in Warsaw.

We are all hoping for new developments in the therapeutic armamentarium for asthma and other allergic diseases, and particularly for therapies to address the increasingly severe and complex allergic symptomatology that we are seeing in our clinics. Today’s symposium will start with reviews on the future use of biological therapies in allergy and asthma. In his presentation, Future Use of Biologicals in Allergy and Asthma – Pro, Andrew Wardlaw will discuss the anticipated uses and benefits of this type of therapy; then Klaus Rabe, speaking on Future Use of Biologicals in Allergy and Asthma - Con, will consider some of the negative aspects. Anti-IgE is the only biological agent currently authorised and available globally for patients with allergic asthma, and our presentations will conclude with William Busse’s presentation Anti-IgE – Beyond the Current Indications; offering insights into a number of IgE-dependent processes which may benefit from this therapy.

We look forward to concluding the symposium with discussion on these exciting presentations!

With best regards,

G. Walter Canonica    Roy Gerth van Wijk
President     President
World Allergy Organization   European Academy of Allergology and Clinical Immunology
Asthma is a disease characterised by variable airflow obstruction, bronchial hyperresponsiveness (AHR) and airway inflammation which is usually but not always eosinophilic. However within this definition there is a considerable heterogeneity in the clinical presentation, physiology and pathology of the disease. This relates to heterogeneity in response to treatment. In order to take full advantage of the new biological therapeutic agents that are becoming available to treat asthma and related diseases we need to understand this phenotypic complexity and relate it to pathogenesis and treatment response.

Asthma (and indeed most airway diseases) can be seen as a syndrome caused by external agents such as smoking, allergens or infection leading to an inflammatory process in the airways which in turn leads to a number of pathophysiological abnormalities. Each of these abnormalities has its own specific aetiologial pathway and can be defined by a distinct immunological process. These abnormalities include the classical airway dysfunction phenotype caused by an abnormality in airway smooth muscle function and pathologically associated with infiltration of the airway smooth muscle with mast cells, a severe exacerbation (SE) phenotype characterised by eosinophilic airway inflammation, a cough phenotype, a bronchiectasis phenotype, and a fixed airflow obstruction phenotype. Patients usually express one or more of these phenotypes which are often dissociated. Any one form of treatment is going to be more effective at treating one of these abnormalities than another. For example bronchodilators effectively treat the airway dysfunction phenotype and steroids the SE phenotype. Biological therapies are very specifically targeted at one immune pathway and therefore generally speaking will only treat one pathophysiological phenotype. Using these agents to treat the totality of ‘asthma’ without any bias towards the phenotype being treated will result in a failure to recognise their benefit. In addition, as they are so expensive, it is important to target patients where they will have the maximum impact. Three antibody based therapies illustrate this point. Anti-IgE (omalizumab) is only effective in patients with atopic asthma whose disease is driven by IgE mediated allergic reactions. Anti-TNF alpha approaches appear to be most effective in treating the airway dysfunction phenotype and anti-IL-5 (mepolizumab) appears to be mainly effective at treating SE, the phenotype most closely associated with eosinophilic inflammation. When targeted at appropriate patients these agents can be both clinically and cost-effective.
The Future use of Biologicals in Allergy and Asthma-Pro

World Allergy Forum
Warsaw EAACI Congress XVIII June 6th-10th
2009

Andy Wardlaw MD PhD

Disclosures

• Research grants from Glaxo Smith Kline (GSK) and AstraZeneca
• Honorariums for advisory boards from GSK and MedImmune
• Honorarium for presentation from Merck Sharpe and Dohme

Definition of Asthma

• Variable airflow obstruction
• Airway hyperresponsiveness
• Chronic airway inflammation which is generally eosinophilic.
• What is the relationship between the physiological impairment and the eosinophilic inflammation?
Eosinophilic Airway Inflammation and Variable Airflow Obstruction (AHR) are Largely Independent

Uncontrolled, Treatment Unresponsive Falls in FEV1

Severe Exacerbations

Variable Airflow Obstruction/AHR

Asthma Symptoms

Eosinophilic Inflammation

Smooth Muscle Dysfunction

79% eosinophils

Rx: Oral corticosteroids

0% eosinophils

Rx: Reduce inhaled steroids. Increase bronchodilators
Current classification of asthma heterogeneity is descriptive, anecdotal, subjective and focused on one or two characteristics of the disease

- Aetiology/Triggers
  - Extrinsic versus Intrinsic
  - Occupational Asthma
  - Aspirin Sensitive Asthma
  - Exercise Induced Asthma
  - Chronic

- Pattern of Airflow Obstruction/Symptoms
  - Severe Exacerbations
  - Nocturnal Asthma
  - Brittle Asthma
  - Refractory asthma
  - Cough variant asthma

- Pathology
  - Eosinophilic versus non-eosinophilic
  - Neutrophilic
Novel approaches to analysis of phenotypic heterogeneity in asthma

- Need to approach phenotyping in a way that is objective and can take account of all the dimensions and characteristics that make up an asthma profile
  - Multi-dimensional phenotyping: Wardlaw et al Clin Exp Allergy 2005

Cluster Analysis

- Group of multivariate techniques to define phenotypes
- Data on multiple variables from cases in a population to form clusters.
- Can include large numbers of variables
- Objective approach to phenotypic classification
  - Hypothesis generating
  - Potential to identify novel phenotypes

Haldar et al AJRCCM 2008:178:218

Summary

- Discordant Symptoms
- Early Onset Asthma
- Concordant Inflammation
- Eosinophil
- Refractory Asthma
- Primary Care Asthma
- Concordant disease

- Obsessive Non-Eosinophilic
- High symptom exposure
- Upper airway disease
- No chronic inflammation
- Life style dysfunction

- Eos Inflammation

- Severe Asthma
- Mixed mode of exacerbation
- Few symptoms
- No chronic inflammation
- Life style dysfunction
What is eosinophilic bronchitis?

**Asthma**
- Cough, wheeze, SOB
- Variable airflow obstruction
- Lower airway hyperresponsiveness
- Sputum eosinophilia

**Eosinophilic bronchitis without asthma**
- Chronic cough
- Sputum eosinophilia
- No variable airflow obstruction
- No lower airway hyperresponsiveness

---

Mast cells/mm² airway smooth muscle

**p<0.001**

Brightling et al NEJM 2002

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Mast Cell Myositis in Mild-Severe Asthma

\[ r = -0.53 \]

\[ p = 0.008 \]

Siddiqui et al manuscript in preparation
Evidence for a role for TNF-alpha in asthma

- TNF-alpha mRNA increased in BAL of subjects with asthma
- TNF is produced by mast cells in the asthmatic airway
- Inhalation of TNF causes airway hyperresponsiveness
Key secondary outcomes

- Significant improvement in symptom VAS with etanercept (mean between treatment difference 39 mm; 95% CI 7 to 72; p=0.01).
- No effect on induced sputum differential or total inflammatory cell count
- No effect on sputum supernatant ECP, IL-8 or cysteinyl-leukotriene concentration
- Significant reduction in sputum supernatant histamine concentration (p= 0.02).

Predictors of response to etanercept
Eosinophil Mediators

Lipid Mediators
LTC4, LTD4, PAF, 15HETE, TRX-A2, PGE 1/2

Cytokines
IL-4, IL-6, IL-13, TGF α/β, GM-CSF

Chemokines
CXCL8, CCL3, CCL5

Eosinophil Receptors
VLA-4, PGL-I, SLe-1, CCR3, PAF-R, C5aR, C3a
Siglec-8

Enzymes
Phospholipase D, Arylsulfatase, Histaminase, Catalase, Acid phosphatase, Non-specific esterases, Glycosaminoglycans, hexosaminidase

Eosinophils as Effector Cells in Asthma

- 1960’s: Eosinophils ameliorating the inflammatory process?
- Mid 1970: Butterworth and colleagues: Eosinophil granule proteins toxic for helminthic parasitic larvae
- Early 1980: Gleich and colleagues: eosinophil granule proteins toxic for airway epithelial cells and marked deposition in asthma deaths
- Mid 1980’s: Bronchoscopy studies in mild asthma show eosinophil inflammation
- Early 1990’s: Th2 cells found in asthma: rise of the mouse model
- Millennium: Anti-IL-5 ineffective
- Post-millennium: eosinophils as regulatory cells?

Eosinophils in Asthma

Asthma Death
Charcot-Leyden Crystal
Background
Eosinophilic airway inflammation → Asthma Exacerbations

Post mortem studies of asthma fatalities exhibit dense pulmonary eosinophilia

A rise in counts measured longitudinally predicts subsequent loss of asthma control

Management protocols aimed at titrating steroid therapy to maintain normal counts lead to superior asthma control

Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial

Green RH et al

74 PATIENTS WITH ASTHMA

Standard clinical care (B11)

Titrating steroid therapy according to sputum eosinophils

12 MONTHS

EXACERBATION FREQUENCY

Heterogeneity in Outcome
Million dollar question

- Are eosinophils markers of a specific steroid responsive pathological pathway associated with severe exacerbations or are they causal?

Studies of anti-IL-5 mAb (mainly mepolizumab) in asthma

- Allergen challenge: inhibited blood and sputum eosinophilia but no effect on early or late response
- Mild asthma: 12 weeks (3 doses) bronchoscopy study: 100% reduction blood eos., median 55% reduction airway eos., mean 79% reduction in bronchial eos.; no effect on lung function or AHR
- Severe asthma: pilot study with very small numbers: no major effect on any of the outcome measures: eosinophilic asthma not selected:
  - Kips JC et al: AJRCCM 2003;167;1655
- Moderate asthma: no effect on spirometry, peak flow or AHR. Hint of an effect on exacerbations
  - Flood-Page et al AJRCCM: 2007;176:1022
- Hypereosinophilic syndrome: clear steroid sparing effect
  - Rothenberg et al NEJM: 2008;358:2530
- Eosinophilic asthma: 12 month study with exacerbations as primary outcome:
  - Haldar et al: DBPC parallel group study of Mepo for 12 months in eosinophilic asthma with exacerbations as the primary outcome

Mepolizumab in the hypereosinophilic syndrome: Rothenberg et al 2008

- 84 patients with HES requiring prednisolone 20-60 mg/day
- DBRCT of 9 months mepo 750mg
- Primary outcome: safe reduction of prednisolone to <10 mg
  - PB eosinophil count
  - Organ flare

Heterogeneous patient group with one common factor:
  - Eosinophil driven disease
**Study Design**

**Summary of longitudinal measurements performed**

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<th>Time Period</th>
<th>Measurement Type</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
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**Subjects: Principal Inclusion Criteria**

I. **Diagnosis of asthma**
   - compatible clinical symptoms
   - evidence of AHR or variable airflow obstruction

II. **Diagnosis of refractory asthma**
   - ATS criteria (poor compliance and exacerbating factors assessed and excluded)
   - diagnosis made by specialist respiratory physician
   - subjects attending Glenfield refractory asthma clinic

III. **Evidence of eosinophilic airway inflammation**
   - sputum eosinophil counts ≥3% at least once in previous 2 years

IV. **History of frequent severe exacerbations**
   - ≥2 or more oral steroid courses in previous 12 months

**Primary Outcome:**

**Severe exacerbations**

- Deterioration in asthma symptoms requiring treatment with high dose oral prednisolone for ≥5 days

- An exacerbation event was complete when the patient’s symptoms had returned to baseline for ≥3 days after stopping high dose prednisolone

- Events were recorded between completing first treatment visit and 2 weeks after completing final treatment visit
Secondary outcome measures

Clinical characteristics
- Symptoms
- QOL
- Nasal polyp symptoms

Airway physiology
- AHR (MCH PC20)
- Post BD FEV1

Eosinophilic inflammation
- Peripheral blood
- Sputum
- Mucosal
- BAL
- Bronchial wash

Airway dimensions (CT)
- Wall area
- Luminal area
- % wall area

Enrolment Pathway

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Metformin (N=20)</th>
<th>Placebo (N=20)</th>
<th>Significance</th>
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</thead>
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<tr>
<td>Gender (male/female)</td>
<td>11/9</td>
<td>12/8</td>
<td>0.36</td>
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<tr>
<td>Age (yr)</td>
<td>48 (24-62)</td>
<td>52 (23-72)</td>
<td>0.34</td>
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<tr>
<td>Height (cm)</td>
<td>170 (154-180)</td>
<td>171 (162-179)</td>
<td>0.6</td>
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<tr>
<td>Weight (kg)</td>
<td>74.5 (63-85)</td>
<td>76.1 (65-84)</td>
<td>0.36</td>
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<td>Body Mass Index (kg/m²)</td>
<td>23.5 (21.5-25.5)</td>
<td>23.9 (22.5-25)</td>
<td>0.18</td>
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<td>Fasting Blood Glucose (mg/dL)</td>
<td>96.8 (88.5-104)</td>
<td>98.1 (89.5-105)</td>
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<td>Standardised Percentage correction</td>
<td>1</td>
<td>0.01</td>
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<td>Inhaled Salbutamol (puff)</td>
<td>3.71 (3.3-4.3)</td>
<td>3.71 (3.3-4.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Asthma Severity Score (1-5)</td>
<td>3.7 (3.3-4.3)</td>
<td>3.7 (3.3-4.3)</td>
<td>0.97</td>
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<td>Baseline PEF (L/min)</td>
<td>466 (378-558)</td>
<td>466 (378-558)</td>
<td>0.97</td>
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<tr>
<td>Exhaled Nitric Oxide (%)</td>
<td>46 (44-48)</td>
<td>46 (44-48)</td>
<td>0.97</td>
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<td>Exhaled Bronchial Challenge</td>
<td>1.2 (1.0-1.5)</td>
<td>1.2 (1.0-1.5)</td>
<td>0.97</td>
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<td>Exhaled NO Levels (ppm)</td>
<td>4.3 (3.5-5.2)</td>
<td>4.3 (3.5-5.2)</td>
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<td>Exhaled NO Levels (ppm)</td>
<td>4.3 (3.5-5.2)</td>
<td>4.3 (3.5-5.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Exhaled NO Levels (ppm)</td>
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<td>4.3 (3.5-5.2)</td>
<td>0.97</td>
</tr>
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<td>0.97</td>
</tr>
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<td>0.97</td>
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<td>4.3 (3.5-5.2)</td>
<td>4.3 (3.5-5.2)</td>
<td>0.97</td>
</tr>
</tbody>
</table>
3. Mepolizumab and eosinophilic inflammation

**Peripheral Blood eosinophil counts**

<table>
<thead>
<tr>
<th>Blood Eosinophil count (x10^9/l)</th>
<th>Mean count</th>
<th>0.06 ± 0.03</th>
<th>0.02 ± 0.01</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between means</td>
<td>0.044 ± 0.03</td>
<td>CI 0.13–0.75</td>
<td>CI 0.00–0.05</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Eosinophil (%)</th>
<th>Mean count (range)</th>
<th>0.72 ± 0.03</th>
<th>1.54 ± 0.07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between means</td>
<td>0.82 ± 0.04</td>
<td>CI 0.37–1.27</td>
<td>CI 0.54–1.13</td>
</tr>
</tbody>
</table>

**Sputum and bronchial wash eosinophil counts**

<table>
<thead>
<tr>
<th>Eosinophil (%)</th>
<th>Mean count</th>
<th>3.4 ± 0.3</th>
<th>2.3 ± 0.2</th>
<th>0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between means</td>
<td>1.1 ± 0.5</td>
<td>CI 0.29–1.91</td>
<td>CI 0.07–2.55</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Eosinophils</th>
<th>Sputum Wash</th>
<th>Mepolizumab</th>
<th>Placebo</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean count</td>
<td>3.1 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>4.4 ± 0.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Difference between means</td>
<td>1.3 ± 0.25</td>
<td>CI 0.05–2.60</td>
<td>CI 1.0 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Tissue and BAL eosinophil counts

<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab</th>
<th>Placebo</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>% A subepithelial eosinophil count</td>
<td>-0.6%</td>
<td>+15.9%</td>
<td>0.06</td>
</tr>
<tr>
<td>p&lt;0.05 within group reduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fold % BAL Eosinophil Count</td>
<td>+1.3 ± 0.23</td>
<td>-1.2 ± 0.27</td>
<td>0.06</td>
</tr>
<tr>
<td>p&lt;0.01 between group change</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Longitudinal change in FeNO

<table>
<thead>
<tr>
<th></th>
<th>Mean FeNO5B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>36.1 ± 5.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>38.7 ± 1.1</td>
<td></td>
</tr>
</tbody>
</table>

4. Mepolizumab and severe exacerbations
Analysing exacerbations

- Intention to treat population included all subjects receiving at least one infusion.

- Modelling of exacerbation data is a poor fit for recognised models:
  - negative binomial p = 0.058
  - parametric p = 0.056
  - poisson p = 0.001

- Present consensus: perform analysis with a recognised model and verify with non-parametric test (Keene et al 2008)

Cumulative exacerbation frequency

Rate: 3.41 vs 1.05 exacerbations / patient year

RR = 0.37 (95% CI 0.32 – 0.92) p = 0.023 (Neg binomial)

p = 0.036 (Non-parametric)

Exacerbations compared with previous year

p = 0.02

Hospital Admissions: Mepolizumab: 3, Placebo: 11; p = 0.068
Eosinophilic airway inflammation and exacerbation frequency

<table>
<thead>
<tr>
<th>Tertiles</th>
<th>ACC sputum eosinophil count</th>
<th>Mepolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (N=38)</td>
<td>0.5 (0.01 - 0.07)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>2 (N=38)</td>
<td>3.4 (1.08 - 1.63)</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>3 (N=38)</td>
<td>12.5 (6.03 - 1)</td>
<td></td>
<td>* p&lt;0.05</td>
</tr>
</tbody>
</table>

* p<0.001

NB: Association not seen for symptoms, AQLQ or lung function

5. Mepolizumab and secondary outcomes

Symptom scores

<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab</th>
<th>Placebo</th>
<th>Mean difference (95% CI)</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juniper ACQ</td>
<td>-0.14 ± 0.06</td>
<td>-0.25 ± 0.04</td>
<td>-0.12 ± 0.07 (-0.29 to 0.05)</td>
<td>0.19</td>
</tr>
<tr>
<td>Visual analogue scale</td>
<td>-0.35 ± 1.23</td>
<td>-0.3 ± 0.99</td>
<td>2.59 ± 1.29 (-0.39 to 0.12)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Summary

- Mepolizumab effectively suppressed eosinophilic inflammation in the blood and airways
- Mepolizumab treatment was well tolerated and was associated with a significant and clinically important reduction in the frequency of severe asthma exacerbations
- Mepolizumab treatment was associated with a significant and clinically meaningful improvement in asthma quality of life. This may be a function of improved asthma control
- Mepolizumab was not associated with an improvement in other clinical markers of asthma control

Conclusions

- Most direct evidence so far that eosinophils cause severe exacerbations in asthma
- More potent strategies for suppressing eosinophilic airway inflammation may lead to a greater improvement in exacerbation control
- The study reinforces the view that eosinophilic airway inflammation is dissociated from symptoms and physiological measures of asthma control - implications for choosing outcome measures with specific anti-eosinophilic therapies

Patient selection is essential

- Of 99 consecutive patients with symptoms of fluctuating airway disease and EAI (sputum eos>3%) who attended our clinics - 44 had asthma - 55 had ‘another diagnosis’
- In lung disease anti-eosinophil strategies should be directed against patients with eosinophilic airway disease not just those with an asthma label
Acknowledgements

Ian Pavord
Pranab Haldar

Peter Bradding
Chris Brightling
Ruth Green

Debbie Parker
Sue McKenna
Bev Hargaden
Will Moreiro
Hilary Pateman

Katy Roach
Fiona Symon
Natalie Neale
Maria Shelley

GSK: Richard Marshall and Ana de Souza
Asthma as a chronic condition is highly prevalent, frequently associated with allergies, and for the most part can be treated adequately, following guidelines, with existing therapies including bronchodilators and/or inhaled corticosteroids, sometimes in combination with leukotriene receptor antagonists or theophylline. Disease modification can be afforded by immunotherapy in selected patients and has undoubted efficacy in patients with respiratory allergies. Novel drugs and the use of biologicals for these conditions are being developed and are targeting the more severe population of asthmatics, and if there was a future role it should be reserved for this indication.

The definition of severe asthma is based on clinical parameters of which the management is directly influenced by risk factors and determinants that individually influence the course of the disease. The estimate for the prevalence of severe asthma lies between 5% and 10% of the population with asthma, and by now a number of risk factors have been identified. Tobacco smoking, female gender, and obesity are some of the determinants that have been described although the precise contribution is not always certain. There is good evidence that severe asthma can be described by various phenotypes and for clinical practice it seems advisable to differentiate individuals that have a more rapid decline in lung function from those that present with frequent exacerbations. For those patients with frequent exacerbations, respiratory viruses seem to play an important role as well as allergen exposure and occupational sensitizers. Furthermore, trigger factors such as nonsteroidal anti-inflammatory drugs are important for a subset of individuals with severe asthma. Patients with a rapid decline in lung function appear to have a different risk factor profile with persistent (eosinophilic) inflammation, persistence of inflammation of the upper airways, and structural changes of the lungs. The common abnormality lies in a poor corticosteroid response which is likely to be multi-factorial and is still insufficiently understood.

Nevertheless, the management of severe asthma relies also on the use of inhaled corticosteroids and bronchodilators, and a limited number of studies have addressed the use of high doses of corticosteroids above those routinely recommended. Leukotriene receptor antagonists are included in several guidelines although their benefit is questionable for this indication. Alternative immunosuppressive therapies have been disappointing so far and there is an urgent need for alternative pharmacological developments. The data available on the use of anti-TNF therapies for severe asthma has been disappointing; anti IL-5 strategies are not tested for this indication; only the monoclonal antibody omalizumab has demonstrated efficacy in this patient group.

Given the complexity of the disease, the role of non-pharmacological strategies, including education and instructions in medication use, need to be stressed. Severe asthma is, undoubtedly, frequently associated with a range of co-morbid conditions and the management strategies need to include pharmacological and non-pharmacological approaches. The role of so-called biologicals is at best very limited, with the exception of anti-IgE for highly selected patients. Finally, clinical trials in the future should be performed in pathologically well phenotyped patients to test the efficacy of novel biological interventions; At present, most of the evidence is lacking.
The Future use of Biologicals in Allergy and Asthma - Con

Prof. Dr. Klaus F. Rabe
Department of Pulmonology
Leiden University Medial Center
The Netherlands
Endotyping Asthma: New Insights into Key Pathogenic Mechanisms in a Complex, Heterogeneous Disease

- Allergen plus predisposition
  - Th2
    - Inflammation and damage
    - Airway hyper-responsiveness plus mediators
      - Symptoms

Anderson GP, Lancet 2008;372:1107-1119

Severe Asthma: What is needed?

Local Factors
- Airway Remodeling
- Inflammation
- Asthma

**Background**

- Inhibition of CD25 subunit IL2R on activated T cells inhibits Th2 type cytokine production in vitro
- Daclizumab [Roche]
  - A humanized mAb that specifically binds to the α-subunit (CD25) of the high affinity IL2R
  - Inhibits IL-2 binding and biological activity and therefore may reduce inflammation
  - FDA: induction regimen for rejection prophylaxis in renal Tx
Asthma symptoms during ICS-stable phase:
- Dacibumab reduced daytime asthma symptoms (p=0.018); use of rescue SABA (p=0.009); and evening peak flows (p=0.029).

| TABLE 2. CHANGE FROM BASELINE TO DAY 84 IN MEASURES OF ASTHMA CONTROL |
|-----------------------------|-----------------------------|-----------------------------|
| Dacibumab | Placebo | P-Value |
| Daytime asthma symptoms | -1.2 ± 0.4 | 0.1 ± 0.4 | 0.018 |
| Nocturnal asthma symptoms | -0.2 ± 0.1 | 0.0 ± 0.1 | 0.136 |
| Rescue short-acting β₂-agonist use, puff/day | -0.9 ± 0.4 | 0.5 ± 0.3 | 0.009 |
| Morning peak flow rates, L/min | 12.1 ± 3.8 | -0.1 ± 3.5 | 0.217 |
| Evening peak flow rates, L/min | 13.1 ± 4.1 | -4.1 ± 3.3 | 0.029 |
| Asthma exacerbations, % | 12.1 ± 2.9 | 7.5 ± 4.2 | 0.35 |
| Asthma exacerbations requiring systemic corticosteroids | 3.75 (6.7%) | 3.25 (5.2%) | 0.41 |

All values are means ± SE, unless noted otherwise.

Asthma symptoms during ICS-taper phase:
- no differences between groups

Severe Asthma: What is needed?

Anti – TNF Treatment for Refractory Asthma

Anti-TNFα in Severe Asthma...

Wenzel, ERS 2007
**Anti-TNFα and Severe Asthma**

Severe Exacerbations in Weeks 1 - 24

Patients with > 1 Exacerbation

<table>
<thead>
<tr>
<th>Dosing</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
<th>100 + 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

Anti-TNFα - Dosing every 4 Weeks s.c.

P = n.s., all Comparisons

S. Wenzel, ERS 2007

---

**Anti-IgE Therapy Reduces Allergen-Induced Eosinophilia in Biopsies in Patients with Asthma**

- Placebo
- Anti-IgE

staining for EG2 post allergen

---

**Severe Asthma: What is needed?**

Anti-IgE Study: Allergen Challenge

- Anti-IgE
- Placebo
Management of Asthma Based on Exhaled Nitric Oxide in Addition to Guidelin-Based Treatment for Inner-City Adolescents and Young Adults: a Randomised Controlled Trial

Daily Telemonitoring of Exhaled Nitric Oxide and Symptoms in the Treatment of Childhood Asthma

A New Perspective on Concepts of Asthma Severity and Control
IgE-dependent activation of mast cells is important in many disease states – asthma, allergic rhinitis, anaphylaxis, and urticaria. Given the contribution of IgE to these processes, and its safety and effectiveness in some patients with asthma, it is logical to presume that omalizumab would provide benefit in other IgE-dependent processes as well. Evidence will be presented that treatment with omalizumab reduces systemic reactions, i.e. anaphylaxis, to immunotherapy in patients with persistent asthma, an at-risk situation for systemic reactions to antigen. In addition, omalizumab has been shown to reduce asthma exacerbations, which are most frequently caused by rhinovirus respiratory infections. Serum IgE levels have been found to be risk factors in the severity of a respiratory infection and consequently a virus provoked exacerbation of asthma. Thus, a reduction in IgE may contribute to fewer asthma exacerbations from colds. An in vitro series of experiments with dendritic cells suggests that dendritic cell bound IgE may be a factor in determining the severity of a cold and hence a risk factor for asthma exacerbations.

References
Anti-IgE – Beyond the Current Indications

William W. Busse, M.D.
University of Wisconsin School of Medicine and Public Health
Madison, WI

IgE activation of mast cells:

- Asthma
- Allergic Rhinitis
- Anaphylaxis
- Urticaria

Future indications for omalizumab may include:

- Persistent asthma of all types
- Asthma exacerbations
- Chronic rhinosinusitis
- Anaphylaxis
  - Food allergies
  - Systemic mastocytosis
  - Chronic urticaria
Goals

- To review evidence that anti-IgE reduces systemic allergic reactions (i.e. anaphylaxis) that may occur during immunotherapy
- To discuss the possible beneficial mechanisms for omalizumab in asthma exacerbations

Anti-IgE’s effect on acute allergic reactions

Effect of Pretreatment with Omalizumab on the Tolerability of Specific Immunotherapy (IT) in Patients with Persistent Symptomatic Asthma Inadequately Controlled with Inhaled Corticosteroids

Patient Recruitment

- Subjects with at least moderate persistent allergic asthma
  - Symptomatic on inhaled corticosteroids
  - FEV₁ ≥ 75% predicted
  - Positive prick skin test to cat, dog or house dust mite standardized extract
- Excluded for severe asthma, oral corticosteroid-requiring exacerbation within 3 months, ED visit or hospitalization within 6 months

Study Design

- Randomized to receive either omalizumab or placebo for 12 weeks
- Followed by cluster immunotherapy with cat, dog or mite extracts
  - 8 visits over 4 weeks
- Omalizumab was continued during first 4 weeks of IT build up
- Maintenance therapy continued for 8 weeks without further omalizumab

Xolair and Immunotherapy: Study Design
(275 Patients, Randomized 1:1)

[Diagram showing the study design with phases and visits]
Demographics

<table>
<thead>
<tr>
<th></th>
<th>OMA N=139</th>
<th>PBO N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>38.2</td>
<td>38.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36.7%</td>
<td>27.2%</td>
</tr>
<tr>
<td>Female</td>
<td>63.3%</td>
<td>72.9%</td>
</tr>
<tr>
<td>Weight (mean, Kg)</td>
<td>84.7</td>
<td>82.8</td>
</tr>
<tr>
<td>Baseline FEV1 (mean, L)</td>
<td>2.93</td>
<td>2.84</td>
</tr>
<tr>
<td>FEV1 Percent Predicted (mean)</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>Serum IgE (mean, IU/ml)</td>
<td>158</td>
<td>186</td>
</tr>
</tbody>
</table>

Allergic Reactions

Systemic reactions were graded on a four-point scale:

Grade 1: Skin symptoms
- generalized urticaria, itching, erythema

Grade 2: Gastrointestinal symptoms
- stomach pain, nausea, vomiting

Grade 3: Respiratory symptoms
- clinically significant nasal symptoms and/or dyspnea, wheezing, persistent cough, chest tightness, stridor, hoarseness, angioedema of the lips or tongue

Grade 4: Cardiovascular symptoms
- cyanosis, hypotension, collapse, arrhythmias, angina pectoris

Proportion of Patients Who Experienced a Systemic Allergic Reaction

- Omalizumab: 13.5% (N=126)
- Placebo: 26.2% (N=122)

P= 0.017
Proportion of Patients Who Experienced a Local Reaction

P = 0.525

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>53.2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>49.2%</td>
</tr>
</tbody>
</table>

Severity of First Systemic Allergic Reaction

<table>
<thead>
<tr>
<th>Grade</th>
<th>Omalizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Skin)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>2 (GI)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3 (Resp)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>4 (CV)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Total Number of Doses of Rescue Medications for Systemic Allergic Reactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Omalizumab (# Doses)</th>
<th>Placebo (# Doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Oral Steroids</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Beta Agonists</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>
Conclusions

- Pretreatment with omalizumab significantly reduced systemic allergic reactions from IT
- Pretreatment with omalizumab resulted in a clinically meaningful shift in severity of systemic allergic reactions from IT
- A significantly higher proportion of omalizumab patients were able to reach target maintenance dose of IT
- Omalizumab was well tolerated

Omalizumab reduces asthma exacerbations
Summary of Asthma Exacerbations by Treatment Phase

<table>
<thead>
<tr>
<th></th>
<th>Stable steroid phase</th>
<th>Steroid reduction phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects with exacerbation (%)</td>
<td>39 (4.4%)</td>
<td>60 (22.3%)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Mean no. of exacerbations per subject</td>
<td>0.28</td>
<td>0.54</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>Mean no. of days per exacerbation</td>
<td>7.6</td>
<td>12.7</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
</tbody>
</table>

Blute et al. JACI 2001: 108:184

Exacerbation

Child or adult with asthma

Rhinovirus

Exacerbation of asthma
- Emergency room visits
- Hospitalization

Upper respiratory tract symptom scores

The effect of virus incubation on plasmacytoid dendritic cell generation of interferon

(M. Gill, unpublished data)

Plasmacytoid Dendritic Cells In Patients with Asthma Secrete Less IFN-α Upon Exposure to Rhinovirus

M. Gill, unpublished data

Does pDC FcεRIα Expression Interfere With The IFN-α Response to Influenza?

M. Gill, unpublished data
**FceRI Crosslinking Inhibits RV-Induced IFN-α Secretion From DCs**

High affinity IgE receptor crosslinking inhibits RV-induced IFN-α secretion from dendritic cells. Purified DCs were exposed to MAV-118 virus in 3 conditions: 1) without the addition of antibody (blue), 2) in co-culture with antibody-treated cells (i.e. IgE-coated, second bar), and 3) in co-culture with antibody-treated cells and RV virus (i.e. IgE-coated and RV virus, third bar). Data in the bar graph represent mean values ± SD of 3 separate experiments. Bars represent mean values ± SD of 3 separate experiments.

M. Gill, unpublished data

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**FceRI-Mediated Signaling in Dendritic Cells**

FceRI interacts with the TLR-7 pathway, which interferes with viral-induced IFN-α secretion.

M. Gill, unpublished data
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