World Allergy Forum Symposium:
“Immune Tolerance”

Tuesday, 12 June 2007, 8:30 - 10:00
Göteborg Convention Centre, Room K2 - K3
XXVI Congress of the EAACI
Göteborg, Sweden
Abstract Submission deadline 5 July 2007

Bangkok – the cosmopolitan city of delightful contrasts

We look forward to welcoming you to Bangkok at the

World Allergy Congress 2007

2 – 6 December 2007

including the 10th WPAS in conjunction with
the 7th Asia Pacific Congress of Allergology and Clinical Immunology
“Immune Tolerance”

Program Agenda

Chairs:

Michael A. Kaliner, Institute for Asthma and Allergy
Wheaton, MD, United States

Anthony J. Frew, Brighton General Hospital
Brighton, United Kingdom

1. Welcome to the World Allergy Forum Symposium and Introduction to “Immune Tolerance”
   Michael A. Kaliner & Anthony J. Frew

2. Concepts in tolerance induction in the lung
   Dale T. Umetsu
   Children’s Hospital Boston
   Boston, MA, United States

3. Modulation of IgE-mediated diseases in children: atopic asthma as a paradigm
   Patrick Holt
   Telethon Institute for Child Health Research
   West Perth, WA, Australia

4. Can omalizumab synergize immunotherapy?
   Thomas Casale
   Creighton University
   Omaha, NE, United States

2007 World Allergy Forum Advisory Board

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# About the World Allergy Organization

The World Allergy Organization (WAO) is an international umbrella organization of 74 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**

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.

## Programs of the World Allergy Organization

### GLORIA

**Global Resources in Allergy™**

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: Symptoms and Treatment of Asthma
- Module 6: Food Allergy
- Module 7: Angioedema
- Module 8: Anaphylaxis
- Module 9: Diagnosis of IgE Sensitization
- Module 10: Chronic Rhinosinusitis and Nasal Polyposis

### World Allergy Forum (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

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.

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**ACI-International – Journal of the World Allergy Organization (ACII - JWAO)** and International Archives of Allergy and Immunology.

Read the latest in global allergy and asthma news and research through subscriptions to WAO's journal partners: ACI International - Journal of the World Allergy Organization (ACII - JWAO) and International Archives of Allergy and Immunology.
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- Albanian Society of Allergology and Clinical Immunology
- American Academy of Allergy, Asthma and Immunology
- American College of Allergy, Asthma and Immunology
- Argentine Association of Allergy and Immunology
- Argentine Society of Allergy and Immunopathology
- Australasian Society of Clinical Immunology and Allergy
- Austrian Society of Allergology and Immunology
- Azerbaijani Society for Asthma, Allergy and Clinical Immunology
- Bangladesh Society of Allergy and Immunology
- Belgian Society of Allergology and Immunology
- Brazilian Society of Allergy and Immunopathology
- British Society for Allergy and Clinical Immunology
- Bulgarian National Society of Allergology
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- Latvian Association of Allergists
- Panamanian Association of Allergology and Clinical Immunology
- Association of Allergy and Clinical Immunology of Serbia and Montenegro

### Regional Organizations

- The Asian Pacific Association of Allergology and Clinical Immunology
- Commonwealth of Independent States Society of Immunology and Allergology
- European Academy of Allergology and Clinical Immunology
- Latin American Society of Allergy, Asthma and Immunology

### Affiliate Organizations

- International Association of Asthmology

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Asthma and allergy are thought to develop as a result of an over-abundance of Th2 cells and/or a relative-lack of regulatory T cells. We have shown that asthma and allergy are regulated by a number of distinct CD4+ T cells that include antigen-specific Th1-like T\textsubscript{reg}, and Th2-like T\textsubscript{reg}, cells, as well as Natural Killer T (NKT) cells. Both Th1-like T\textsubscript{reg} and Th2-like T\textsubscript{reg} cells arise following antigen exposure and express Foxp3, and both can potently inhibit the development of allergen-induced airway hyperreactivity (AHR), a cardinal feature of asthma. In contrast, NKT cells appear to be antigen-nonspecific, but are able to greatly exacerbate the development of allergen-induced AHR. The specific mechanisms and interactions that link Th2, T\textsubscript{reg} and NKT cells in the airways are not yet clear.
Concepts of Tolerance Induction in the Lung

Dole T. Umetsu, MD, PhD
Harvard Medical School
Division of Immunology
Children’s Hospital Boston

Asthma and allergy are immunological diseases caused by adaptive immune responses

Allergen-specific immune deviation protects against the development of AHR
Respiratory exposure to OVA inhibits the induction of AHR

![Graph showing the effect of OVA on AHR](image)

Protection against AHR is mediated in part by OVA-specific T\(_{\text{Reg}}\) Cells

![Graph showing the effect of T\(_{\text{Reg}}\) on AHR](image)

OVA-specific T\(_{\text{Reg}}\) cells inhibit AHR

- The protection against AHR was mediated by OVA-specific Th2-like T\(_{\text{Reg}}\) cells (Nature Medicine. 8:1024-32. 2002).
  - Induced with respiratory tolerance.
  - Required ICOS-ICOSL signaling.
  - CD8α+ DCs producing IL-10 induced.
  - expressed IL-10, GATA3 and Foxp3.
Allergen-specific immune deviation protects against the development of AHR

HKL as an adjuvant prevents AHR

Activated T Cells Simultaneously Produce IL-10 and IFN-γ
**IL-10⁺, IFN-γ⁺ T_{Reg} Cells Inhibit AHR**


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**Inhibition of AHR by IL-10⁺, IFN-γ⁺ T_{Reg} Cells Was Mediated by IL-10, not IFN-γ**


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**Antigen-specific T_{Reg} cells inhibit AHR**

- Airway inflammation and AHR were inhibited by T_{Reg} cells (*Nature Immunol.* 5:1149-1156. 2004).
  - Induced with CD8α⁺ DCs producing IL-12 and IL-10.
  - Required ICOS-ICOSL signaling.
  - T_{Reg} cells produced IFN-γ and IL-10.
  - Expressed T-bet and Foxp3.
- In both systems, antigen-specific T_{Reg} cells developed from CD25⁻ Foxp3⁻ precursor cells.
- A spectrum of antigen-specific T_{Reg} cells may exist.
Allergen-specific T cells

- In both allergic and non-allergic humans, allergen-specific T cells could arise from similar precursor cells, and recognize the same allergen-epitopes.
  - in allergic individuals T cells produced Th2 cytokines.
  - in nonallergic individuals T cells had inhibitory function.

- In nonallergic individuals, allergen-specific T cells with regulatory cell activity are present.
  - Previous studies have generally assumed that if a T cell proliferates to allergen, it is allergen specific.
  - To directly examine allergen-specific T cells in both allergic and nonallergic humans, we adopted a class II tetramer-based approach.

Identification of HLA-DR4 Rye grass (Lol p1) specific epitopes

HLA-DR4 Patient Population

- Screened 262 individuals for HLA type
  - 28 (11%) were HLA-DR4 positive (DRB1*401 by high resolution sequence).
    - 12 were rye grass sensitive (allergic)
    - 11 were negative for all allergens (nonallergic)
    - 5 were negative for rye grass, but positive for other allergens (intermediate)
**Peptide 13 Activates HLA-DR4 Human T Cells**

![Graph showing IL-5 and IFN-γ production for different peptides.](image)

**Tetramer+ cells increase in number over 3 days**

- **A** Response with peptide 13
  - Control Tetramer: 0.21, 0.44
  - Rye grass tetramer: 0.56, 2.96
- **B** Response with Lol p protein
  - Control Tetramer: 0.44, 1.64
  - Rye grass tetramer: 0.51, 0.67

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**Rye grass tetramer staining**

- Control tetramer: 0.56, 0.40
- Rye grass tetramer: 2.96, 1.64
- Control tetramer: 0.32, 0.35
- Rye grass tetramer: 0.48, 0.59
**Tetramer^+ cells in allergic and nonallergic subjects**

A

Peptide 13 - Allergic

- Control tetramer
- Rye grass tetramer

B

Peptide 13 - Intermediate

- Control tetramer
- Rye grass tetramer

C

Peptide 13 - Non Allergic

- Control tetramer
- Rye grass tetramer

**Tetramer^+ cells in allergic and nonallergic individuals**

C

- Allergic

- Non allergic

IL-2 does not increase tetramer^+ cells in nonallergic individuals

A

Allergic (A-6)

- Day 3
- Day 4
- Day 5

B

Non Allergic (NA-4)

- Control tetramer
- Control tetramer + IL-2
- Rye grass tetramer
- Rye grass tetramer + IL-2
Cytokine production in tetramer\(^+\) cells

Summary

- In mice, allergen-specific T\(_{\text{Reg}}\) cells with distinct characteristics can be induced.
  - T\(_{\text{Reg}}\) cells producing IL-10 and expressing Foxp3 and GATA3.
  - T\(_{\text{Reg}}\) cells producing IL-10 and IFN-\(\gamma\), and expressing Foxp3 and T-bet.
  - Both are effective in inhibiting AHR and inflammation.
- In humans, allergen-specific class II tetramer\(^+\) cells are present in allergic but not nonallergic individuals.

Summary

- Possible explanations for these results in humans:
  - Allergen-specific T cells are deleted in non-allergic individuals. Or they are anergic and cannot be expanded.
  - The antigen-epitopes that non-allergic individuals respond to are distinct from those used by allergic individuals.
  - Tetramer technology is not sensitive enough to identify allergen-specific T\(_{\text{Reg}}\) cells in non-allergic individuals.
    - Allergen-specific T\(_{\text{Reg}}\) cells are present at a very low frequency and cannot detected with current technology.
    - Immunization with allergen might expand the number of allergen-specific T\(_{\text{Reg}}\) cells.
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Thomas Forsthuber, Univer of Texas, San Antonio
Gordon Freeman, DFCI, Harvard Medical School
Arlene Sharpe, Harvard Medical School
Modulation of IgE mediated diseases in children: atopic asthma as a paradigm

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West Perth, WA, Australia

Abstract
Current treatment paradigms for atopic asthma focus on normalisation of immunological and/or lung function in subjects with established disease. This approach has a range of theoretical limitations, including the decreasing plasticity of T-cell memory responses over time which limit the effectiveness of immunotherapy, the parallel decreasing reversibility of changes in lung function over time, and the ever widening range of environmental factors capable of triggering exacerbation of symptoms as the disease progresses. This presentation will review arguments in favour of an alternative approach i.e. intervention at very early stages of disease before chronicity becomes established. The target age group of principal interest in this context are preschool children and/or those in early primary school. The underlying theoretical basis for the interventions to be discussed is provided by recent findings from birth cohort studies. Notably, a series of studies indicate that both early sensitisation to inhalant allergens and early lower respiratory tract viral infections independently increase risk for development of persistent asthma by the end of the preschool years. Additionally, these two inflammatory pathways can interact synergistically to generate very high Odds Ratios for asthma at 5-6 years, and hence attenuation of either pathway has the potential to have a significant impact on disease prevalence within the population at large. A series of plausible intervention strategies will be discussed, based on recent findings related to asthma aetiology. The targets for these strategies include the maturation process underlying the postnatal acquisition of overall immune competence, development and consolidation of allergen-specific Th-memory, and airways inflammation in infants and young children triggered by atopic responses to inhalant allergens and/or responses to viral pathogens.

References
Modulation of IgE related disease in children
Atopic asthma as a paradigm

Patrick G Holt FAA
Telethon Institute for Child Health Research, Perth

Atopic asthma: current treatment paradigms
and potential impediments to success

- decreasing plasticity of immune responses over time
- decreasing reversibility of inflammation-induced changes in lung function
- progressively increasing range of “trigger” factors for symptom induction
- role of individual pathogenic factors changes as disease progresses

Alternative approach

gene x environment interactions ×
established atopic asthma

treatment

normalise

immune function

lung function

earlier intervention → disease prevention
Progression from infant wheeze to chronic asthma
A working model

Infection: sensitisation interaction & asthma risk

<table>
<thead>
<tr>
<th>Significant predictors</th>
<th>Never sensitised (n=70)</th>
<th>Sensitised after 2yrs (n=26)</th>
<th>Sensitised before 2yrs (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any 1st year wLRI</td>
<td>1.4 [0.4 - 5.1] p=0.6</td>
<td>0.5 [0.1 - 3.5] p=0.5</td>
<td>3.4 [1.5 - 6.4] p=0.020</td>
</tr>
<tr>
<td>2 or more wLRI</td>
<td>1.0 [0.1 - 0.1] p=1.0</td>
<td>insufficient number</td>
<td>7.1 [1.3 - 38.4] p=0.023</td>
</tr>
<tr>
<td>Any febrile LRI</td>
<td>1.0 [0.2 - 3.4] p=1.0</td>
<td>1.4 [0.2 - 9.9] p=0.8</td>
<td>4.2 [1.5 - 11.8] p=0.006</td>
</tr>
<tr>
<td>Any RV/RSV wLRI</td>
<td>0.8 [0.2 - 4.0] p=0.8</td>
<td>0.9 [0.1 - 6.4] p=0.9</td>
<td>4.1 [1.4 - 11.8] p=0.02</td>
</tr>
</tbody>
</table>

*Sub-Johnston et al

JACI in press
Progression from infant wheeze to chronic asthma
A working model

What options are available for early intervention targeted at halting progression?

Pathways to wheeze in childhood

Synergism between these pathways creates highest O.R. for asthma
Attenuation of EITHER may be sufficient to prevent progression to full blown disease
**Potential interventions for PRIMARY prevention**

*initiation phase of asthma*

1. **Accelerate normal maturation of immune function by enhancement of environmental microbial stimulation**

   e.g. probiotics; bacterial extracts; CPG; BCG; M. vacciae

   Theoretical target: "generic" mechanism(s) controlling resistance to infection, sensitisation and inflammatory damage (Th-cells; APC; Treg)

   **The challenge: target(s) very diverse**

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**Potential interventions for PRIMARY prevention**

*initiation phase of asthma*
2. Selectively inhibit sensitisation to major indoor allergens

The "natural" immune response to repeated mucosal antigen exposure is induction of TOLERANCE

**INGESTED OR INHALED PROTEIN ANTIGENS**

- Initial IgE responses
- Selective suppression of IgE antibody production
  - Preservation of variable levels of IgG/IgA/T-helper cell function

*Oral tolerance to food antigens*............Wells et al 1991
*Tolerance to inhaled antigens*............Holt et al 1991

*Hypothesis*: mucosal tolerance operates at diminished efficiency in HR infants
Trial rational: push exposure towards the “tolerogenic” end of the dose curve

NIH Immune Tolerance Network: Allergy/asthma Prevention Trial

PROTOCOL ITN025AD

Centres: Perth, Melbourne, New York, Stockholm, Berlin

Target: 200 High risk children (18-30mths) not yet sensitised to inhalants

Inhalants of interest: HDM, Cat, timothy grass

Protocol: Daily high dose aeroallergen mix -> oral mucosa for 3 yr followup
(double blind/placebo controlled)

Aim: 50% reduction in sensitisation AND current asthma @ outcome age

Parallel mechanistic studies: T-cell immunity/lung physiology

recruiting started July 2006

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**Potential interventions for PRIMARY prevention**

birth

infancy

early childhood

- virus

- maturational deficiency in immune competence

- Th2-memory priming

- Th1-memory asymptomatic

- Th2-memory reactivation

- intermittent wheeze

- airway inflammation

- airway inflammation

- intermittent wheeze

- alterations in lung growth & differentiation

- URTI

- recurrent wheeze

- wURT1

- intermittent wheeze

Current asthma @ 6YRS

3. Conventional immunotherapy (SCIT; SLIT; allergen/CPG etc) ..........but at younger ages

**NB**: PAT trials in Europe preventing progression from AR to asthma in 6-12yr olds
Potential interventions for PRIMARY prevention

4. Th2 antagonists and other selective anti inflammatory drugs as "disease modifiers" in children [steroid effects appear to be transient]

Initially: anti-IgE, Leukotriene antagonists and anti-IL-5

1yr old children

Associations between immunophenotypes and wheezing phenotypes
Multiple logistic regression analyses

<table>
<thead>
<tr>
<th>Study group</th>
<th>Current asthma</th>
<th>Airways hyperresponsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population (n=172)</td>
<td>Eosinophils (OR 5.39 [2.06 - 13.84]; p = 0.003)</td>
<td>Eosinophils (OR 26.09 [7.01 - 120.69]; p = 0.000)</td>
</tr>
<tr>
<td></td>
<td>IgE-IL-SHED (OR 1.07 [1.11 - 2.17]; p = 0.800)</td>
<td>IFN-γ/PHA (OR 1.62 [1.36 - 2.17]; p = 0.023)</td>
</tr>
<tr>
<td>HCMH (n=75)</td>
<td>Eosinophils (OR 12.19 [2.12 - 70.11]; p = 0.001)</td>
<td>Eosinophils (OR 273.49 [16.14 - 4603.88]; p = 0.000)</td>
</tr>
</tbody>
</table>

Heaton, Holt et al. Lancet 2005
5. Maximise protection of infants against strong respiratory pathogens

   e.g. develop more effective vaccines and/or passive antibodies for use in early infancy
**wLRI in early life**

Both RV and RSV wLRI are risk factors for asthma at 5y

<table>
<thead>
<tr>
<th></th>
<th>RV wLRI OR (95% CI), p</th>
<th>RSV wLRI OR (95% CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma ever</td>
<td>3.2 (1.4-7.3), 0.003</td>
<td>4.8 (1.3-17.1), 0.009</td>
</tr>
<tr>
<td>Current asthma</td>
<td>2.8 (1.2-6.6), 0.02</td>
<td>2.7 (0.7-9.6), 0.1</td>
</tr>
<tr>
<td>Persistent wheeze</td>
<td>2.8 (1.2-6.6), 0.01</td>
<td>3.5 (1.1-12.1), 0.04</td>
</tr>
</tbody>
</table>

Infections during year 1 may be most crucial.

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**Conclusions**

- Increasing range of ethically scientific defensible options becoming available for early intervention → atopy prevention
- In various stages of clinical testing
- Early pediatric treatment aimed at atopy prophylaxis in high risk children likely to join the ranks of "standard practise" in the foreseeable future
Learning Objectives:

1. Understand the mechanisms of action of omalizumab and immunotherapy.
2. Discuss the rationale for combining omalizumab and immunotherapy for the treatment of allergic diseases.
3. Summarize the efficacy and safety of omalizumab pretreatment for patients undergoing allergen-specific immunotherapy.

Current therapies for allergic rhinitis and asthma include allergen avoidance; pharmacologic interventions such as topical and systemic corticosteroids, and immunotherapy. Although pharmacologic agents are often effective for many patients, their role is sometimes limited by their inability to completely relieve symptoms, and in some cases, the induction of deleterious side effects. Immunotherapy regimens can be highly effective in controlling symptoms of allergic rhinitis and asthma and can offer advantages over pharmacotherapy for those patients who have symptoms that are refractory to medications or those who cannot tolerate the side effects. However, immunotherapy is associated with the risk of allergic reactions to the extract injections. Furthermore, the effectiveness of allergen-immunotherapy for allergic respiratory diseases is not always evident, especially in asthma.

Omalizumab, a monoclonal antibody against IgE has been approved in many countries for the treatment of moderate to severe persistent allergic asthma. Omalizumab has been shown to be safe and effective for the treatment of children and adults with seasonal and perennial allergic rhinitis as well as allergic asthma. It causes a dose-related decrease in serum IgE levels that is associated with improvement in symptoms. Omalizumab has been shown to both prevent the development of symptoms, and treat established allergic disorders. Omalizumab does not completely ameliorate symptoms of allergic respiratory symptoms, and upon discontinuation, serum IgE levels return to pre-treatment levels. Furthermore, there are no data concerning long lasting immune tolerance as a result of anti-IgE therapy.

Thus, there is a need for safer and more effective therapies capable of inducing an immune tolerant state. The combination of anti-IgE and allergen immunotherapy holds promise for such therapy.

The rationale for using the combination of anti-IgE and allergen immunotherapy comes from pre-existing data about the biologic and immunologic effects of both therapies. Allergen immunotherapy has been used for more than ninety years for the management of allergic disorders, including seasonal and perennial allergic rhinitis, allergic asthma and hymenoptera sensitivity. Immunotherapy is the only antigen-specific immunomodulatory treatment routinely available to clinicians. It can provide long-term benefits and modify the natural history of allergic diseases, preventing the development of neo-sensitization and asthma in children. The immunomodulatory effects of immunotherapy are due to a number of mechanisms. Immunotherapy blunts seasonal increases in IgE levels and leads to increases in allergen-specific IgG levels, especially IgG4. This results in decreased IgE-mediated histamine release and inhibition of IgE-mediated antigen presentation to T-cells. Furthermore, the binding capacity of IgG4 is increased, whereas that for IgE is decreased after long term immunotherapy. In addition, immunotherapy has profound effects on lymphocytes. Although somewhat controversial, immunotherapy appears to shift the balance of T-lymphocyte subsets away from a Th2 phenotype and toward a Th1 phenotype. Furthermore, immunotherapy leads to the production of allergen-specific IL-10. IL-10 has a number of biological consequences that could be important in mediating the immunotolerogenic effects of immunotherapy. These effects include modulation of IL-4 induced B-cell IgG production in favor of IgG4, inhibition of IgE-dependent mast cell activation, inhibition of human eosinophils including decreased cytokine production and survival, suppression of IL-5, and induction of allergen-specific anergy. Finally, the importance of not only IL-10, but regulatory T-cells and dendritic cells in mediating the therapeutic effects of immunotherapy is just being elucidated.

Omalizumab decreases serum IgE and the expression of FcεR1 on key immune effector cells including dendritic cells, monocytes, mast cells and basophils. Each of these effects could lead to important immunologic changes that could enhance the immune tolerance to allergens delivered by immunotherapy. However, unlike immunotherapy, omalizumab has not been shown to provide long-lasting immunotolerogenic and therapeutic effects after discontinuing treatment.
The rationale for combining omalizumab plus allergen immunotherapy includes the prospects of improved clinical benefits and immunotolerogenic effects. Furthermore, by decreasing serum IgE levels and FceRI expression, omalizumab should make immunotherapy safer.

In a study conducted by the Omalizumab Rhinitis Study Group, the effects of adding omalizumab to immunotherapy were examined in children. Subjects underwent a prescreening phase and then over a twelve-week period received immunotherapy up to a maintenance dosage. Subjects were then randomized to receive either omalizumab or placebo as an add-on therapy for twenty-four additional weeks. Inclusion criteria included 6 to 17 years of age, two year history of moderate-to-severe seasonal allergic rhinitis due to birch and grass pollen, FEV1 values greater than 70% and serum IgE levels between 30 and 1,300 IU/ml. 221 subjects were enrolled. The combination of immunotherapy plus omalizumab was more effective than either therapy alone or placebo. For example, the combination of immunotherapy plus omalizumab versus immunotherapy alone produced a reduction in seasonal allergic rhinitis symptoms of 35% for the birch and 45% for grass immunotherapy groups, respectively; rescue medication scores of 78% for birch and 81% for grass immunotherapy; and seasonal allergic rhinitis symptom load of 40% for both grass and birch groups; and a safety profile at least as good as immunotherapy alone.

More recently, the results of a NIH/ImmuneTolerance Network sponsored study examining the effects of pre-treatment of ragweed allergic rhinitis patients with omalizumab prior to immunotherapy was published. The hypothesis was that pre-treatment of ragweed allergic patients with omalizumab will condition the recipient so that subsequent administration of ragweed allergen immunotherapy is safer, clinically more effective and immunologically more efficient at inducing a long-lasting immune tolerance to ragweed. The specific aims were to:

1. Examine whether omalizumab given nine weeks prior to rush immunotherapy (RIT) followed by twelve weeks of dual omalizumab plus immunotherapy is safer and more effective than immunotherapy alone (primary objective) and omalizumab alone and placebo (secondary objectives) in preventing symptoms of ragweed-induced seasonal allergic rhinitis;

2. Study the immunologic mechanisms of action associated with these therapies;

3. Study whether there is an induction of tolerance after discontinuing these therapies as manifested by persistent inhibition of in vivo challenges and prolonged in vitro immunologic changes indicative of tolerance.

Omalizumab preceding immunotherapy should theoretically provide greater safety for immunotherapy by not only reducing serum IgE and high affinity IgE receptor expression, but perhaps by leading to a different mode of antigen presentation. In addition, omalizumab should allow more rapid antigen administration and the use of greater amounts of antigen in immunotherapy.

This was a phase II, double-blind, parallel group, three center, placebo-controlled study. Patients were screened between April 7 and approximately May 13, 2003. Omalizumab [0.010mg/kg/IgE (IU/ml)] or omalizumab placebo pre-treatment was then begun for nine weeks. This was followed by a five hour rush or placebo immunotherapy day. Subsequently, patients received omalizumab or placebo and immunotherapy or placebo immunotherapy for twelve weeks up to September 29, 2003.

Patients were followed over a second ragweed season off immunotherapy and omalizumab to determine whether there are long-lasting effects of the therapy.

The primary endpoint was the average daily allergy severity score which included sneezing, nasal congestion/stuffiness, itchy nose, throat and palate; itchy, watery eyes; and rhinorrhea. Secondary endpoints included incidence and severity of adverse events, the number of days with rescue medication use, the number of rescue medication capsules used, RQLQ scores, daily AM/PM symptom scores, minimal symptom days, individual allergy symptom scores, and in vivo/in vitro immunologic assays. Major inclusion/exclusion criteria included a history of ragweed seasonal allergic rhinitis symptoms for greater than or equal to two years requiring pharmacotherapy, a positive skin prick test to ragweed, IgE levels between 10 and 700, no asthma, and no prior treatment with monoclonal antibodies or immunotherapy.

The groups were evenly divided in regards to age and gender. The mean age was approximately 33 years and there was a slight predominance of females. Serum IgE levels range from 10 to 650 with a mean of 91 to 118 in the four groups. 159 total subjects were randomized. Of these 159 patients, 123 completed all treatments. Ragweed-specific IgG levels increased >11-fold in immunotherapy patients, and free IgE levels declined >10-fold in omalizumab patients.

The number, scope and severity of adverse events associated with RIT were highest in those patients receiving immunotherapy only. Only small differences in the percentage of patients with adverse events were noted between treatment arms receiving omalizumab plus immunotherapy, omalizumab alone and placebo.
In contrast, the patients receiving immunotherapy only had a much greater rate of allergic-like reactions during RIT, and the percentage of these patients having allergic-like reactions during the RIT was allergen dose-dependent, as shown in Figure 2. More patients in the immunotherapy only group (20.5%) versus the group receiving omalizumab plus immunotherapy (13.9%) received epinephrine for allergic-like reactions on the RIT day. The percentages of patients with serious adverse events during RIT were 2.6, 0, 15.0, and 5.0 for the omalizumab plus immunotherapy, omalizumab only, immunotherapy only and placebo only groups, respectively. Allergic-like reaction rates in the omalizumab alone and placebo groups were 0 and 2.7%, respectively.

Overall rates of allergic reactions during RIT (including those treated before or after July 1, 2003) were 33.3% omalizumab plus IT, 29.7% omalizumab plus placebo; 56.4% placebo plus immunotherapy; and 18.9% placebo/placebo. Pairwise comparisons of adverse events in each group illustrate that immunotherapy alone was associated with a greater than five-fold, significant increase in risk of adverse events compared to placebo (OR=5.41; p=0.001). This significant increase is lost with the addition of omalizumab to RIT, which carried only an approximately two-fold risk of adverse events compared to placebo (OR=2.12; p=0.19). After RIT, comparison of groups receiving build-up or maintenance immunotherapy with or without omalizumab revealed a trend towards a decreased risk of adverse events with the addition of omalizumab (OR=0.39), although statistical significance was not reached (p=0.064), possibly due to the low frequency of events. No significant differences in the incidence of immediate post-injection adverse events were observed between groups during the build-up and maintenance phase.

Results of a post-hoc blinded analysis of patients judged to have anaphylactic reactions (defined as reactions involving two or more organ systems concurrently and/or severe enough to require epinephrine; judged by independent observers) during RIT also indicated a protective effect of omalizumab (Table II). In pair-wise analysis, immunotherapy alone was shown to significantly increase the risk of anaphylaxis compared to placebo (OR=12.08; p=0.007), whereas the addition of omalizumab reduced this increased risk to levels that were no longer significant (OR=2.10; p=0.615). A comparison of groups receiving immunotherapy (omalizumab + IT vs IT-only) demonstrated that the addition of omalizumab resulted in a significant, five-fold decrease in risk of anaphylaxis due to RIT (OR=0.17; p=0.026).

Using the same definition (of anaphylaxis), 0% of patients in the omalizumab plus immunotherapy arm versus 9.7% in the placebo plus immunotherapy arm had anaphylaxis during the weekly build-up/maintenance phase of immunotherapy, but this difference did not reach statistical significance (p=0.238), perhaps reflecting the low number of anaphylactic events during IT.

The average daily allergy severity scores were significantly better in the omalizumab plus immunotherapy group versus the immunotherapy alone group. Furthermore, in protocol correct patients, the combination of omalizumab plus immunotherapy was better than omalizumab alone, immunotherapy alone or placebo alone (Figure 3).

**FIG 2.** RIT time-dependent and dose-dependent allergic reactions among patients dosed after July 1, 2003. The data represent percentages of patients with acute allergic reactions based on the time after RIT was initiated in hours and the corresponding dose of Amb a 1 in the RIT (in patients receiving omalizumab plus immunotherapy and placebo plus immunotherapy). IT, Immunotherapy; OM, omalizumab.

**FIG 3.** Average daily allergy severity scores over the ragweed pollen season for per protocol patients. Area under the curve analysis indicated a statistically significant improvement in severity scores for patients treated with omalizumab and immunotherapy versus immunotherapy alone (P = 0.02). The length of the ragweed season differed by site: Creighton University had a length of 46 days; University of Wisconsin, Madison 39 days; and University of Iowa, 43 days. IT, Immunotherapy; OM, omalizumab.
Can omalizumab synergize immunotherapy – continued

There are still some important questions regarding this approach including:

How Long Should Omalizumab Pretreatment Be For Asthma Trials?

- Data to date:
  - Nasal challenges: 2 wks
  - FcεRI expression: 2 wks
  - Skin challenges: 8-10 wks
  - Asthma improvement: 12-16 wks
  - Rush immunotherapy: 9 wks

- Data suggest that to achieve a safer IT regimen – should treat for >12 weeks.

Unanswered Questions Include:

- How long do you need to treat with both?
- Can you stop the omalizumab after reaching maintenance IT?
- What are the immunologic and clinical endpoints of interest, and when do you measure them?
- Will this approach work for moderate/severe asthma?
- Other?

References (listed chronologically)


