World Allergy Forum Symposium:
Advances in Tolerance Induction to Allergens

2013 AAAAI Annual Meeting
Sunday, 24 February 2013
10:45 – 12:00
San Antonio, TX, USA

Moderators:
Ruby Pawankar (Japan)
Wesley Burks (United States)

New Frontiers in the Mechanisms of Tolerance Induction to Allergens
Paul Bryce (United States)

Early Intervention for Primary Tolerance to Allergens
Katrina Allen (Australia)

Update on the Role of SLIT in Tolerance Induction to Allergens:
Safety and Efficacy
Giovanni Passalacqua (Italy)

www.worldallergy.org
“Advances in Tolerance Induction to Allergens”

Program

Moderators:
Ruby Pawankar, MD PhD
Nippon Medical School
Tokyo, Japan

A. Wesley Burks, MD
University of North Carolina
Chapel Hill, NC, United States

1. Welcome to the World Allergy Forum Symposium and Introduction to “Advances in Tolerance Induction to Allergens”
   Ruby Pawankar, MD PhD
   Nippon Medical School
   Tokyo, Japan

2. New Frontiers in the Mechanisms of Tolerance Induction to Allergens
   Paul Bryce, PhD
   Northwestern University
   Chicago, IL, United States

3. Early Intervention for Primary Tolerance to Allergens
   Katrina Allen, MD PhD
   Royal Children’s Hospital
   Parkville, VIC, Australia

4. Update on the Role of SLIT in Tolerance Induction to Allergens: Safety and Efficacy
   Giovanni Passalacqua, MD
   IRCCCS San Martino Hospital-University of Genoa
   Genoa, Italy

2012-2013 World Allergy Forum Advisory Board

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The World Allergy Organization (WAO) is an international alliance of 89 regional and national allergy, asthma and clinical immunology societies. Through collaboration with the Member Societies, WAO provides a wide range of educational and outreach programs, symposia and lectureships to allergists/immunologists around the globe and conducts initiatives relating to clinical practice, service provision, and physician training in order to better understand and address the challenges facing allergists/immunologists worldwide. WAO helps expand the knowledge, expertise and skills of young physicians establishing careers in allergy through Research Fellowships with international placements at renowned allergy centers.

Mission Of The World Allergy Organization
WAO’s mission is 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.

WAO Meetings
World Allergy Congress™ (WAC)
WAO hosts the World Allergy Congress™ (WAC) — its main scientific meeting — biennially in different regions of the world. Please join us in Milan, Italy in 2013 and Seoul, South Korea in 2015.

World Allergy Organization Journal
The World Allergy Organization Journal (WAO Journal) provides a global forum for the exchange of research and information on allergy, asthma, and clinical immunology. The journal supports this scientific interaction among members of the World Allergy Organization, an alliance of 89 societies worldwide, through publication of original research, clinical reviews, position papers, and epidemiological studies that contribute to current knowledge in patient care. Articles cover diagnosis, therapeutic options, crisis management, and treatment efficacy. Authors and reviewers represent all geographic regions, providing a truly global perspective. Published monthly online, with access on computers and mobile devices, the journal ensures the widest availability of practice-relevant science at the point of care.

WAO Online Resources
As a leading global online destination for allergy, asthma and clinical immunology the WAO website supports and enhances WAO educational activities and provides materials specifically designed for continued learning and reference.

Popular resources include:
- Specially commissioned educational synopses on major topics posted in the Allergic Diseases Resource Center
- Interactive case studies that challenge allergists to diagnose unusual cases
- Online learning programs including the Immunology Online Lecture Series, Asthma and Allergic Rhinitis Online Lecture Series, and the case-based interactive learning modules on Allergic Rhinitis as well as those with CME on Food Allergy and Drug Allergy
- An archive of webinars recorded at major meetings, and audio recordings of interviews with key opinion leaders around the world
- A special section, Defining the Specialty, which provides easy access to WAO publications and other resources that help to define the specialty of allergy and immunology including the WAO White Book on Allergy
- Disease-specific sections of the website including the Allergic Rhinitis Working Group, Small Airways Working Group, and HAE International Alliance.

The WAO website is HONcode certified. www.worldallergy.org
WAO Programs for Education, Research and Patient Care

World Allergy Forum ® (WAF)
The World Allergy Forum ® (WAF) program brings cutting edge symposia to major allergy meetings throughout the world. 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. WAF is the longest running educational program series sponsored by WAO and currently provides two or three placements a year with up to 1,000 attendees at each program. WAF is supported by an unrestricted educational grant from Novartis. View presentations for free at www.worldallergy.org/waf.

Emerging Societies Program (ESP)
In order to advance the WAO mission of supporting developments that will enable allergists to better serve patients now and in the future, the Emerging Societies Program (ESP) aims to disseminate information on and share experiences about new treatments for allergic disease and about new indications for available therapies. As a response to an area of need identified by ESP Delegates, the ESP has also started to offer World Allergy Training Schools (WATS) in various regions of the world. All ESP meetings and training schools are conducted with the help and support of WAO Member Societies and held in conjunction with a Member Society’s annual meeting and in partnership with the American College of Allergy, Asthma and Immunology (ACAAI). View all ESP activities at www.worldallergy.org/esp in various regions of the world. All ESP meetings and training schools are conducted with the help and support of WAO Member Societies and held in conjunction with a Member Society’s annual meeting and in partnership with the American College of Allergy, Asthma and Immunology (ACAAI). View all ESP activities at www.worldallergy.org/.

WAO Publications
WAO papers support and promote the specialty of allergy and help set standards for clinical practice and training. A full bibliography is available at www.worldallergy.org/publications/.

World Allergy Week
In 2011, based on feedback from WAO Member Societies over recent years, WAO inaugurated the first annual World Allergy Week as a way for WAO Member Societies to collaborate in a global effort to disseminate information of worldwide importance about allergic and immunologic diseases and asthma. Participation covered a wide spectrum of activities including promotions through websites and social media avenues, patient information sessions, and interviews for radio and television programs. The next World Allergy Week will be held from 8 to 14 April 2013. Watch for updates and view last year’s activities at www.worldallergyweek.org.
The World Allergy Organization (WAO), a world federation of allergy, asthma, and clinical immunology societies, consists of 89 Member Societies. All active members of dues-paying Member Societies are Individual Members of WAO.

**WAO Member Societies**

Albanian Society of Allergology and Clinical Immunology  
National Association for Private Algerian Allergists  
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  
Australian Society of Clinical Immunology and Allergy  
Austrian Society of Allergology and Immunology  
Azerbaijan Society for Asthma, Allergy and Clinical Immunology  
Bangladesh Society of Allergy and Immunology  
Belgian Society for Allergy and Clinical Immunology  
Brazilian Society of Allergy and Immunopathology  
British Society for Allergy and Clinical Immunology  
Bulgarian Society of Allergology  
Canadian Society of Allergy and Clinical Immunology  
Chilean Society of Allergy and Immunology  
Chinese Society of Allergy and Immunology  
Colombian Allergy, Asthma, and Immunology Association  
Croatian Society of Allergology and Clinical Immunology  
Cuban Society of Allergology  
Czech Society of Allergology and Clinical Immunology  
Danish Society of Allergology  
Egyptian Society of Allergy and Clinical Immunology  
Egyptian Society of Pediatric Allergy and Immunology  
Finnish Society of Allergology and Clinical Immunology  
French Society of Allergology  
Georgian Association of Allergology and Clinical Immunology  
German Society for Allergy and Clinical Immunology  
Hellenic Society of Allergology and Clinical Immunology  
Honduran Society of Allergy and Clinical Immunology  
Hong Kong Institute of Allergy  
Hungarian Society of Allergology and Clinical Immunology  
Icelandic Society of Allergy and Immunology  
Indian College of Allergy, Asthma and Applied Immunology (ICAAI)  
Indonesian Society for Allergy and Immunology  
Israel Association of Allergy and Clinical Immunology  
Italian Association of Territorial and Hospital Allergists  
Italian Society of Allergy and Clinical Immunology  
Japanese Society of Allergology  
Jordanian Society for Allergy and Clinical Immunology  
Korean Academy of Allergy, Asthma and Clinical Immunology  
Kuwait Society of Allergy and Clinical Immunology  
Latvian Association of Allergists  
Lebanese Society of Allergy and Immunology  
Malaysian Society of Allergy and Immunology  
Mexican College of Clinical Immunology and Allergy  
Mexican College of Pediatricians in Allergy and Clinical Immunology  
Mongolian Society of Allergology  
Moroccan Society of Allergy and Clinical Immunology  
Netherlands Society of Allergology  
Norwegian Society of Allergology and Immunopathology  
Panamanian Association of Allergy and Clinical Immunology  
Paraguayan Society of Immunology and Allergy  
Peruvian Society of Allergy and Immunology  
Philippine Society of Allergy, Asthma and Immunology  
Polish Society of Allergology  
Portuguese Society of Allergy and Clinical Immunology  
Romanian Society of Allergology and Clinical Immunology  
Russian Association of Allergology and Clinical Immunology  
Serbian Association of Allergologists and Clinical Immunologists  
Allergology and Clinical Immunology Society (Singapore)  
Slovenian Association for Allergology and Clinical Immunology  
Slovakian Society of Allergy and Clinical Immunology  
Allergy Society of South Africa  
Spanish Society of Allergy and Clinical Immunology  
Swiss Society for Allergology and Immunology  
Allergy, Asthma and Immunology Society of Thailand  
Turkish National Society of Allergy and Clinical Immunology  
Ukrainian Association of Allergologists and Clinical Immunologists  
Uruguayan Society of Allergology  
Venezuelan Society of Allergy and Immunology  
Vietnam Association of Allergy, Asthma and Clinical Immunology  
Zimbabwe Allergy Society

**Associate Member Societies**

Belarus Association of Allergology & Clinical Immunology  
Ecuadorian Society of Allergy and Immunology  
Ecuadorian Society of Allergology and Affiliated Sciences  
Iranian Society of Asthma and Allergy  
Moldavian Society of Allergology and Immunology  
Swedish Association for Allergology  
Tunisian Society of Respiratory Diseases and Allergology

**Regional Organizations**

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

**Affiliate Organizations**

British Society for Immunology  
GA2LEN (Global Allergy and Asthma European Network)  
International Association of Asthma

Apply for your National Allergy Society to become a WAO Member Society at www.worldallergy.org/wao_societies/apply.php.

For WAO membership information please contact the Secretariat

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Tel: +1 414 276 1791 • Fax: +1 414 276 3349  
e-mail: info@worldallergy.org  
Web site: www.worldallergy.org
Dear Colleagues,

A warm welcome to the forty-third symposium in the World Allergy Forum (WAF) series: Advances in Tolerance Induction to Allergens. Recognizing the importance of food allergy, the World Allergy Organization (WAO) is delighted to bring this symposium to the 2013 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI). WAO is very grateful to AAAAI for hosting the World Allergy Forum every year since this educational program commenced. This continues to be a great sign of long term collaboration with the AAAAI.

WAO is proud to announce that the year 2013 marks the 16th anniversary of the World Allergy Forum. The first WAF was presented at the AAAAI Annual Meeting in San Francisco in 1997 and WAO is appreciative that this symposium is an annual event at the AAAAI Annual Meeting. Since 1997, WAF has flourished and become the longest continuing educational program of World Allergy Organization (WAO).

With the increasing prevalence of allergic diseases globally there is an urgent need to better understand the complexity and severity of these diseases and to work towards developing preventative strategies. This WAF Symposium will examine the advances in our understanding of the mechanisms of tolerance to allergens as well as early intervention strategies both for food allergy and inhalant allergy. Prof. Paul Bryce will begin the symposium by examining the new frontiers in the mechanism of tolerance induction to allergens. Prof. Katrina Allen will focus on early intervention and the role of tolerance in primary prevention in food allergy. Prof. Giovanni Passalacqua will conclude today’s symposium by focusing on the updates on the role of SLIT in tolerance induction to allergens; including both safety and efficacy. There will be an open discussion following the formal lectures.

The WAO Board hopes that you enjoy today’s program with its wealth of information. If you would like to access the faculty materials after the session they will be available at: http://www.worldallergy.org/educational_programs/world_allergy_forum/

WAO also gratefully acknowledges the unrestricted educational grant from Novartis that supports educations programs such as this conjoint program at the AAAAI meeting.

With best regards,

Symposium Chairs

Ruby Pawankar, MD, PhD, FAAAAI
President
World Allergy Organization

A. Wesley Burks, MD, FAAAAI
President
American Academy of Allergy, Asthma & Immunology
Immunological tolerance is a critically important process that limits and prevents immune-mediated diseases. This includes both responses to self and to environmental allergens. Regulatory T cells play a vital role in this. Consequently, defects in these cells lead to complex autoimmunity and severe allergy. Approaches to restore tolerance have been limited and many immunotherapy approaches have limited impact on restoring long-lived non-responsiveness. Recently, the role of the spleen in tolerance has begun to be appreciated and several methods to induce tolerance have been reported. In particular, the role of splenic marginal zone macrophages in sampling antigens to promote tolerance has been exploited. These studies have supported scavenger receptors, including SIGNR1 and MARCO, as being potential targets for induction of tolerance.
New Frontiers in the Mechanisms of Tolerance Induction to Allergens

Paul J Bryce
Division of Allergy-Immunology

Immune Tolerance

Unresponsiveness of the immune system to antigens
Protects against reactions to self and non-harmful antigens
Failure of tolerance underpins autoimmunity and allergy
- Multiple sclerosis - myelin antigens,
- Type 1 Diabetes - insulin or islet cell antigen,
- Allergy - environmental proteins

Key mechanisms to prevent reactive immunity

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anergy</td>
<td>Unresponsive to Stimulation</td>
</tr>
<tr>
<td>Deletion</td>
<td>Actively killed</td>
</tr>
<tr>
<td>Regulated</td>
<td>Actively encouraged to behave differently</td>
</tr>
</tbody>
</table>

[Diagram showing Anergy, Deletion, and Regulated with corresponding antigen concentration levels]
**Regulatory T cells**

- **Mechanisms of suppression**
  - Soluble: TGF-β, IL-10, IL-35
  - Cell-surface: Receptor/Ligand binding
  - Scavenger: IL-2 consumption

- **Interactions with other cells**
  - CD4+, CD8+ T cells
  - Dendritic cells
  - B cells
  - Macrophages
  - Osteoblasts
  - NK cells
  - NKT cells
  - Mast Cells

**Regulatory T cells in tolerance**

IPEX Syndrome: Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome

- Mutations in FoxP3

Severe autoimmune and allergic phenotype
Lymph node-generated Regulatory T cells are required for oral tolerance

Tolerance versus Desensitization

Evidence supporting tolerance by Oral Immunotherapy is lacking

Key mechanism remains desensitization

- Loss of activation potential
  - Basophil activation test (surface CD63/CD200c)
  - Recoverable

OIT does not induce tolerance in a murine model of food allergy
Tolerance Promoting Advances

Mannosylation of antigen promotes IL-10 producing Tregs via SIGNR1

Encapsulated Antigen (Kawakita et al, Allergy, 2012)
Liposomal encapsulation promotes Tregs via SIGNR1 and CR3

Coupled Antigen

ECDI-Antigen Coupling

In vitro
Venous
Spleen

Peanut Proteins
ECDI
Autologous Cell
Self Apoptotic Tolerance

Thymus
Positive & Negative selection

Intestine
Oral tolerance induction

Spleen
Clearance of apoptotic cells by marginal zone macrophages and CD8α+ dendritic cells
Maintains tolerance to self-antigens
Tolerance Promoting Advances

- Mannosylation of antigen promotes IL-10 producing Tregs via SIGNR1

Encapsulated Antigen (Kawakita et al, Allergy, 2012)
- Liposomal encapsulation promotes Tregs via SIGNR1 and CR3

Coupled Antigen

ECDI-Antigen Coupling

Autologous Cell

Peanut Proteins

ECDI

"Self"

Apoptotic

In vitro Venous Spleen

Tolerance

Thymus

Intestine

Positive & Negative selection

Oral tolerance induction

Spleen

Clearance of apoptotic cells by marginal zone macrophages and CD8α+ dendritic cells

Maintains tolerance to self-antigens

Multiple Sclerosis

2008(105):14527-32

Fixed Antigen-Induced Tolerance Induction in Food Allergy

Anaphylaxis to Peanut

Th2 Cytokines to Peanut

Peanut-specific IgE

Fixed Antigen-therapy may be a method to promote long lasting tolerance to food allergens

Smarr CB*, Hsu CL*, Byrne AJ, Miller SD, Bryce PJ.

Coupled Antigen Tolerance is dependent on Tregs

Symton Scores
Fixed Antigen-Induced Tolerance Induction in Food Allergy

Barrier to utilization

Use of autologous cells carries problems

- Quantity of cells
- GMP handling for coupling
- Limited time frame

Biodegradable Nanoparticles efficiently induce tolerance

Polystyrene nanoparticles

- 500nm homogeneous spheres
- FDA approved for drug delivery
Fixed Antigen-Induced Tolerance Induction in Food Allergy

Fixed Antigen-therapy does not trigger responses in primed mice

Fixed Antigen-therapy does not trigger degranulation in primed cells in vitro

Unpublished

MAST
FcεRI

Barriers to utilization
Use of autologous cells carries problems
Quantity of cells
GMP handling for coupling
Limited time frame

Biodegradable Nanoparticles efficiently induce tolerance
Polystyrene nanoparticles
500nm homogeneous spheres
FDA approved for drug delivery

Polystyrene beads (PSB) coupled with myelin proteolipid protein (PLP) epitope in experimental model of multiple sclerosis

Getts et al, Nature Biotechnology, 2012

MARCO is critical for nanoparticle coupled tolerance
Member of the Scavenger receptor family that are critical for removal of waste material

MARCO is critical for nanoparticle coupled tolerance

Summary

Immunological tolerance is a natural process of preventing inappropriate immune responses

Regulatory T cells are central to this process

Desensitization is dominant mechanism behind current immunotherapy

Novel antigen-delivery approaches enhance Regulatory T cells

Scavenger receptors may be novel target
Early Intervention for Primary Tolerance to Allergens

Katrina Allen, MD PhD
Royal Children’s Hospital
Parkville, VIC Australia

There have been dramatic changes in timing of first exposure to solid foods for children over the last 40 years, ranging from exposure prior to 4 months of age for most infants in the 1960s, to guidelines recommending delaying solids until after 6 months of age introduced in the 1990s. Infant diet, specifically age of weaning and age at introduction of allergenic foods, has long been thought to play a role in food allergy. However, controversy surrounding the relationship between timing of introduction of foods and development of food allergy has led to a plethora of inconsistent infant feeding guidelines both between and within countries. This presentation will discuss the history of changing guidelines for optimal timing of introduction of solids in general and allergenic solids (such as cow’s milk, egg and peanut) in particular and the evidence (or lack thereof) underpinning recommendations at each of these time points. Future guideline modification about timing of introduction (both for high risk infants but also for the general population), and breastfeeding and weaning practices will require careful review of emerging literature to provide a true evidence base to inform public health practice such as infant feeding guidelines.

Early intervention for primary tolerance to food allergens

Professor Katie Allen FRACP PhD

Department of Allergy and Immunology,
Department of Gastroenterology and Nutrition
University of Melbourne Department of Paediatrics
Murdock Children’s Research Institute
Royal Children’s Hospital
Melbourne, Australia

Rise in prevalence of food allergy-induced anaphylaxis

Poulos et al JACI 2007

Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants

McDermott, C., Gohara, P.**, Jennifer L. Kellie, Who Hin; L.*, Patricia S. Martin, William Morris; James; L.**, Lyle G. Guitt, PhD;*** Andrew J. Law, PhD;*** Melanie C. Matheson, PhD;** Arvind K. Prasad, MBBS, MBB; PhD, FAFHAN; FIAAF; Melina Wale, MBBS, FIAAF; W.,*** Min L. K. Tang, MBBS, FIAAF; INFA, FFAAF, PhD;**
Devi Prasad C. S. Prasad, MBBS, MD, PhD;*** Anthony J. John, MBBS, FIAAF, PhD;*** for the HealthAllergy

Institute
Melbourne, Australia
Factors potentially contributing to increased risk of food allergy

Allen, KJ. & Koplin, JJ. Epidemiology of Food Allergy in Eigenmann et al. (eds) Food Allergy 1e, 2010 Elsevier

Infant dietary factors

Breastfeeding
- Type: exclusive or not
- Timing: prolonged or not

Formula
- Choice of formula:
  - Cow’s milk formula
  - Partially/Extensively hydrolysed
  - Other

Solids
- Age of weaning
- Age of introduction of allergenic solids
  - Egg
  - Peanut

Could the timing of introduction of solids and allergens play a role in the changing prevalence of food allergy?
Potential explanation for rise in prevalence

- Changes in timing of exposure to allergenic foods:
  - Progressive delay in timing of first exposure to solid foods
    - 1960s: Average age 2 months
    - 1970s: Introduction of guidelines recommending delay until after 4 months
    - 1980s: Guidelines recommending delay until after 6 months
    - 2000s: Introduction of allergenic foods after 1 year of age (up to 3 years for peanuts)

Age at first introduction of cow's milk products and other food products in relation to infant atopic manifestations in the first 2 years of life
– The KOALA Birth cohort

- Delayed introduction of cow's milk products was associated with a higher risk for eczema.
- Delayed introduction of other food products was associated with an increased risk for atopy in the first 2 years of life
  - eczema,
  - recurrent wheeze
  - any sensitization

Snijders et al., Paediatrics 2008

![Image]

**Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy**

<table>
<thead>
<tr>
<th>Food</th>
<th>Peanut</th>
<th>Sesame</th>
<th>Tree Nut</th>
<th>Egg</th>
<th>Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td>9.9 (1.02–9.5)</td>
<td>&lt;0.001</td>
<td>5.3 (5.3–5.4)</td>
<td>&lt;0.001</td>
<td>8.5 (5.1–7.7)</td>
</tr>
<tr>
<td><strong>Adjusted for age</strong></td>
<td>4.9 (4.8–5.0)</td>
<td>&lt;0.001</td>
<td>5.3 (5.2–5.4)</td>
<td>&lt;0.001</td>
<td>8.5 (8.3–8.7)</td>
</tr>
<tr>
<td><strong>Adjusted for age group and food allergy in infancy</strong></td>
<td>1.2 (1.0–1.5)</td>
<td>&lt;0.001</td>
<td>2.7 (2.7–3.9)</td>
<td>&lt;0.001</td>
<td>8.5 (8.3–8.7)</td>
</tr>
</tbody>
</table>

Increased risk of peanut, sesame, and tree nut allergy but not egg and cow’s milk allergy

Du Toit et al. JACI 2008;122:984-91

![Image]
### Delayed introduction of egg increases the risk of egg allergy

<table>
<thead>
<tr>
<th>Age at introduction of egg (months)</th>
<th>4-6</th>
<th>7-9</th>
<th>10-12</th>
<th>&gt;12</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>485</td>
<td>933</td>
<td>730</td>
<td>98</td>
</tr>
<tr>
<td>% egg allergic (%)</td>
<td>5.6</td>
<td>7.8</td>
<td>10.1</td>
<td>27.6</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0</td>
<td>1.4 (0.9-2.3)</td>
<td>1.9 (1.2-3.0)</td>
<td>6.5 (1.6-21.6)</td>
</tr>
<tr>
<td>*Adjusted for family history of allergy, eczema diagnosis prior to the introduction of egg and parent-reported reactions to one or more foods in the infant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Koplin et al. J Allergy Clin Immunol 2010

### Relationship between egg introduction and egg allergy stratified by family history risk

<table>
<thead>
<tr>
<th>Age introduced to egg (months)</th>
<th>Low allergy risk infants*</th>
<th>High allergy risk infants†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>% allergic</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>4-6</td>
<td>289</td>
<td>1.4</td>
</tr>
<tr>
<td>7-9</td>
<td>514</td>
<td>2.9</td>
</tr>
<tr>
<td>10-12</td>
<td>404</td>
<td>4.5</td>
</tr>
<tr>
<td>&gt;12</td>
<td>30</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Association between first type of egg introduced into infant diet and egg allergy

<table>
<thead>
<tr>
<th>Type of Egg</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% allergic</td>
</tr>
<tr>
<td>Cooked egg given first†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6 months</td>
<td>150</td>
<td>2.0</td>
</tr>
<tr>
<td>7-9 months</td>
<td>398</td>
<td>8.3</td>
</tr>
<tr>
<td>10-12 months</td>
<td>348</td>
<td>10.9</td>
</tr>
<tr>
<td>Baked egg given first‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6 months</td>
<td>311</td>
<td>7.6</td>
</tr>
<tr>
<td>7-9 months</td>
<td>499</td>
<td>8.2</td>
</tr>
<tr>
<td>10-12 months</td>
<td>361</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*Adjusted for family history of allergy, eczema diagnosis prior to the introduction of egg and parent-reported reactions to foods in the infant
Weaning practices and egg allergy
Koplin et al JACI 2010

<table>
<thead>
<tr>
<th>Age at introduction of solids (months)</th>
<th>N</th>
<th>% egg allergic</th>
<th>Adjusted OR (95% CI)</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>69</td>
<td>4.4</td>
<td>1.0</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>254</td>
<td>9.0</td>
<td>1.7 (0.9-6.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>636</td>
<td>8.8</td>
<td>1.2 (0.4-4.3)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>996</td>
<td>9.4</td>
<td>1.2 (0.4-4.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td>106</td>
<td>5.7</td>
<td>0.7 (0.2-2.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of breastfeeding (months)</th>
<th>N</th>
<th>% egg allergic</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>201</td>
<td>5.5</td>
<td>1.0</td>
<td>0.088</td>
</tr>
<tr>
<td>1-3</td>
<td>311</td>
<td>7.7</td>
<td>1.1 (0.5-2.2)</td>
<td></td>
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<tr>
<td>4-6</td>
<td>328</td>
<td>10.4</td>
<td>1.1 (0.6-2.3)</td>
<td></td>
</tr>
<tr>
<td>7-9</td>
<td>283</td>
<td>10.9</td>
<td>0.9 (0.5-1.9)</td>
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</tr>
<tr>
<td>10-12</td>
<td>312</td>
<td>11.5</td>
<td>0.9 (0.4-1.8)</td>
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</tr>
<tr>
<td>&gt;12</td>
<td>655</td>
<td>11.0</td>
<td>0.7 (0.4-1.4)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for family history of allergy, age at introduction of egg, duration of breastfeeding, maternal smoking during pregnancy, parents’ country of birth and eczema diagnosis in the infant.

Does maternal consumption of egg during pregnancy or breastfeeding increase risk? Koplin et al JACI 2010

<table>
<thead>
<tr>
<th>Maternal egg consumption</th>
<th>N</th>
<th>% egg allergic</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>124</td>
<td>9.7</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>1898</td>
<td>9.2</td>
<td>0.9 (0.5-1.6)</td>
<td>0.85</td>
<td>1.08 (0.57-2.03)</td>
<td>0.82</td>
</tr>
<tr>
<td>Breastfeeding†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>227</td>
<td>8.8</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>1678</td>
<td>10.6</td>
<td>1.2 (0.7-1.9)</td>
<td>1.07</td>
<td>1.07 (0.56-2.03)</td>
<td>1.01</td>
</tr>
</tbody>
</table>

*Adjusted for family history of allergy and age at introduction of egg into the infant diet
†Adjusted for duration of breastfeeding, family history of allergy and infant history of eczema diagnosis during breastfeeding. Excludes infants who were breastfed for less than 1 month.

Public Health Implications

• Introduction of egg at 4-6 months is safe and may even be protective
• This could not be accounted for by reverse causation
• Cooked egg rather than baked egg introduced at 4-6 mth is more PROTECTIVE
• Prolonged breastfeeding, maternal ingestion of allergen and other feeding factors NOT associated with egg allergy risk
These studies have underpinned new guidelines

- Avoid allergenic foods if ALLERGIC

- No evidence that avoidance of any foods PREVENTS food allergy

American Academy of Pediatrics guidelines 2008

- No evidence that maternal dietary restrictions during pregnancy prevent allergic disease
- No evidence that delaying introduction of solids (including highly allergenic foods such as peanut, eggs and fish) beyond 4-6 months of age is protective

“Window of tolerance” for the introduction of complimentary food

ASCIA Recommendations for introduction of solids I

• Introduce complementary solid foods from around 4-6 months.

• There is little evidence that delaying the introduction of complementary solid foods beyond 6 months reduces the risk of allergy.

ASCIA Recommendations for introduction of solids II

• There have been some suggestions that delaying introduction of foods may actually increase (rather than decrease) allergy, however at this stage this is not proven.

Breastfeeding

• Breastfeeding during the period that foods are first introduced may help prevent the development of allergy to those foods.

• Exclusion of allergenic foods from the maternal diet has not been shown to prevent allergies.
What about formula for allergy prevention?

Meta-Analysis: Formulas containing Hydrolysed Protein for Prevention of Allergy
Osborn & Sinn, 2003 - The Cochrane Library

Reviewer’s conclusions:

- “When babies are not exclusively breastfed, using hydrolyzed infant formulas instead of ordinary cow’s and soy milk formulas can reduce allergies in babies and children.”

- “There is insufficient evidence to determine whether feeding with an extensively hydrolyzed formula has any advantage over a partially hydrolyzed formula [for primary allergy prevention].”

Kramer and Kakuma, Optimal Duration of Exclusive breastfeeding, Cochrane Review 2009
New studies have not substantiated these findings

- MACs study
- GINIplus study
Conclusions

• There is no need to delay the introduction of allergenic solids – eg eggs and peanuts
• There is no need for mothers to avoid certain allergenic foods whilst pregnant or breastfeeding
• The ideal time for introducing solids is around 6 months
• Hydrolysed formulas do not appear to protect against allergic disease
Update on the Role of SLIT in Tolerance Induction to Allergens: Safety and Efficacy

Giovanni Passalacqua, MD
IRCCS San Martino Hospital-University of Genoa
Genoa, Italy

Sublingual immunotherapy (SLIT) is under observation since more than 25 years, as a viable alternative to the traditional standard route of administration. So far, there are about 70 RDBPC trials confirming its clinical efficacy (in most trials >20% over placebo) in both adults and children. The largest trials have been conducted with grass allergens, but also trials with ragweed and mites are available in literature. The clinical efficacy of SLIT was confirmed by several meta-analyses, although the heterogeneity of the studies (doses, patients’ selection, outcomes) limit their robustness. The safety of SLIT has been well ascertained, since only 6 cases of anaphylaxis (and no fatal event) has been reported so far. Due to the safety profile, SLIT has been proposed as a possible approach to food allergy, venom allergy and atopic dermatitis. Principal unmet needs remain the standardization of extracts, the design of clinical trials and the methodological aspects.
SUBLINGUAL IMMUNOTHERAPY

Giovanni Passalacqua

Allergy & Respiratory Diseases
Dept. Internal Medicine-
University of Genoa ITALY

1970ties
ORAL IT

1986, Scadding et al
1st DBPC trial

1993, SLIT is
Mentioned in an
EAACI pos pap

1997, Tari,
1st pediatric trial

2001: ARIA
document

2004: Preventive effect
Compliance

2005: SLIT in children
below the age of 5

2005-2011: Large randomized controlled trials
Studies on the mechanism of action

25 Years

CLINICAL EFFICACY:
WHICH LEVEL OF EVIDENCE?

Sub-lingual Immunotherapy: WAO Position Paper 2009
THE LITERATURE

65 RDBPC TRIALS
8 RANDOMIZED OPEN TRIALS
7 COMPARATIVE (SLIT vs SCIT)
6 TRIALS IN OTHER DISEASES

TREATMENT DURATION
Less or equal 6 months: 25 studies
Less or equal 12 months: 18 studies
More than 12 months: 22 studies

PATIENTS ENROLLED
≤ 20 : 4 studies       ≤ 150 : 13 studies
≤ 50 : 21 studies     > 150 : 11 studies
≤ 100 : 16 studies
### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Control Group</th>
<th>Placebo N[^a]</th>
<th>Allergen N[^a]</th>
<th>Randomization</th>
<th>Primary Endpoint</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durham et al. 2006</td>
<td>2006</td>
<td>Placebo control</td>
<td>82</td>
<td>82</td>
<td>Randomized</td>
<td>Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis</td>
<td>Durham SR, JACI 2006</td>
</tr>
<tr>
<td>Pfaar 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Wahn 2009</td>
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<td></td>
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<td></td>
<td></td>
<td>Yellow</td>
<td></td>
</tr>
<tr>
<td>Ott 2009</td>
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<td></td>
<td></td>
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<td></td>
<td>Blue</td>
<td></td>
</tr>
<tr>
<td>Pfaar 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Bufe 2009</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Yellow</td>
<td></td>
</tr>
<tr>
<td>Cortellini 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blue</td>
<td></td>
</tr>
</tbody>
</table>


---

**Sublingual immunotherapy with once-daily grass allergen tablets:**

A randomized controlled trial in seasonal allergic rhinoconjunctivitis

Durham SR, JACI 2006

---

**Figures:**

- **Figure 1:** Mean rhinoconjunctivitis symptom scores
- **Figure 2:** Mean rhinoconjunctivitis mediocrity scores
- **Figure 3:** Induction of blocking antibodies

---

**Passalacqua and Canonica. Immun Allergy Clin North Am 2011**
### Systematic reviews of sublingual immunotherapy (SLIT)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Disease</th>
<th>Allergens</th>
<th>Effect Size</th>
<th>p-value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calamita, 2006</td>
<td>303 adults + children</td>
<td>Asthma 5 pollens, 4 mite</td>
<td>-0.38 (p=0.07)</td>
<td>No change in symptom score</td>
<td>Significant reduction in medication score</td>
<td></td>
</tr>
<tr>
<td>Wilson, 2005</td>
<td>959 adults + children</td>
<td>Rhinitis 16 pollens, 6 mite</td>
<td>-0.42 (p=0.002)</td>
<td>Decreased symptoms and medications for rhinitis</td>
<td>Asthma not evaluable</td>
<td></td>
</tr>
<tr>
<td>Penagos, 2006</td>
<td>484 children</td>
<td>Rhinitis 5 pollens, 4 mite</td>
<td>-0.56 (p=0.02)</td>
<td>Decreased symptoms and medications for rhinitis</td>
<td>No sub-analysis feasible</td>
<td></td>
</tr>
<tr>
<td>Penagos, 2008</td>
<td>441 children</td>
<td>Asthma 3 pollen, 3 mite</td>
<td>-1.42 (p=0.02)</td>
<td>Decreased symptoms and medications for asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compalati, 2009</td>
<td>858 adults + children</td>
<td>Rhinitis, Asthma</td>
<td>Mite 8 rhinitis, 9 asthma</td>
<td>Rhinitis -0.95; Asthma -0.95 = 0.02</td>
<td>Significant effect on symptoms and drug intake for both rhinitis and asthma</td>
<td></td>
</tr>
<tr>
<td>Di Bona, 2010</td>
<td>2791 adults + children</td>
<td>Rhinitis</td>
<td>Grass</td>
<td>-0.32</td>
<td>P &lt; .0001</td>
<td>Decreased symptoms and medications for rhinitis. Greater effect in adults</td>
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<tr>
<td>Radulovic, 2011</td>
<td>4589 adults + children</td>
<td>Rhinitis</td>
<td>Grass, Mite, Other</td>
<td>SMD -0.49; P &lt; 0.00001</td>
<td>Similar size effect also for medications</td>
<td></td>
</tr>
</tbody>
</table>

### Allergy 2011

**Sublingual Immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis.**

Calderon M et al

Clin Exp Allergy 2011
### Sublingual Immunotherapy for Allergic Respiratory Diseases: An Evaluation of Meta-Analyses

**Authors:** Calderon MA, Wilson D, Durham S, and Arce Montesinos MD

**Journal:** *JACI 2009*

#### Table: Sublingual Immunotherapy for Allergic Respiratory Diseases

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Disease</th>
<th>Trials</th>
<th>Effect size (on symptoms)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calamita, 2006</td>
<td>305 adults + children</td>
<td>Asthma</td>
<td>3-pollens 4-mite</td>
<td>-0.38 (p=0.07)</td>
<td>No change in symptom score. Significant reduction medication score.</td>
</tr>
<tr>
<td>Wilson 2005</td>
<td>199 adults + children</td>
<td>Rhinitis</td>
<td>16-pollens</td>
<td>-0.42 (p=0.002)</td>
<td>Decreased symptoms and medications for rhinitis. Asthma not evaluable.</td>
</tr>
<tr>
<td>Penagos 2006</td>
<td>484 children</td>
<td>Rhinitis</td>
<td>5-pollens 4-mite</td>
<td>-0.56 (p=0.05)</td>
<td>Decreased symptoms and medication for rhinitis. No sub-analysis feasible.</td>
</tr>
<tr>
<td>Penagos 2008</td>
<td>441 children</td>
<td>Asthma</td>
<td>3-pollens 3-mite</td>
<td>-1.42 (p=0.05)</td>
<td>Decreased symptoms and medications for asthma.</td>
</tr>
<tr>
<td>Compeeliet 2009</td>
<td>166 adults + children</td>
<td>Rhinitis Asthma</td>
<td>Mite 9-pollens 9-mite</td>
<td>Rhinitis -0.95; Asthma -0.85</td>
<td>Significant effect on symptoms and drug intake for both rhinitis and asthma.</td>
</tr>
<tr>
<td>St-Bea 2010</td>
<td>291 children</td>
<td>Rhinitis</td>
<td>Grass</td>
<td>-0.33 (p = 0.01)</td>
<td>Decreased symptoms and medications for rhinitis. Greater effect in adults.</td>
</tr>
<tr>
<td>Radechovic 2011</td>
<td>4990 adults + children</td>
<td>Rhinitis</td>
<td>25 grass 8-mite 5-other</td>
<td>SMD: 0.49; P &lt; 0.00001</td>
<td>Similar size effect also for medications.</td>
</tr>
<tr>
<td>Calderon 2011</td>
<td>1990 adults + children</td>
<td>Conjunctivitis</td>
<td>12 pollen</td>
<td>Overall: -0.35 ± 10% placebo</td>
<td>Significant difference also for individual symptoms.</td>
</tr>
</tbody>
</table>

#### Publication Biases

- Discrepancy in reporting results
- Heterogeneity
  - All allergens pooled together

---

**Sublingual Immunotherapy for Allergic Rhinitis (Review)**

**Authors:** Radulovic S, Calderon MA, Wilson D, Durham S

*Sublingual Immunotherapy for allergic rhinitis (Review)*

Copyright © 2011 The Christiana Care Health System, Inc. Published by John Wiley & Sons, Inc.

**49 (Out of 60)**
**RDBPC Trials**
**Suitable for Pooling:**
- 2333 Silt
- 2256 Placebo
SLIT

No fatal event reported since 1986

At the end of the story, we got our 6 anaphylaxes
Dunsky, Allergy 2006 (8 allergens)
Patriarca, Allergy 2006 (latex, rush)
Elfan, Allergy 2007 (mix pollens-mite)
In 41 studies with information on the total number of AEs, 1047 adverse reactions in a total of 386,149 doses were identified (2.7 reactions/1,000 doses).

In 49 studies with information on the number of patients, the AEs were 529 per 4378 patients (12%).

In the trials that specified the severity of reaction, the occurrence of severe AE was 0.56 per 1,000 doses.

Overall, 14 serous AEs probably related to the treatment were found.

Safety of a SQ-standardised sublingual immunotherapy controlled trial.
Kleine-Tebbe, Allergy Feb 2006

ONCE A DAY REGIMEN

Severity of oral pruritus
SLIT: POST MARKETING SURVEYS

<table>
<thead>
<tr>
<th>Author</th>
<th>N pats</th>
<th>Age range</th>
<th>Follow-up</th>
<th>AE % of patients</th>
<th>AE/1,000 doses</th>
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</thead>
<tbody>
<tr>
<td>Di Rienzo</td>
<td>268</td>
<td>2-15 years</td>
<td>3 years</td>
<td>3 %</td>
<td>0.1/1,000</td>
</tr>
<tr>
<td>Lombardi</td>
<td>198</td>
<td>&gt;14 years</td>
<td>3 years</td>
<td>7.5 %</td>
<td>0.5/1,000</td>
</tr>
<tr>
<td>Pajno</td>
<td>354</td>
<td>5-15 years</td>
<td>36 months</td>
<td>6 %</td>
<td>0.15/1,000</td>
</tr>
<tr>
<td>Agostinis</td>
<td>36</td>
<td>3-5 years</td>
<td>2 years</td>
<td>5 %</td>
<td>0.07/1,000</td>
</tr>
<tr>
<td>Di Rienzo</td>
<td>128</td>
<td>3-5 years</td>
<td>2 years</td>
<td>5.4 %</td>
<td>0.2/1,000</td>
</tr>
</tbody>
</table>

ALLERGOIDS

Chemical modification of peripheral aminoacidic residues:
Decreased IgE affinity

Preservation of conformation:
Tcell binding

Monomeric allergoid:
Retained characteristics.

Efficacy

Less IgE binding.
Safety

Biodistribution.
Safety

Efficacy

QUALITY OF EVIDENCE

Dose dependency
Large effect
Reproducible effect

RECOMMENDATION

COST/BENEFIT PREFERENCE

SAFETY

GRADE: THE NEW EBM SYSTEM

Coseasonal SLIT reduces the development of asthma in children with allergic rhinitis.
Novembre E. et al, JACI 2004

SLIT NO SLIT

37 8 26 18

NO ASTHMA

ASTHMA

79 children

Allergic rhinitis only

Follow-up: 3 yrs

PREVENTIVE EFFECTS OF SUBLINGUAL IMMUNOTHERAPY IN CHILDHOOD. AN OPEN RANDOMIZED CONTROLLED STUDY

MAURIZIO MAROGNA MD1, D. TOMASSETTI1, A. BERNASCONI1, F. COLOMBO1, ALESSANDRO MASSOLO BS2, A. DI RIENZO BUSINCO4, GIORGIO W CANONICA MD3, GIOVANNI PASSALACQUA MD3 AND SALVATORE TRIPOLI MD4

1 Pneumology Unit, Cuasso al Monte, Macchi Hospital Foundation, Varese
2 Department of Animal Biology, University of Pavia, Pavia
3 Allergy & Respiratory Diseases, Department of Internal Medicine, Genoa University
4 Pediatric Allergy Unit, S. Pertini Hospital, Rome

AAAI 2008, 101: 261
**GRADE: THE NEW EBM SYSTEM**

QUALITY OF EVIDENCE
- Dose dependency
- Large effect
- Reproducible effect

COST/BENEFIT

SAFETY

RECOMMENDATION

---

**PREVENTIVE EFFECTS OF SUBLINGUAL IMMUNOTHERAPY IN CHILDHOOD. AN OPEN RANDOMIZED CONTROLLED STUDY**

MAURIZIO MAROGNA MD¹, D. TOMASSETTI¹, A. BERNASCONI¹, F. COLOMBO¹, ALESSANDRO MASSOLO BS¹, A. DI RIENZO BUSINCO¹, GIORGIO W CANONICA MD², GIOVANNI PASSALACQUA MD² AND SALVATORE TRIPODI MD³

1 Pneumology Unit, Cuasso al Monte, Macchi Hospital Foundation, Varese
2 Department of Animal Biology, University of Pavia, Pavia
3 Allergy & Respiratory Diseases, Department of Internal Medicine, Genoa University
4 Pediatric Allergy Unit, B. Pariati Hospital, Rome

AAAI 2008, 101: 261

---

**Coseasonal SLIT reduces the development of asthma in children with allergic rhinitis.**

Novembre E. et al, JACI 2004

<table>
<thead>
<tr>
<th>SLIT</th>
<th>NO SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>37</td>
<td>18</td>
</tr>
</tbody>
</table>

79 children
Allergic rhinitis only
Follow-up: 3 yrs
Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet

Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study

Contradictions to the use of sublingual immunotherapy include:
Sustained 3-year efficacy of pre- and causeonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis

The effect persists one year after discontinuation

Onset of the effect in the pollen seasons
Sublingual immunotherapy with Dermatophagoides monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-γ- and interleukin-10-production

Cosmi et al
Clin Exp Allergy 2006
WHAT IS STILL MISSING?

WHICH WEAK POINTS?

Methodological aspects (heterogeneity of trials)
Confirmation of the preventative effects
Choice of the best regimen of administration
Optimal dose for other relevant allergens
Adherence to treatment
Polysensitized patients/multiple allergens

METHODOLOGICAL ISSUES

- HETEROGENEITY OF TRIALS
- DOSES
- PATIENTS’ SELECTION
- PRIMARY OUTCOME
- SAMPLE SIZE CALCULATION
- ITT/PP ANALYSIS
- REPORTING
Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care

Patients with symptoms out of the season

Allergen content of grass pollen preparations for skin prick testing and sublingual immunotherapy

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Conc. (µg/ml)</th>
<th>Prn (µg/ml)</th>
<th>Pm (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alergopharm</td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Al &amp; Galilei</td>
<td>20</td>
<td>96</td>
<td>41</td>
</tr>
<tr>
<td>Alergopharm</td>
<td>20</td>
<td>96</td>
<td>41</td>
</tr>
<tr>
<td>Allergologis</td>
<td>10</td>
<td>96</td>
<td>41</td>
</tr>
<tr>
<td>Al &amp; Galilei</td>
<td>10</td>
<td>96</td>
<td>41</td>
</tr>
</tbody>
</table>

The Consolidated Standards of Reporting Trials (CONSORT) Statement applied to allergen-specific immunotherapy with inlet allergens: A Global Allergy and Asthma European Network (GA²LEN) article

SCIT: 46 trials
CONSORT: 1 trial
Flowchart: 16 trials
Dropouts: 12 trials
Randomization: 16 trials

SLIT: 48 trials
CONSORT: 3 trial
Flowchart: 20 trials
Dropouts: 16 trials
Randomization: 12 trials
Recommendations for appropriate sublingual immunotherapy clinical trials

Thomas K. Coma, MD,*, G. Walter Coma, MD,*, Anne Banquet, MD,*, Linda In, MD,*, Robert Lackey, MD,*
Francis B. Belton, MD,§ and Giovanni Piepoli, MD,§

JACI, Oct 09

Practical aspects of SLIT

Preparation
- Vials: Disposable single dose vials
- Soluble tablets

Build-up
- 4 weeks
- 10 days
- 1 day (rush) none

Maintenance
- Twice weekly
- Each other day
- Once daily

Regimen
- Presessional
- Pre-coseasonal (inseason reduction)
- Pre-coseasonal (no reduction)
- Continuous

Review article
Administration regimens for sublingual immunotherapy to pollen allergens: What do we know?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variable</th>
<th>Number of studies</th>
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<tbody>
<tr>
<td>Build-up duration</td>
<td>&gt;15 days</td>
<td>44/60</td>
</tr>
<tr>
<td></td>
<td>≤15 days, no updosing</td>
<td>10/60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6/60</td>
</tr>
<tr>
<td>Frequency of dosing at</td>
<td>Once weekly</td>
<td>2/60</td>
</tr>
<tr>
<td>maintenance</td>
<td>Twice weekly</td>
<td>3/60</td>
</tr>
<tr>
<td></td>
<td>Three weekly</td>
<td>20/60</td>
</tr>
<tr>
<td></td>
<td>Daily</td>
<td>31/60</td>
</tr>
<tr>
<td>Formulation</td>
<td>Solution</td>
<td>51/60</td>
</tr>
<tr>
<td></td>
<td>Tablets</td>
<td>5/60</td>
</tr>
<tr>
<td>Timing (for pollen allergens)</td>
<td>Pre-seasonal</td>
<td>3/41</td>
</tr>
<tr>
<td></td>
<td>Coseasonal</td>
<td>2/41</td>
</tr>
<tr>
<td></td>
<td>Pre-coseasonal (no reduction)</td>
<td>27/41</td>
</tr>
<tr>
<td></td>
<td>Continuous</td>
<td>8/41</td>
</tr>
</tbody>
</table>
**Evidence of adherence to allergen-specific immunotherapy**

Gianenrico Senna, Emunia Ridolo, Moses Calderon, Carlo Lombardi, Giorgio W. Canonico and Giovanni Passalacqua

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Age</th>
<th>Compliance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morena et al. [20]</td>
<td>316</td>
<td>Adults</td>
<td>80</td>
</tr>
<tr>
<td>Lombardi et al. [21]</td>
<td>80</td>
<td>Adults</td>
<td>79</td>
</tr>
<tr>
<td>Parente et al. [22]</td>
<td>800</td>
<td>Children</td>
<td>70</td>
</tr>
<tr>
<td>Passalacqua et al. [23]</td>
<td>44.3</td>
<td>Adults/children</td>
<td>70</td>
</tr>
<tr>
<td>Passalacqua et al. [24]</td>
<td>71</td>
<td>Children</td>
<td>80</td>
</tr>
<tr>
<td>Roder et al. [25]</td>
<td>158</td>
<td>Adults/children</td>
<td>87</td>
</tr>
</tbody>
</table>

Current Opinion in Allergy and Clinical Immunology (2008, 2:44–546)
Adherence to SLIT in preschool children
Pajno G and Passalacqua G in preparation

% dropout patients

1st year 2nd year

0.035

0.032

NS

3-4 years

4-5 years

5-6 years

415 children, 3-18 years, 272 male

Oral itching

Mild 36

Moderate 4

Angioedema lips

Mild 8

Moderate 1

Rhinitis

Mild 3

Mild 1

Oral itching

Mild 12

Moderate 1

Cough

Mild 5

Mild 1

Nausea/abdominal pain

Mild 3

Mild 4

Vomiting/diarrhea

- -

Asma

- -

Generalized urticaria

- -

Anaphylaxis

- -

Total 72 episodes

44.44% patients

4,3/1000 doses

102 episodes

40.32% patients

4,5/1000 doses

NS
Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis

415 children, 3–18 years, 272 male

<table>
<thead>
<tr>
<th>SINGLE ALLERGEN n (%)</th>
<th>MULTI ALLERGENS n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass 140 (82)</td>
<td>Grass + pariet 6 (2)</td>
</tr>
<tr>
<td>Parietaria 4 (3)</td>
<td>Grass + olive 18 (7)</td>
</tr>
<tr>
<td>Birch 14 (9)</td>
<td>Grass + birch +alder+basement</td>
</tr>
<tr>
<td>Ragweed 4 (3)</td>
<td>Grass + ragweed 9 (4)</td>
</tr>
<tr>
<td>Olive -</td>
<td>Grass + mugwort</td>
</tr>
<tr>
<td></td>
<td>Birch +basement +alder</td>
</tr>
<tr>
<td>TOTAL 172 (100)</td>
<td>253 (100)</td>
</tr>
</tbody>
</table>

THE SAFETY OF SUBLINGUAL IMMUNOTHERAPY WITH ONE OR MORE ALLERGENS IN CHILDREN

Fabio Agostinis, Marcello Cottini, Carlo Lombardi, Giorgio Walter Canonica, Giovanni Passalacqua

<table>
<thead>
<tr>
<th></th>
<th>Single allergen</th>
<th>Multiple allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>162 pts 16,744 doses</td>
<td>253 pts 22,666 doses</td>
</tr>
<tr>
<td>Oral itching</td>
<td>36 mild 4 moderate</td>
<td>48 mild 5 moderate</td>
</tr>
<tr>
<td>Angioedema lips</td>
<td>8 mild 1 mild</td>
<td>11 mild 1 moderate</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3 mild 2 mild</td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td>12 mild 2 moderate</td>
<td>22 mild 2 moderate</td>
</tr>
<tr>
<td>Cough</td>
<td>5 mild 7 mild</td>
<td></td>
</tr>
<tr>
<td>Nausea/abdominal pain</td>
<td>3 mild 4 mild</td>
<td></td>
</tr>
<tr>
<td>Vomiting/diarrhea</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>Asma</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>Generalized urticaria</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>72 episodes 44.44% patients</td>
<td>102 episodes 40.32% patients</td>
</tr>
</tbody>
</table>

44.44% patients

5,071,000 doses 5,071,000 doses

NS
SLIT: PERSPECTIVES
An unique opportunity to treat safely several severe allergic conditions

Food allergy
Latex allergy
Atopic dermatitis

Hymenoptera venom?

Sublingual immunotherapy for peanut allergy: Clinical and immunologic evidence of desensitization.
KIm et al
JACI, 2011