World Allergy Forum:
“Sublingual Immunotherapy — Is There a Role?”
Saturday, March 4, 2006 - 10:45 a.m. – 12:00 p.m.
Miami Beach Convention Center
Room A201-205
American Academy of Allergy, Asthma and Immunology
Annual Scientific Meeting
Miami Beach, Florida, U.S.A.
You Are Invited To Attend

Life-Threatening Allergy - An Homage to Clemens Von Pirquet

Sunday, 11 June 2006
1:30 p.m. – 3:15 p.m.

Chairs:
Michael A. Kaliner
Anthony J. Frew

Epidemiology of Anaphylaxis
Aziz Sheikh

Mechanisms of Anaphylaxis
Richard F. Lockey

Management of Anaphylaxis
F. Estelle R. Simons

Supported through an unrestricted educational grant from

Novartis
“Sublingual Immunotherapy – Is There a Role?”

Program

Moderator:
Michael A. Kaliner, Institute for Asthma and Allergy
Wheaton, Maryland, U.S.A.

1. Welcome to the World Allergy Forum Symposium and Introduction to “Sublingual Immunotherapy – Is There a Role?”
Michael A. Kaliner, Institute for Asthma and Allergy
Wheaton, Maryland, U.S.A.

2. An Analysis of Long-Term Efficacy and Safety of Sublingual Immunotherapy: Criteria for Appropriate Patient Selection
G. Walter Canonica, University of Genova DIMI
Genova, Italy

3. Mechanisms of Sublingual Immunotherapy – How Does It Differ from Injection Immunotherapy?
Anthony J. Frew, Brighton General Hospital
Brighton, United Kingdom

4. Is the US Ready for Sublingual Immunotherapy?
Linda Cox, Allergy & Asthma Center
Fort Lauderdale, Florida, U.S.A.

2005 – 2007 World Allergy Forum Advisory Board

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Michael A. Kaliner, U.S.A.

Vice Chair
G. Walter Canonica

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Ulrich Wahn
About the World Allergy Organization

World Allergy Organization (WAO)
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 and Allergic Conjunctivitis
Module 2: Allergic Conjunctivitis (Expanded Version)
Module 3: Allergic Emergencies
Module 4: Immunotherapy
Module 5: Symptoms and Treatment of Asthma
Module 6: Food Allergy

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.

PAAA: Prevention of Allergy and Allergic Asthma
Prevention of Allergy and Allergic Asthma (PAAA) is a collaborative project with the World Health Organization providing guidelines and recommendations for prevention of the allergen-specific immunological sensitization necessary for disease.

Emerging Societies Meetings
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.

WAO Journals
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.
WAO Member Societies*

National Member Societies

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
Azerbaijan 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
Canadian Society of Allergy and Clinical Immunology
Chilean Society of Allergy and Immunology
Chinese Allergology Society and Chinese Allergists
Chinese Hong Kong Institute of Allergy
Colombian Allergy, Asthma and Immunology Association
Croatian Society of Allergology and Clinical Immunology
Cuban Society of Allergology
Danish Society of Allergology
Ecuadorian Society of Allergy and Immunology
Egyptian Society of Allergy and Clinical Immunology
Estonian Society of Allergy and Clinical Immunology
French Society of Allergy and Clinical Immunology
German Society for Allergy and Clinical Immunology
Georgian Association of Allergology and Clinical Immunology
Hellenic Society of Allergology and Clinical Immunology
Hungarian Society of Allergology and Clinical Immunology
Icelandic Society of Allergy and Clinical Immunology
Indian College of Allergy, Asthma and Applied Immunology
Indonesian Society for Allergy and Immunology
Israel Society of Allergy and Clinical Immunology
Italian Society for Allergology and Clinical Immunology
Japanese Society of Allergology
Korean Society of Allergology
Lebanese Society of Allergy and Immunology
Malaysian Society of Allergy and Immunology
Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology
Mexican College of Allergy, Asthma and Clinical Immunology
Mongolian Society of Allergology
Netherlands Society of Allergology
Norwegian Society of Allergology and Immunopathology
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
Allergy Society of South Africa
Singapore Society of Immunology, Allergy & Rheumatology
Spanish Society of Allergology and Clinical Immunology
Swedish Association for Allergology
Swiss Society for Allergology and Immunology
Allergy and Immunology Society of Thailand
Turkish National Society of Allergy and Clinical Immunology
Ukrainian Association of Allergologists and Immunology
Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnam Association of Allergy, Asthma and Clinical Immunology
Zimbabwe Allergy Society

Associate Member Societies

Czech Society of Allergology and Clinical Immunology
Ecuadorian Society of Allergology and Affiliated Sciences
Egyptian Society of Pediatric Allergy and Immunology
Italian Association of Territorial and Hospital Allergists
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
CIS 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

*As of February 2006

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 28th Symposium in the World Allergy Forum Series, ‘Sublingual Immunotherapy – Is There a Role’? I am particularly pleased to moderate this session today. Prof. G. Walter Canonica and Prof. Anthony J. Frew will share their extensive European experience with sublingual immunotherapy, and Dr. Linda Cox will discuss whether there is a place for sublingual immunotherapy in the United States. SLIT has become popular in Europe and may offer some advantages to selected populations of patients in the US as well. Today’s program will help enlighten us as to the populations of patients who may benefit.

The World Allergy Forum is the longest-running educational program of the World Allergy Organization, and we are grateful for the unrestricted educational grant from Novartis and Genentech which enables us to bring you this program today.

I am lucky to preside over WAO at this time; the Organization has become very active in a wide range of activities, the leadership is extremely dynamic, and our position in the world of allergy is firmly established. Over the next two years, we plan a global agenda to strengthen allergy both for patients and allergists; we plan to make WAO more visible, of greater service to our member societies, and to establish strong and broad partnerships with our national and regional societies. Where we already have strong allergy societies, we will cooperate with them while always giving recognition to their skills and strengths. Where we have newer or less established societies, we will partner with and strengthen these fledgling groups through our Emerging Societies Program. In areas where there are no allergists, WAO will help local allergists to make the governing bodies aware of the need for allergy and work to create an environment where allergy and asthma sufferers can get access to well-trained physicians.

As part of our goal to promote our specialty, in January 2006 the WAO Specialty and Training Council published the results of a survey of allergy needs and practices in member countries in our two journals, Allergy & Clinical Immunology International– Journal of the World Allergy Organization (ACII-JWAO), and the International Archives of Allergy and Immunology. This important document will be followed by the publication of a provisional WAO position statement entitled Key Clinical Competencies for the Specialty of Allergy and Clinical Immunology, then later this year we will publish a third statement defining What is an Allergist.

We continue to serve our members through our educational programming. In a 2006 partnership with the American College of Allergy, Asthma and Immunology (ACAAI), we are implementing an American version of the Global Resources in Allergy program (GLORIA) to provide 5-10 lectures per year to Regional, State and Local Allergy Societies in the US using the GLORIA lecture modules presented by WAO and ACAAI lecturers. Applications for the USA-GLORIA can be submitted by all Regional, State and Local Allergy Societies wishing for the involvement of WAO at their local meeting.
We are actively planning the next World Allergy Congress, which will take place December 2-6, 2007, in Bangkok Thailand. The meeting will have several unique features. It will begin with an international symposium on Immunotherapy cosponsored by WAO, EAACI and AAAAI. The meeting will run for 3 ½ days thereafter, ending with an overlapping international symposium on Food Allergy, cosponsored by the ACAAI and WAO.

A global organization will only be as good as its ability to communicate. WAO is fortunate to have Richard F. Lockey as Editor-in-Chief of the WAO Web site, and Johannes Ring as Editor of JWAO. The monthly email newsletter, WAO News and Notes, is designed to keep everyone informed of clinical advances in the field of allergy and to provide a ready means of rapid communications. If you are not receiving this free of charge communication, please contact us at www.worldallergy.org and share your email information.

As we look to the future, we recognize that allergy is a rapidly developing and expanding field, but recognition of the importance of allergy is still underappreciated, and the time when allergy is accepted as a subspecialty of medicine and pediatrics akin to cardiology and gastroenterology is still on the horizon. WAO is committed to strengthening allergy through active educational and research partnerships with our 74 member societies. In the end, the many millions of patients with asthma and allergy will benefit as the importance of allergic diseases is recognized and taught more widely.

With my best regards,

Michael A. Kaliner
President, World Allergy Organization
An Analysis of Long-Term Efficacy and Safety of Sublingual Immunotherapy: Criteria for Appropriate Patient Selection

G.W.Canonica, MD, FAAAAI
University of Genova
Genova, Italy

Prof. G. Walter Canonica, FAAAAI, is Professor and Chairman of Allergy and Respiratory Diseases at the Department of Internal Medicine, Genoa University, Italy

G. Walter Canonica is an internationally renowned expert on immunotherapy and allergic respiratory diseases, and has authored over 350 full papers in international journals. His main research interests encompass investigation of different subsets of T lymphocytes and their functional role in basic and clinical research (allergy, organ specific autoimmunity, CNS degenerative diseases and cancer); molecular events and interactions between immunocompetent cells, inflammatory cells, epithelial cells in allergic inflammation and airways remodeling; new antiallergic drugs and new strategies in the treatment of allergic disease; and clinical and immunopharmacological activities of biological response modifiers such as cytokines, monoclonal antibodies, allergen specific Immunotherapy, and corticosteroids.

From 2003-2005 Prof. Canonica served as the Secretary-General of the World Allergy Organization (WAO) and is the 2005-2007 President-Elect of WAO. His numerous national and international roles include Vice President of INTERASMA – International Association of Asthmaology, Secretary-General of the Federation of the Italian Medical Societies-FISM, and Chairman of the EAACI-CME Continuing Medical Education Council. He is a Past-President of the Italian Society of Respiratory Medicine.

Abstract

Sublingual Immunotherapy-SLIT, is the youngest non-injective route of IT. The first experimental approaches were performed two decades ago. Safety of SLIT was reviewed in a number of official position papers, and was considered a good reason to promote further studies.

At present, several DBPC trials are published, and a general consensus on the clinical efficacy of SLIT in allergic rhinitis has been reached in Europe. To further support this position, Durham and coworkers published a metanalysis study demonstrating SLIT efficacy on both symptom and medication score reduction in allergic rhinitis patients (1). The same study found no evidence for such an effect in pediatric patients. With the availability of more studies for review, we recently performed a metanalysis in pediatric patients with the findings of Evidence 1a for both rhinitis and asthma symptom and medication scores reduction (2). Some of our studies demonstrated the clinical efficacy of SLIT and a concomitant effect on nasal inflammation. In a recently completed long term study (3 years) in birch allergic subjects, we confirmed clinical efficacy, nasal inflammation decrease and pulmonary function improvement (3). The long-lasting persistence of the allergen extract at sublingual level has been demonstrated by our group using radiolabelled allergen. The absorption has been also monitored.

Comparative studies of Subcutaneous Immunotherapy (SCIT) vs SLIT are not sufficient to support a better effect of one of the two. The only DBPC DDummy study failed to demonstrate any statistical difference between the two treatments, and both were effective compared to placebo. Like SCIT-injective IT, SLIT has been found to prevent asthma onset and new sensitizations. It has been ascertained that SCIT has long lasting effect in several trials. SLIT was found, in a 10 year survey, to exert a 5 year significant effect after cessation of therapy. High dosages recently demonstrated a better effect compared to low ones (4).

The safety of SLIT is reported as one of the added values of this treatment, and there has never been a report of a fatal or near fatal reaction. SLIT safety has been confirmed in clinical trials and in post marketing surveillance studies. SLIT was recently demonstrated to be as good in very young children (< 3 years of age) as it is reported to be in the published literature about adults. These last data strongly support the eligibility of young children to receive SLIT, in view of its efficacy, safety and preventive effect on disease progression (5).

References

An Analysis of Long-Term Efficacy and Safety of Sublingual Immunotherapy: Criteria for Appropriate Patient Selection

Azienda Ospedaliera Universitaria San Martino
Università degli Studi di Genova

Canonica G.W., FAAP, FACC
Allergy and Respiratory Diseases
Dipartimento di Medicina Interna
16132 Genova, Italy

J.A.C.I. 2003

Noninjection routes for Immunotherapy

Canonica G.W.
&
Passalacqua G.

SCIT

CLINICAL USE

RCTs

Mechanisms

Safety

Preventive effect

SLIT

RCTs: efficacy safety mechanisms

LNIT

RCTs: efficacy safety mechanisms

OIT

ANECDOCTAL REPORTS

RCTs

LBIT

ANECDOCTAL REPORTS

RCTs

A promising route....
More data are needed...

EAACI Pos Pap 1993

...a viable alternative to SCIT in adults...
..safety in children has to be confirmed....

WHO Pos Pap 1998

SLIT can be administered in adults and children...

ARIA Pos Pap 2001

*TODAY: 34 DBPC STUDIES*

Absorption and distribution kinetics of the major Parietaria Judaica (Par J 1) allergen administered by non-injectable extract to healthy human beings.

M. Bagnasco, G. Mariani, G. Passalacqua, C. Motta, M. Bartolomei, P. Falagiani, G. Mistrello, G. W. Canonica

*JACI 1997; 100:199*
Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers

M. Bagnasco et al
Clin.Exp.Allergy 2001
Sublingual immunotherapy for allergic rhinitis: a meta-analysis

Dr D R Wilson et al.
University Hospital Birmingham NHS Trust, UK

Allergy, 2005

Symptom scores (21 studies)
Medication scores (17 studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>mean±SD</th>
<th>Phenergan n</th>
<th>mean±SD</th>
<th>Odds ratio</th>
<th>95% CI</th>
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</tbody>
</table>


Wilson D., Torres Lima I, Durham S.

22 dbpc TRIALS
979 patients
8 studies < 6 months
10 studies < 1 year
4 studies > 1 year

SYMPTOMS: - 0.34 [-0.66 - -0.15] p= 0.002
DRUGS: -0.43 [-0.63 - -0.23] p= 0.0003

STANDARDS FOR PRACTICAL
ALLERGEN-SPECIFIC IMMUNOTHERAPY

E Alvarez-Cuesta (chairman),
J Bonnet, G W Canonica,
S Durham, H-J Malling, E Valovirta

EAACI
Immunotherapy Task Force 2005
**SIT Efficacy by E.B.M.**

**SCIT:** Ia for Asthma  
Ib for Rhinitis  

**SLIT:** Ia for Rhinitis  
Ib for Asthma

*E.A.C.I Immunotherapy Task Force 2005*

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**Efficacy of sublingual immunotherapy in allergic rhinitis in children**

**Meta-analysis of RCT**

*Penagos M. & Canonica G.W.*

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**Symptom Score**

**Rhinitis**

<table>
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<tr>
<th>Qual.</th>
<th>SCIT</th>
<th>Penalo</th>
<th>Q2</th>
<th>Wgt</th>
<th>DQI (pooled)</th>
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**Efficacy of SLIT in children with Allergic Rhinitis.**

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12
Medication score
Rhinitis

Efficacy of SLIT in children with Allergic Rhinitis.

Bronchial Score
Asthma

Canonica GW. Efficacy of SLIT in children with Allergic Rhinitis.

Medication Score
Asthma

Canonica GW. Efficacy of SLIT in children with Allergic Rhinitis.
CLINICAL, FUNCTIONAL AND IMMUNOLOGICAL EFFECTS OF SUBLINGUAL IMMUNOTHERAPY IN BIRCH POLLENOSIS: A 3-YEAR RANDOMIZED CONTROLLED STUDY

Maurizio Marogna, Igino Spadolini, Alessandro Massolo, Giorgio Walter Canonica, Giovanni Passalacqua

JACI, June 2005
Coseasonal SLIT reduces the development of asthma in children with allergic rhinitis. 
*Novembre E. et al, JACI 2004*
Post-marketing surveillance study on the safety of SLIT in pediatric patients
Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW
Allergy, 1999

Safety of sublingual IT in adults: a post marketing surveillance study
C. Lombardi, S. Gargioni, A. Tiri, P. Falagiani, G. Passalacqua
Allergy 2001

ARIA: Allergic rhinitis and its impact on asthma
JACI 2001

Several other papers have now been published and pharmacosurveillance data has shown that sublingual specific immunotherapy does not induce severe side effects in children. In this Position Paper, it is proposed that sublingual specific immunotherapy can be administered in children and adults

<table>
<thead>
<tr>
<th>SYSTEMIC IMMEDIATE SIDE EFFECTS</th>
<th>SCIT</th>
<th>SLIT</th>
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<tbody>
<tr>
<td>Grade II</td>
<td>23</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Grade III</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade IV</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SLIT and SCIT are significantly effective in birch pollen hayfever compared with placebo
SLIT showed significantly fewer and milder side effects compared with SCIT
Khinkl et al. Allergy 2004
Safety of SLIT with a monomeric allergoid in very young children

M. Agostini, L. Tellarini, G. M. Canonica, G. Passalacqua

38 children:
33 male + 5 female
Age range: 1y11m - 3y10m
Mean age: 3 years
8 RC, 4 A, 10 RC+A
28 mite SLIT + 36 grass SLIT

SLIT: POST MARKETING SURVEYS

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>N pats</th>
<th>Age range</th>
<th>Follow-up</th>
<th>AE % of patients</th>
<th>AE/1,000 doses</th>
</tr>
</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>Lomberdi</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>5.6 %</td>
<td>0.2/1,000</td>
</tr>
</tbody>
</table>

André et al. Int Arch Allergy Immunol 2003

Rhinitis daily score

18
Efficacy and Safety  Rhinocconjunctivitis symptom and medication score
Excluding subjects not treated 8 weeks prior to season (pooled data) (protocol correct analysis)

% Difference from placebo (Group 1+5), N=202

-10 -5 0 5 10 15 20 25 30 35 40

2,500 SQ-T, N=111 25,000 SQ-T, N=116 75,000 SQ-T (Group 4 + 6), N=211

Entire pollen season Symptom score Medication score

SLIT
UNMET NEEDS

• Optimal dose/effect range ☺➕
• Long term efficacy ☺➕
• Preventive effect ☺
• Adherence to treatment ☺
• Cost/effectiveness ☺
• Efficacy and safety in children ☺
• Local immune response ➕
• Immunological Mechanisms ☺➕
Mechanisms of Sublingual Immunotherapy

Professor Tony Frew trained in Cambridge, London, Nottingham, Oxford and Stoke-on-Trent. He developed an interest in allergy while working with Professor Barry Kay at the Royal Brompton Hospital, London, and undertook post-doctoral research in Vancouver, Canada. After 13 years in Southampton, he recently moved to Brighton to set up a new department. His main research interests are the health effects of air pollution, and clinical trials of allergen immunotherapy; he has published over 200 papers in the peer-reviewed literature. Prof Frew has an active clinical practice in acute general internal medicine, respiratory medicine and clinical allergy. He has served on the EAACI Executive Committee since 1995 and is currently President of EAACI. He has served on the Professional Education and International Committees of AAAAI, and is Treasurer for his National Allergy Society (BSACI).

Abstract

Specific allergen immunotherapy (SIT) involves the administration of allergen extracts to modify or abolish symptoms associated with atopic allergy. Several mechanisms have been proposed to explain the beneficial effects of SIT. Conventional injection regimes induce allergen-specific IgG antibodies, especially of the IgG4 subclass. It is not clear whether these contribute directly to efficacy, by blocking the allergic response, or whether they are an epiphenomenon, unrelated to the true mode of action. T-cells are also affected by SIT, with a reduction in T-cell and eosinophil recruitment in response to allergen challenge, and a shift in the balance of Th1 and Th2 cytokine expression. These changes are thought to reflect induction of IL-10 secreting T-regulatory cells, which would also account for the induction of IgG4 antibodies.

Against this background, what do we know about the way that sublingual immunotherapy (SLIT) may work? Allergens applied to mucosal surfaces are handled differently from allergens given parenterally. This makes sense conceptually, as the immune system needs to respond vigorously to pathogens that manage to penetrate the body’s external defences, while it does not need to respond to antigens that are simply sitting on the mucosal surfaces. Consequently, the default mode for antigens encountered at the mucosal surface is tolerance.

From work in experimental animals, we know that IgE responses to allergens can be reduced or prevented by prior administration of allergen by the oral or inhalation routes [1]. It is likely that the route of allergen processing and presentation is a critical determinant of the subsequent T-cell response. In naïve mice, locally administered allergen is taken up by mucosal dendritic cells and then presented to T-cells together with IL-12, thereby biasing the response towards a Th1 profile and away from the pro-allergic Th2 profile [2,3]. It is less clear whether this mechanism can suppress established allergic responses, which is the situation that needs to be achieved by SLIT.

When allergen is given by the sublingual route to allergic humans, it is retained in the buccal region much longer than if the allergen is simply placed in the mouth and then swallowed, suggesting that allergens are indeed taken up locally [4]. However, the immunological response to SIT in humans is relatively modest, and most studies have not found any change in specific IgE, specific IgG or T-cell cytokine balance [5]. In some studies, T-cell proliferative responses to allergens and mitogens were attenuated and more IL-10 was produced after SLIT, compared to untreated allergic controls. IL-10 production after SLIT was similar to the level seen in healthy non-atopic control subjects, suggesting that SLIT may restore a more normal pattern of T-cell responses [6].

Ultimately the adoption of SLIT depends more on the demonstration of clinical efficacy rather than proving precisely which mechanism it may work through. Mechanistic studies do have a place in guiding future developments, but in vitro surrogate measures are no substitute for clinical endpoints!

References


Mechanisms of SLIT

Possible immunology of SLIT

- Oral tolerance
  - NB not direct tolerisation of target organ as may happen with local nasal IT
- Antigen presentation via dendritic cells in buccal mucosa
- Evidence of immune deviation, compared to injection route

Absorption of *P. judaica* given by different routes

Bagnasco et al.
*J Allergy Clin Immunol*
1997; 100:122-129
**Timecourse of absorption of sublingual Der p2**

Plasma radioactivity (% peak)

- **Allergen**
- **Allergoid**

swallow

minutes after administration

Bagnasco IAAI 2005;138:197-202

---

**Dendritic cells in oral mucosa**

Allam J-P et al JACI 2003;112:141-8

- oLC constitutively express FcεRI,
  - Even in non-atopics
- Compared to skin LC, oLC express
  - ↑ MHC class I and II
  - ↑ CD40
  - ↑ CD80/B7.1 and CD86/B7.2

---

**FcεRI expression on oral and skin dendritic cells**

Allam J-P et al JACI 2003;112:141-8
MHC expression on oral and skin dendritic cells

Allam J-P et al JACI 2003;112:141-8

Co-stimulatory molecules on oral and skin dendritic cells

Allam J-P et al JACI 2003;112:141-8

Antibody responses to SLIT
Antibody responses to SIT with ragweed in adults

Hedlin et al CEA 1990; 20:491-500

Antibody responses to SIT with D. pteronyssinus

McHugh et al JACI 1990; 88:521-31
**Allergen-specific IgG**

<table>
<thead>
<tr>
<th>Year</th>
<th>Act-Act</th>
<th>Act-Plac</th>
<th>Pi-Pi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Smith H et al JACI 2004;114:831-7

---

**T-cell responses to immunotherapy**

- Response to injection SIT
  - Role of IL-10 & T-regulatory cells
- Evidence of similar effect with SLIT

---

**Allergen Immunotherapy**

- Degranulation of mast cells
- Allergic mucosal inflammation & symptoms
- Th0
- Th1
- Th2
- IL-4, IL-13
- IL-5
- Eosinophil
- IL-12, IFN
- IgE

---
Interleukin-10

- Cytokine synthesis inhibitor factor (Th2 clones)
- T-cells, monocytes, macrophages, epithelium
- inhibits production of IL-1β, IL-6, IL-8, TNF-α, MIP-1α by monocytes
- reduces IL-2, IFN-γ from Th1 cells
- reduces neutrophil recruitment
- stimulates mast cell growth
- enhances IgE production (from committed B cells)

Allergen Immunotherapy

Immune Deviation

The role of IL-10 and TGF-β in the differentiation and effector function of T regulatory cells

Levings MK, Bacchetta R, Schulz U, Roncarolo MG
Int Arch Allergy Immunol 2002;129:263-276
SLIT in Birch Pollinosis
Marogna et al JACI 2005;115:1184-88

- Open, randomised controlled trial
- 3 years SLIT (12x SIT dose)
  - 79 randomised
  - 29/39 SLIT, 23/40 controls completed
- Baseline year 2000
- Active Rx 2001-3
- Follow-up off Rx 2004

SLIT reduces salbutamol use
Marogna et al JACI 2005;115:1184-88
SLIT reduces nasal eosinophils
Marogna et al JACI 2005;115:1184-88

Immunomodulation during SLIT in allergic children

- RCT of 6 months SLIT with D.pter
- 47 active; 39 placebo
- After 6 months, reduced serum
  - IL-13, ECP, prolactin
- No change in serum
  - CD40, ACTH

Ippoliti PAI 2003;14:216-221

SLIT reduces PBMC proliferation to Phl pratense Fanta IAAL 1999;120:218
Conclusions

- Oral tolerance exists
- Antigen persistence after SLIT
- Distinct phenotype of oral dendritic cells
- Variable IgG response to SLIT
- T-cell response suggests induction of regulatory T cells
- Further work required!
Is the US ready for Sublingual Immunotherapy?

Linda Cox, MD

Linda Cox, MD runs a solo adult and pediatric allergy and immunology practice in Ft. Lauderdale, Florida and is assistant clinical professor of medicine at the University of Miami School of Medicine and Nova Southeastern University School of Osteopathic Medicine. She is a Past President of the Broward County Medical Association and of the Florida Allergy Asthma and Immunology Society. Dr Cox has been chair of the American Academy of Allergy, Asthma and Immunology’s Immunotherapy and Allergy Diagnostics Committee since 2004, and is the current chair of the American College of Allergy, Asthma and Immunology’s Immunotherapy and Diagnostic Committee. Dr Cox chaired the AAAAI/ACAAI Task Force on Sublingual Immunotherapy which recently completed a comprehensive review of the literature on sublingual immunotherapy, to be submitted for publication in the near future. Dr Cox is also chair of the AAAAI’s Rhinitis, Sinusitis and Ocular Diseases (RSOD) Interest Section, in which capacity she has been actively assisting with the planning of the 2006 Annual Meeting.

Abstract

Introduction

Sublingual immunotherapy (SLIT) has been used with increasing frequency in Europe and is being viewed with increased interest by US allergists. In light of this, the ACAAI and AAAAI Immunotherapy & Allergy Diagnostics Committees formed a Joint Task Force with the purpose of providing a comprehensive updated report on SLIT for the North American allergy community. Members of the SLIT task force include academic and community-based allergists. The information in this paper is derived from the Joint Task Force’s report. In addition, due to the ‘speculative’ nature of the presentation - “Is the US ready for sublingual immunotherapy” some of the research information was obtained through personal communications.

The SLIT Task Force reviewed 103 articles with references through October 2005. The committee was divided into work groups that reviewed dosing, efficacy, immunologic response, safety, and practical considerations. Each work group reviewed each of the articles and extracted those articles that were relevant to their section. The focus of this presentation will be on practical considerations related to implementing SLIT in the US, focusing on issues such as costs, safety and adherence. There will also be some discussion of the other topics reviewed because they impact considerably on the practical consideration issues.

Sublingual Immunotherapy in the US

In parts of Europe, sublingual is the predominant route of immunotherapy, but in the US - aside from growing interest - SLIT has not received widespread acceptance. This is possibly because it has been associated with a low-dose form of immunotherapy called provocation-neutralization, discussed in the “Immunotherapy procedures that have not been proven effective” section of the “Immunotherapy for aeroallergen disease” chapter or the “Unconventional and unproven theories” chapter in Middleton’s Allergy textbook. (1)

An application for a new CPT code (new category 3 - emerging technology) for sublingual immunotherapy extract preparation in mid-2003 prompted the JCAAI to contact the ACAAI and AAAAI Immunotherapy Committees for comments, and subsequently lead to the development of an ACAAI and AAAAI SLIT Joint Task Force in early 2004 (Jay Portnoy and Linda Cox co-chairs, Hal Nelson, Larry Borish, Bob Lanier and Ira Finegold) which was assigned the task of working with AAOA, representing the otolaryngology allergy community, to write guidelines for studies to properly validate SLIT in the USA.

The Task Force felt no action was needed until an FDA approved formulation for SLIT was developed. At around the same time the AAAAI Immunotherapy Committee discussed SLIT in a conference call and came up with the following ‘questions to be answered’ as well as a similar decision that no action was needed until an FDA approved formulation for SLIT was developed:

- Currently there is no FDA approved product for SLIT:
  - What studies/steps would be necessary to develop an FDA approved SLIT extract?
  - If SLIT is recommended and manufacturers do not change product inserts, who is liable in the case of an adverse event?
- Is there enough information to determine the recommended maintenance dose(s) for SLIT?
- Is treatment for multiple allergens feasible with SLIT or would each allergen be kept in a separate vial?
- What is the cost-benefit analysis of SLIT considering it may require up to 300 times the SCIT maintenance dose and multiple allergens are utilized?
- Is there enough safety data to approve or advise against home administration of SLIT?
In November of 2004, Greer Laboratories (Lenoir, NC) began a safety and dosing study of standardized allergenic extracts/vaccines administered by the sublingual-oral route with the intent to obtain FDA approval for a SLIT formulation. At this time the ACAAI and AAAAI Immunotherapy and Allergy Diagnostics Committees began the Joint Task Force comprehensive review project.

SLIT Costs: How much will the treatment cost, who will pay for it and how much are they (insurers, patients and/or government) willing to pay?

Allergen dosing
It is difficult to predict the likely cost of SLIT without having a clear concept of what dose and dosing frequency is required to achieve optimal efficacy. In the SLIT Joint Task Force review the dosing regimens varied from daily to once weekly. The individual sublingual allergen doses varied between 10 ng Fel d 1 [2] and 314 mcg Amb b 1 [3] per dose and cumulative monthly doses (CMD) between 0.017 and more than 500 times the customary subcutaneous maintenance dose recommended by the Joint Task Force Allergen Immunotherapy Practice Parameters (JTFAPP) and the WHO Position Paper on Allergen Immunotherapy [4, 5].

The optimal maintenance dosing frequency of SLIT has not been established. Dosing regimens varied from daily [2, 3, 6-16], three times a week [17], twice weekly [18] to once weekly. [19] One 4-year open study of various allergens compared one drop daily (6 mcg Der p 1 CMD) with 5 drops 3 times a week [13 mcg Der p 1 CMD], and demonstrated that the daily lower dose regimen resulted in a greater magnitude of decrease in skin prick end-point titration reactivity (0<.001), a higher rate of no drug use (p = .013) and at least 50% reduction in drug consumption compared with pretreatment use (p = .001). [7]

Another study compared 3 dosing regimens with an open control group. There were two pre- and co-seasonal regimens. The higher dose administered was 0.4 mcg major grass allergen daily (12 mcg CMD) while the lower dose administered was 0.3 mcg 3 times week (5.1 mcg CMD) [20]. In addition, there was one pre-seasonal regimen. There was a significant improvement in symptoms and drug intake in all SLIT groups compared with the open control group (p < .0001). The best clinical results were seen in the 2 pre- and co-seasonal regimens (p<.0001) with greater improvement in drug intake scores (p = .026), paradoxically, in the 3 times a week regimen with the lower cumulative maintenance dose.

Only two randomized-controlled (RC) studies were specifically designed to compare the response to different doses. [6, 21]. One randomized-controlled study compared 2 maintenance dose regimens administering 85 and 375 times the usual SCIT dose, (24 drops of 300 IR vs. 40 drops of 100 IR per week) and found greater improvement in symptom-medication scores in the higher dose group (p = .024) [21]. The other dose response study was a randomized, placebo controlled multi-center, multi-country study of 855 patients with grass-induced allergic rhinitis who were treated with either placebo or one of 3 treatment doses (2,500, 25,000 and 75,000 SQ-T units of Phleum pratense) daily for a mean duration of 18 weeks. [6] There was a significant improvement in medication and symptoms scores only in the highest dose treatment group, 75,000 SQ-T (equivalent to 15 mcg Ph p 5 or a cumulative monthly dose 22.5 times that recommended by the same company for SCIT).

Table 1

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Medication Scores</th>
<th>Symptoms Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,500 SQ-T (~0.5 mcg Phl p 5)</td>
<td>P = .38</td>
<td>P = .96</td>
</tr>
<tr>
<td>25,000 SQ-T (~ 5 mcg Phl p 5)</td>
<td>P = .96</td>
<td>P = .46</td>
</tr>
<tr>
<td>75,000 SQ-T (~15 mcg Phl p 5)</td>
<td>Reduced by 28% (p = .047)</td>
<td>Reduced by 16% (p = .0071)</td>
</tr>
<tr>
<td>If only pts treated with 75,000 SQ-T for at least 8 weeks were considered:</td>
<td>Reduced by 29% (p = .012)</td>
<td>Reduced by 21% (p = .002)</td>
</tr>
</tbody>
</table>

How much will the treatment cost?
In the above study as an example, the effective SLIT dose was equivalent to 15 mcg of major grass allergen administered daily which is in the 5 to 20 mcg range recommended for maintenance subcutaneous immunotherapy (SCIT). Using this dose and schedule, the ALK-Abello January 15 2006 list price for standardized grass (the company that sponsored the study) was used, and the recommended maintenance dose for standardized grass is 8000 BAU per dose (5).

Standardized grass 100,000 BAU/ml $89.90 US per 10 ml = $8.9/ml
4,000 BAU = $0.359 US per dose x 30 days = $10.78 per month

In comparison with SCIT, the maintenance cost for the allergen extract (CPT code 95165) would be $0.359 per dose if administered on a monthly basis with greater costs during the build-up phase. SCIT would have the additional administration fee cost (~ 95115 single injection, 95117 multiple injection ~ $14-$20–reimbursement varies by location and insurer)

Polysensitized patients: Virtually all of the studies reviewed by the SLIT Joint Task Force utilized single allergen and none employed non-cross reacting allergens. Polysensitized patients appear to be ‘the rule’ rather than the exception in the US. A 3 year prospective open study of polysensitized patients designed to evaluate the efficacy of SLIT treatment with multiple pollen allergens demonstrated significant improvement in medication and symptom scores compared with baseline. (Personal communication Martin Kagi, MD Zurich, Switzerland).

Adding dust mite and cat sensitivity to the above example, and using the same catalogue for list price:

Cat 10,000 BAU/ml = $127.0 per 10 ml = $12.7/ml
2000 BAU (2000-3000 BAU recommended maintenance dose) x 10 ml = $2.5 per dose x 30 days = $76.2 per month

Dust mite: 10,000 AU/ml = $126.0 per 10 ml = $12.6/ml
2600 AU (600 AU D. pteronssinus, 2000 AU D. farinae recommended maintenance dose) x 10 ml = $3.2 per dose x 30 days = $98.28 per month
Total SLIT extract cost for a cat, dust mite and grass allergic patient in the above example would be: $185.26 per month or $2223.12 per year.

In comparison, SCIT costs:
Build-up phase: ~28 dose increments (JITAIAPP sample build-up) x $20 (95117 for administration) = $560 plus $172.9 (95165 extract preparation): Total = $732 for build-up phase ~ 6 months Maintenance: monthly administration: $20 (95117 for administration) + $6.17 (95165 extract) = $26.17 per month

The above example is only speculative and based on the one placebo-controlled dose response SLIT study’s dose and schedule as well as the current list price for the company (ALK-Abello) who sponsored the study.

Who will pay for it?
Currently there is no CPT code for sublingual immunotherapy.

“Immunotherapy (desensitization, hyposensitization) is defined as the parenteral administration of allergenic extracts as antigens at periodic intervals, usually on an increasing dosage scale to a dosage which is maintained as maintenance therapy. Indications for immunotherapy are determined by appropriate diagnostic procedures coordinated with clinical judgment and knowledge of the natural history of allergic diseases.

The CPT code 95165 used to bill for preparation of antigens for allergen immunotherapy is defined as: “Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy single or multiple antigens (specify number of doses)” and included in the group of codes (95115-95199) which are described as “professional services necessary for allergen immunotherapy.” (22).

Considering the CPT definition of immunotherapy as the “parenteral administration of allergenic extracts”, it can be inferred that the 95165 CPT code is intended for preparation of allergen extracts that will be administered by means of the parenteral route. Some insurers will reimburse for SLIT using a CPT for unlisted services (see below Kansas BCBS Blue Shield Report excerpt):

**Allergy Immunotherapy – Sublingual Drops**
Sublingual drops are medically necessary and not considered experimental/investigational as published in the MAC-01-04 (May 27, 2004) Blue Shield Report. Sublingual drops should be billed using CPT code 95199.

**How much are they (insurers, patients and/or government) willing to pay?**
Current state of US health care: Health care coverage purchased by employers with little input from consumers/patients/employees. The concept of managed care providing ‘complete medical coverage’ from hospital bills to prescription medication is waning and health care is moving toward health savings accounts and “consumer directed health care” (Donald Fisher June 25, 2005 Allergy Partners Annual meeting). This translates into patients who will have a greater say in health care decisions as well as more responsibility for their health care costs. With patients determining how their health care dollars are spent, factors such as time/convenience, one of the advantages of SLIT, may become more important. On the other hand, the increased treatment costs may make SLIT too costly for individuals in lower incomes or on ‘tighter’ budgets.

**Safety**
The US has been struggling with a medical malpractice ‘crisis’ for several years. In response to the crisis many physicians practice ‘defensive’ medicine reluctant to take any risks in patient treatment including new or novel treatments. SLIT would represent a novel form of immunotherapy. It is generally administered in the home setting, which accounts for its greater convenience compared with SCIT. However, the home setting does not have trained personnel and equipment available to assess, treat and document adverse reactions.

Below is an excerpt from a response to questions regarding potential SLIT liability issues.

“Regarding your question on allergist liability in connection with home administration of SLIT, malpractice liability requires a showing of negligence and negligence is usually measured against either the standard of care of what a reasonably prudent physician would do. So if the allergist had met the standard of practice in preparation of the SLIT and had provided the patient with proper instructions and given informed consent, then the allergist would generally not be liable. But in the case of a new therapy, where the standard of practice is not yet established, it might be hard for the allergist to demonstrate that they had acted consistent with accepted standard of care. Sorry not to be more concrete - this is always a fact specific determination. Certainly risk is minimized by properly informing the patient and documenting it.” (Personal communication, Rebecca Burke for JCAAI)

In the SLIT Joint Task Force review there were 66 sublingual immunotherapy studies utilizing unmodified allergen extracts that provided some information about SLIT-related adverse events.

- In the approximately 1,181,000 doses administered to 4,765 patients in the 66 studies reviewed there were no serious life-threatening reactions reported.
- In six studies of allergoid SLIT, with a total of approximately 70,000 doses in 380 patients there were no serious life-threatening reactions reported.
- In the 41 studies that provided specific information on total number of adverse events there were 1,047 adverse reactions for a total of 386,149 doses (2.7 reactions per 1000 doses).
- In 49 studies that provided specific information on total number of patients with adverse reactions, 529/4,378 patients (12%) reported an adverse reaction.
- In the studies that specified the type of reaction 169/314,959 (0.056% of doses administered) were classified as systemic reactions.
- 58 studies with allergen SLIT contained enough information to classify serious adverse events. In 3,984 patients treated for a total of 5,377 SLIT-treatment-years with a total of 1,019,826 doses there were 16 serious adverse events of which 14 were probably SLIT related.
Table 2: Sublingual Immunotherapy Serious Adverse Reactions:

In 58 studies, 3,984 patients treated with a total of 1,019,826 doses in 58 studies were 14 probably SLIT-related serious adverse events

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of SAE patients</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calderon (21)</td>
<td>1</td>
<td>1 mild uvula edema hospitalized for observation in the highest dose group (~ 15 mcg Phil p 5)</td>
</tr>
<tr>
<td>Ficchi (23)</td>
<td>1</td>
<td>Severe (4/4) vomiting</td>
</tr>
<tr>
<td>Godzio (28)</td>
<td>1</td>
<td>1 severe asthma: treatment beta-agonist and systemic steroids</td>
</tr>
<tr>
<td>Grasclaude (26)</td>
<td>2</td>
<td>2 persistent asthma</td>
</tr>
<tr>
<td>Hirsch (25)</td>
<td>1</td>
<td>One drop-out because of worsening of asthma and generalized weakness for weeks with 1 episode of severe bronchial obstruction.</td>
</tr>
<tr>
<td>Mitsch (24)</td>
<td>3</td>
<td>Severe abdominal pain when SLIT was taken with antibiotics. (1x) ‘Severe’ worsening of their allergy (2x)</td>
</tr>
<tr>
<td>Pradalier (16)</td>
<td>1</td>
<td>Generalized urticaria for 48 hours</td>
</tr>
<tr>
<td>Rolnick-Werninghaus (17)</td>
<td>1</td>
<td>Asthmatic crisis requiring hospitalization</td>
</tr>
<tr>
<td>Tari (29)</td>
<td>3</td>
<td>Severe Asthma (3)</td>
</tr>
<tr>
<td>Lima (11)</td>
<td>2</td>
<td>Motorbike accident Epiglottitis</td>
</tr>
<tr>
<td>Total number of SAE</td>
<td>16 (allergy-SAE: 14)</td>
<td></td>
</tr>
<tr>
<td>Total of asthma exacerbations</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total doses given</td>
<td>1,019,826</td>
<td>Allergy-SAE: 1.4/100,000 doses</td>
</tr>
<tr>
<td>Total treatment years</td>
<td>5,377</td>
<td>1 allergic SAE per 384 treatment years</td>
</tr>
<tr>
<td>Number of patients</td>
<td>3,984</td>
<td>1 SAE per 249 patients</td>
</tr>
<tr>
<td>Only allergy exacerbations SAE</td>
<td>14</td>
<td>1 treatment related allergic SAEper 285 pts</td>
</tr>
</tbody>
</table>

1 asthma exacerbation per 498 patients

Safety in very young children:

JTAIP Summary statement 53: Children < 5 years of age may have difficulty cooperating with an immunotherapy program (refers to SCIT). Therefore the physician should carefully consider the benefits and risks of immunotherapy and individualize treatment in patients < 5 years of age. (A)

One of the other purported advantages of SLIT over SCIT is greater safety. Currently in the US, SCIT is generally not initiated in children < 5 years. The greater safety of SLIT may make allergen immunotherapy a feasible option for this age population.

In the SLIT Task Force review there were two observational and one post-marketing survey SLIT studies specifically designed to assess safety of SLIT in young children. (23, 30, 31). In the first study, thirty-three children with intermittent (12 patients) or mild persistent (17 patients) asthma or persistent rhinitis (33 patients), aged 1 year 11 months to 3 years 10 months (mean 3 years 2 months) were treated with a monomeric allergoid (Lofarma, various allergens, 4 drops of 3000 AU/ml daily) (30).

The mean follow-up was 22.3 months and approximately 22,200 doses were administered. Two children experienced one episode of abdominal pain (5% of patients; 0.071% per 1000 doses). One was mild and the other was characterized as moderate, requiring a temporary dose adjustment. The parents’ assessment in 21 children was highly improved, moderately improved in nine, slightly improved in nine and unchanged in two children.

In the second study, sixty-five children aged 38-80 months (mean ± SD, 60 ± 10 months) were treated with SLIT to various pollens or dust mite for a mean 246 ± 161 days. (23) The target maintenance dose was 300 IR three times a week (“300 times higher than standard dose recommended” with SCIT). The investigators compared two subgroups: 38-60 months (33 pts, 52 ± 6 months) and 61 to 80 months (32 patients, 70 ± 10.6 months). There were six AEs (urticaria, 1 gastrointestinal and 1 orolabial itch) in five (15%) patients in the younger group and seven AEs (2 urticaria, 3 gastrointestinal, and 2 orolabial itch) in six (18%) patients in the older group. Six AEs occurred during the build-up phase and 7 in the maintenance phase. The severity of the AEs ranged from mild to moderate and none resulted in discontinuation of treatment.

The third study was a post-marketing survey of 126 children aged 3 to 5 years [mean age 4.2 years] with allergic rhinitis and/or asthma treated for 2 years with SLIT to various allergens. (31) Side-effects were recorded by the parents in diary cards. The total number of doses was 39,000. Nine side effects were reported in seven children (5.6% of patients and 0.2 per 1000 doses). All side-effects occurred during the induction phase. There were two local (oral itching) side-effects that required no treatment. There were 7 systemic reactions: One was an episode of mild abdominal pain that did not require treatment. The remaining six cases were moderate abdominal pain with diarrhea, which were controlled by a dose reduction achieved by changing the SLIT method from sublingual-swallow to sublingual-spit.

Adherence

Another factor to consider with SLIT is how adherence will be monitored. Adherence can potentially impact the efficacy and safety of the treatment. Insurers considering reimbursement for SLIT have expressed concern about the former (personal communication Tracy Woody, Greer Laboratories) whereas prescribing physicians should consider both safety and efficacy and the patient’s likely adherence with this home-based treatment.

Few of the studies reviewed provided information about treatment adherence. Only one multi-center, observational study was specifically designed to provide a quantitative measure of SLIT adherence. (32) Eighty-six patients with allergic rhinitis and/or asthma prescribed SLIT for a single relevant allergen (41 HDM, 45 pollens) were treated with a monomeric allergoid prepared as a soluble tablet for a mean of 18 ± 2 weeks (pollen) or one year (HDM). Adherence was assessed through unscheduled telephone interviews after one year of treatment for HDM treated patients or at the beginning of the pollen...
season for the pollen treated group. During the interview, patients were asked to count the remaining tablets. The count of the taken/expected tablets was 5,080/5,248 (96.8 %) in the HDM group and 3,952/4,050 (97.6%) in the pollen group. Omitted doses were reported in 11 patients with most postponing 1-2 doses because of concurrent illness or forgetfulness. One patient skipped multiple doses due to work schedule. In a randomized 4 year open study of 511 patients with allergic rhinitis and/or asthma to various allergens adherence was assessed by measuring with a pipette the remaining volume of extract in the returned vials and comparing it with the amount expected to be consumed during a given treatment period. (33) At the end of the observational year 311 patients were randomized to the SLIT group and 192 patients to the medication only group. Adherence to SLIT over the 3-year period was excellent (>80%) in 195 out of 271 (72%) patients, good (from 60 to 80%) in 49 out of 271 (18%) patients and poor or insufficient in 27 out of 271 (10%) of patients.

Since this treatment is administered at home with no direct medical supervision, prescribing physicians would need to provide specific instructions on how to manage adverse reactions, unplanned treatment interruptions, situations in which the dose should be withheld and dosing adjustments for any or all of these variables. In addition to assessing a patient’s likely adherence to SLIT, physicians should consider the patient’s ability to follow these instructions before prescribing this treatment.

Is the US ready for sublingual immunotherapy?

What questions, raised by the AAAAI Immunotherapy and Allergy Diagnostic Committee 2003 conference call have been answered?

- Currently there is no FDA approved product for SLIT:
  - What studies/steps would be necessary to develop an FDA approved SLIT extract?
    - **Answer:** Greer has completed phase 1 safety and dosing studies for the sublingual-oral route.
  - If SLIT is recommended and manufacturers do not change product inserts who is liable in the case of an adverse event?
    - **Answer:** Not sure if this can be answered.
- Is there enough information to determine the recommended maintenance dose (s) for SLIT?
  - **Answer:** No, dose response studies are likely to be needed for each formulation (i.e. ALK tablet, Greer glycerin-aqueous solution).
- Is treatment for multiple allergens feasible with SLIT or would each allergen be kept in a separate vial?
  - **Answer:** Maybe, at least one study has been completed but not yet published.
- What is the cost-benefit analysis of SLIT considering it may require up to 300 times the SCIT maintenance dose and multiple allergens are utilized?
  - **Answer:** Cannot answer because the dose requirement is needed to determine cost.

**Sublingual immunotherapy reference list**

5. Li JT, Lockey RF, Bernstein IL et al. Allergen Immunotherapy: A Practice Parameter. Annals of Allergy, Asthma & Immunology. 2003; 90 (suppl)


World Allergy Forum:
“Sublingual Immunotherapy — Is There a Role?”
Saturday, March 4, 2006 - 10:45 a.m. – 12:00 p.m.
Miami Beach Convention Center
Room A201-205
American Academy of Allergy, Asthma and Immunology
Annual Scientific Meeting
Miami Beach, Florida, U.S.A.
You Are Invited To Attend

Life-Threatening Allergy - An Homage to Clemens Von Pirquet

Sunday, 11 June 2006
1:30 p.m. – 3:15 p.m.

Chairs:
Michael A. Kaliner
Anthony J. Frew

Epidemiology of Anaphylaxis
Aziz Sheikh

Mechanisms of Anaphylaxis
Richard F. Lockey

Management of Anaphylaxis
F. Estelle R. Simons

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