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Local Immunotherapy in Allergy

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A promising new approach to curing allergies

The incidence of allergies is increasing worldwide. Beside the well-established symptomatic treatments and subcutaneous immunotherapies, formerly known as de- or hyposensitization, a new form of treatment, local immunotherapy, has been developed in recent years. Local immunotherapy, though still controversially discussed, promises to be a curative, noninvasive, and easily applicable treatment for allergies.

This volume summarizes the most current information on local immunotherapy compiled by internationally renowned specialists. In the methodology section, general aspects of local immunotherapy are presented including its history, allergen resorption and biodistribution, mechanisms of oral tolerance and practical experiences. The second section devoted to efficacy and safety presents findings from international placebo-controlled studies on nasal and sublingual immunotherapies with different allergens and for different allergic conditions including asthma and eczema. Possible side effects are also discussed. The concluding chapter critically evaluates the future prospects of this new method, pointing out still unresolved issues such as the exact immunological mechanisms, its long-term effects, or the standardization of dose and application intervals/duration.

This state-of-the-art account will be of particular interest to scientists working in the field of allergy, clinical allergologists, pharmacists, and representatives from the pharmaceutical industry.

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Local Immunotherapy in Allergy: Prospects for the Future

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**The following is the complete introductory chapter written by the physician faculty of Allergychoices Inc. and staff of Allergy Associates of La Crosse (WI, USA)
The entire books can be ordered through karger.com**

Local Immunotherapy in Allergy

Morris, D.L.; Kroker, G.F. ; Sabnis, V.K. ; Morris, M.S.

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ABSTRACT

Specific immunotherapy is a very powerful tool which is currently underutilized in the treatment of allergies. Sublingual immunotherapy (SLIT) has many advantages over subcutaneous immunotherapy (SCIT), and has been well proven to work for many pollens and dust mites. Multiple studies have shown SLIT improves symptoms and reduces the reliance on medications.

Sublingual treatment has been studied in Europe and is endorsed by the World Health Organization Committee on Immunotherapy as a viable alternative to subcutaneous immunotherapy (SCIT).

CONCLUSION: SLIT offers another option for patients who are not currently candidates for subcutaneous immunotherapy. Because of improved safety, convenience and compliance, sublingual immunotherapy should be used as a first line treatment option.

Specific immunotherapy is the ideal way to treat allergies. The primary goal is to desensitize the patient for the underlying cause of allergy symptoms by making them more tolerant to specific allergens. Immunotherapy is a powerful tool to decrease nasal and eye allergy symptoms as well as asthma. It is a common understanding in the allergy profession that immunotherapy is currently underutilized.

Specific immunotherapy using subcutaneous injections (SCIT) has been used for almost 100 years. It is clearly helpful for allergic rhinitis from pollens. Treatment of asthma, especially from molds, is not as clearly successful. Factors such as the inconvenience and expense of traveling for allergy shots contribute to a dropout rate greater than 50% over a multi-year course of treatment.^[1] Some children and adults dislike injections or have had reactions to allergy shots.

Sublingual immunotherapy (SLIT) has many advantages over subcutaneous treatment. It has shown efficacy for allergic rhinitis and asthma due to dust mites, pollens, and molds.^[2,3,4,5,6,7,8] Pollen studies include Parietaria,^[9,10,11,12,13] grass,^[14,15,16,17,18,19,20,21] ragweed,^[22] and trees.^[23,24] SLIT works for children^[3,6,7,17,23] as well as adults. SLIT can be used for food allergies to help patients develop tolerance to specific foods.^[25,26] Treatment of children with atopic dermatitis^[27] or nasal allergy may even help prevent the progression to asthma.

The mechanism of action for SLIT, as well as SCIT, has not been fully elucidated. It has been shown that sublingual antigens stay in the mucosa for up to 20 hours after administration.^[28] Studies using radioactive labeled Parietaria delivered sublingually showed plasma levels peaked in two hours.^[29] One likely mechanism is that the sublingual antigens act on ganglionic cells (antigen presenting cells) in the mucosa to develop tolerance to the allergens. Local “mucosal immunity” appears to play a significant role.^[30] Because sublingual swallow delivery has been more efficacious than sublingual spit, oral tolerance mechanisms in the gut may also be a factor.^[31,32]

Sublingual treatment has been used for many years. Many allergists in the U.S. (especially otolaryngic allergists)^[33] use sublingual treatment for inhalant as well as food allergies. Case reports of treatment for food allergies and respiratory inhalant allergies were published in 1969 and 1970^[34,35] in the U.S. In our clinic, we have treated over 60,000 patients in the past 35 years. Double-blind, placebo controlled studies from Europe began in the 1990s. These papers were mainly from Italy and France.

In 1990, effectiveness was well documented by Dr. Tari using sublingual dust mite antigens for 12 to 18 months.^[7] Allergic rhinitis and asthma symptoms improved in the children treated. There was a significant decrease in symptoms as well as medication use. In 1994, after 24 months of treatment, the same researchers found a decrease of specific IgE antibodies to dust mites.^[36]

A review article by Dr. G. Walter Canonica in 2001^[37] reported on 18 studies using SLIT in double blind, placebo controlled trials. Sixteen of these studies involving the most common allergens showed improved symptoms and decreased medication in rhinitis. Studies also showed efficacy for asthma and were done in adults and children. Safety profiles were good using the current dosing regimens.^[9,21,38,39,40] No life threatening reactions have occurred.

There are various methods using local immunotherapy. Nasal immunotherapy has shown efficacy but only shows local immunologic changes.^[41] Sublingual-spit was not as effective as sublingual-swallow delivery. Sublingual-swallow technique has been found to be most effective. Sublingual-swallow IT shows localized as well as systemic immunologic changes.^[2,7,11,16,36] The antigen, as a liquid or tablet, is held under the tongue for twenty seconds to two minutes and the remainder is swallowed. Doses are given up to three times per day. Most methods use daily doses during buildup and often less frequent doses during maintenance. In our clinic we use daily administration.

Single antigen, relatively rapid, buildup protocols have been shown to effectively treat dust mites.^[2,3,5,7,8] Treatment should be continued for at least 24 months.

Single antigens such as trees, grass, ragweed, or other pollens can be treated by pre-seasonal, high-potency regimens. This can be maintained throughout the year or decreased to a lower dose during the season.^[17]

Doses of single antigens are .5 to 200 times stronger than those used for subcutaneous immunotherapy (SCIT). Efficacy and safety has been shown in a wide range of dosages. The attached TABLES 1-4 summarize the analyses of specific studies and compares doses, dosing schedules, and results. The optimal dosing regimen has not yet been identified. The increased cost of the antigens is typically offset by the decrease in the number of office visits needed for injections.

“Threshold” dosing is a good way to start treatment for multiple antigens.^[33] Using the serial end point titration technique,^[42] the initial doses are based on the first positive intradermal test. For multiple antigens, the drops are given three times per day. Doses are increased as objective improvement is seen on follow-up skin testing. Mold allergies respond particularly well to this method.

Foods can be treated based on in vitro specific IgE level testing (such as Pharmacia Unicap) or challenge testing. Dosage depends on the severity of the food allergy. The more severe food allergies require smaller doses. Antigens are used three times daily until tolerance develops. Specific IgE levels are rechecked typically every six to twelve months. Doses are not increased until specific IgE levels start to decline.

Contact sensitivity to nickel can be improved using sublingual doses of nickel sulfate.^[43,44] Nickel sulfate is used to test intradermally and a sublingual dose is chosen to start that is weaker than the first positive skin reaction (using a modified serial end point titration technique).^[42]

The World Health Organization position paper^[31] published in 1998 found that properly conducted double blind, placebo controlled trials have shown the effectiveness of sublingual-swallow immunotherapy with grass, Parietaria and mite vaccines. The ARIA (Allergic Rhinitis and Impact on Asthma)^[32] guidelines published in 2001 gave specific indications for usage.

Because of improved convenience, compliance, and safety, sublingual immunotherapy opens the door for expansion of immunotherapy to a first line

TABLE 1**Subcutaneous Immunotherapy Dosing Guidelines**

Antigen	mcg/potency	Effective Dose	Effective Concentration	Reference
Dust mite	124 mcg/10,000 AU	7-11.9/mcg Der p1	1200 AU/ml	[45,46]
Dust mite	50 mcg/10,000 AU	10 mcg Der f1	4000 AU/ml	[46]
Grass	370 mcg/100,000 BAU	15 mcg	8000 BAU/ml	[47]
Short ragweed	325 mcg/1:10w/v	6-24 mcg Amb a1	1:30-1:250 w/v	[48,49]

Assumptions and abbreviations used in all tables:

*** = calculated dosages**

- Comparison is by monthly maintenance dose
- European baseline SCIT dosage is lower than the U.S. (this may account for some of the variability and higher x's)
- IR= Index of Reactivity
- mcg = micrograms
- N/A= not available
- ssx=symptom scores
- ↑ = increase
- ↓ = decrease
- NC = no change
- AU= Allergy Unit
- BU= Biological Unit
- BAU= Bioequivalent Allergy Unit
- STU= Specific Treatment Unit

TABLE 2

Double-Blind Placebo Controlled Sublingual Studies: Dust Mite

Monthly Maintenance Dose and Dose Ratio

Reference	Number of Study Patients	Disease & Duration	Maintenance Dose/Month	Results p<0.05	Safety	SLIT/ SCIT ratio		
						Der p1 (in mcg)	Der f1 (in mcg)	Note: * = Calculated dosage
Mungan et al ^[5] <i>Ann Allergy 1999</i>	5 Active 11 Placebo	Rhinitis& Asthma 12 mos	867 IR	↓ ssx ↓ meds Nc IgE D1 ↑IgG4 12m	1 patient buccal pruritis	N/A	N/A	86
Tari et al ^[96] <i>Allergol Immunopathol 1994</i>	30 Active 28 Placebo children	Rhinitis& Asthma 24 mos	4875 STU	↓ IgE D1 ↑IgG4 18m ↑IgG 12m	None	N/A	N/A	5
Bahceciiler et al ^[9] <i>Ped Pulmonology 2001</i>	8 Active 7 Placebo children	Rhinitis& Asthma 5 mos	69.3 mcg Der p1 121.2 mcg Der f1	↓ asthma ssx, score ↓ meds ↓ ID test ↑Peak Flo	None	69.3 mcg*	121.2 mcg*	5.8---9.9 Der p1* 12.2 Der f1*
Pajno et al ^[9] <i>Allergy 2000</i>	12 Active 12 Placebo children	Asthma 24 mos	10.4 mcg Der p1 5.2 mcg Der f1	↓ meds by year 2 ↓Asthma flares ↓ noc ssx	4 fatigue 1 lip swell 1 oral pruritis No rx need	10.4 mcg*	5.2 mcg*	3.25
Tari et al ^[7] <i>Allergol et Immunopathol 1990</i>	30 Active 28 Placebo	Rhinitis& Asthma 18 mos	4875 STU	↓ ID ↓ ssx ↓ meds ↑ spec IgG	3 hives 8 mild asthma 4 GI	N/A	N/A	5
Guez, et al ^[4] <i>Allergy 2000</i>	36 Active 36 Placebo	Rhinitis 24 mos	187 mcg Der p1 144.2 mcg Der f1	NS	2 oral pruritis	187 mcg*	144.2 mcg*	15.6—28.7 Der p1* 14.4 Der f1*
Bousquet et al ^[2] <i>Allergy 1999</i>	42 Active 43 Placebo	Rhinitis & Asthma 24 mos	309.6 mcg Der p1 541.8 mcg Der f1	↓ ssx ↑ AM peak flow ↑ IgG4	3 urticaria & throat itching 1 asthma	309.6 mcg*	541.8 mcg*	200
Allergy Associates of LaCrosse WI USA			36 mcg Der f1				36 mcg*	3.6 Der f1*

Assumptions:

* = calculated dosages

European baseline SCIT dosage is lower than the U.S. (this may account for some of the variability and higher ratios)

SLIT/SCIT ratio = sublingual immunotherapy monthly maintenance dose/subcutaneous monthly maintenance dose

Abbreviations Key:

IR= Index of Reactivity

mcg = micrograms

N/A= not available

ssx=symptom scores

meds= medication use

TABLE 3

Double-Blind Placebo Controlled Sublingual Studies: Grass Pollen

Reference	Number of Study Patients	Disease & Duration	Maintenance Dose/Month	Results p<0.05	Safety	Monthly Maintenance Dose and Dose Ratio		SLIT/SCIT Ratio Note: * = Calculated dosage 0.5*
						Types of Grass	Monthly Maintenance Dose (in mcg)	
Marcucci et al [60] <i>Allergy</i> 2001	30 active 20 control children	Seasonal Allergic Rhinitis 7 months	7.5 mcg	None (safety study)	No side effects or rxns	5 major grass allergens	7.5 mcg*	0.61*
Di Rienzo [17] <i>Allergol et Immunopathol</i> 1999	48 children 5-12 years four grps: Pre-co, co, control	Rhino-conjunctivitis 5 ½ months	Group A: 9.1 mcg Group B: 9.1 mcg Group C: 6.5 mcg	↓ ssx in 3 active grps	Mild edema, erythema of eyelids in 2 pts	5 grasses: Phleum Lolium Dactylis Poa Festuca	Group A: 9.1 mcg* Group B: 9.1 mcg* Group C: 6.5 mcg*	0.61* 0.61* 0.43*
Hordijk [18] <i>Allergol et Immunopath</i> 1998	27 active 30 placebo	Rhinitis Conjunctivitis 10 months	82,327 BU	↓ ssx	Minor local symptoms	Timothy Velvet Orchard Bermuda Sweet V.	N/A	N/A
Clavel et al [19] <i>Allergy</i> 1998	62 active 58 placebo	Rhinitis Conjunctivitis 6 months	576 mcg Ph1 p5	↓ ssx	Oral itching; wheezing in some patients	5 major grass pollens	576 mcg* Ph1 P5	38.4*
Gozalo et al [91] <i>Allergol et Immunopathol</i> 1997	35 active 19 control (1st yr : 42 active)	Ocular Nasal Respiratory 7 mo 1 st yr 12 mo 2 nd yr	81.24 BU	↓ ssx	2.7 % mild rxns ; some needing antihist.	Lolium perenne (rye grass)	N/A	N/A
Quirino et al [92] <i>Clin Exp Allergy</i> 1996	10 active 10 placebo	Seasonal rhinitis 12 months sublingual & injection groups	SLIT-81.2 BU SCIT=34.3BU	↓ ssx ↓ meds	None reported	Five Grasses: Dg,Fp,Lp, Pfp,Pp	N/A	2.37*
Feliziani et al [21] <i>Allergol et Immunopathol</i> 1995	18 active 16 placebo	Ocular Rhinitis 3.5—4 mos	260 BU	↓ Overall ssx	None reported	Orchard Meadow Rye, timothy, sweet vernal	N/A	N/A
Pradaliar et al [15] <i>Allergy</i> 1999	62 active 61 placebo	Ocular Rhinitis Asthma 4.5 mos	255 mcg Ph1 P5	↓ Ocular ssx ↓ Asthma ssx	"minor side effects"	Orchard, meadow, ryegrass, sweet vernal & timothy	255 mcg* Ph1 P5	17*
Allergy Associates of LaCrosse WI USA			270 mcg			Bermuda, Kentucky Blue Meadow fescue, Orchard, Rye, Redtop, Timothy Sweet Vernal	270 mcg*	18*

TABLE 4

Controlled Sublingual Studies: Ragweed Pollen

Reference	Number of Study Patients	Disease & Duration	Maintenance Dose/Month	Results p<0.05	Safety	Monthly Maintenance Dose and Dose Ratio	
						Amb a1 (in mcg)	SLIT/ SCIT ratio Note: * = Calculated dosage
Valle et al ^[53] <i>Allergol et Immunopathol 2000</i>	19 active 14 control (meds only)	Rhinitis & Asthma 3 months	36 mcg Amb a 1	↓ nasal challenge ↓ skin reactivity ↓ ssx	1 lip itching	36 mcg	6
Allergy Assoc of La Crosse USA			180 mcg Amb a 1			180 mcg*	7—30*

Assumptions:

* = calculated dosages

European baseline SCIT dosage is lower than the U.S. (this may account for some of the variability and higher ratios)

SLIT/SCIT ratio = sublingual immunotherapy monthly maintenance dose/subcutaneous monthly maintenance dose

Abbreviations Key:

mcg = micrograms

ssx=symptom scores

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