

Sublingual Immunotherapy Research

Efficacy

Sublingual Immunotherapy for Allergic Rhinitis

Wilson, D.R., Torres, L.M., Durham, S.R. Sublingual immunotherapy for allergic rhinitis. (*Cochrane Review*), *The Cochrane Library*, Issue 2. 2003; Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database of Systematic Reviews* 2010, Issue 12. Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.pub2.

- Symptoms decrease by 42%
- Medications decrease by 43%
- “Overall there was a significant reduction in both symptoms ($p=0.002$) and medication requirements ($p=0.00003$) following immunotherapy”

This systematic review of sublingually administered allergen immunotherapy (SLIT) represents an update of a review first published in *The Cochrane Library* in 2003. The original review included data from 22 randomized controlled trials (979 patients) and demonstrated the efficacy of this form of treatment based on meta-analysis of symptom severity scores (SMD-0.42; 95% confidence interval (CI) -0.69 to -0.15). Ongoing research in this area has been considerable, and this review has now been updated to include studies published since 2003. The number of studies included has almost trebled to 60 (with 49 being suitable for pooling in meta-analysis), and the number of patients in meta-analysis has increased over four-fold, reflecting a trend towards larger, better-designed and more powerful trials.

The overall results of the meta-analysis differ little from those seen in 2003, with the overall effect for symptom scores SMD -0.49; 95% CI -0.43 to -0.21. These data continue to support the clinical efficacy of SLIT for allergic rhinitis.

Since the original systematic review in 2003, SLIT has become established as an effective and low-risk alternative to allergen injection immunotherapy, which carries a significant morbidity and a requirement for delivery within specialist centers capable of meeting CSM recommendations. SLIT is recommended to be initiated in secondary care and the first dose taken under medical supervision, whereas maintenance treatment is recommended to be self-administered in the patient's home.

The original systematic review by Wilson, et al. changed the field of SLIT for allergic rhinitis – encouraging significant investment in the further evaluation of a treatment with proven efficacy. This latest review includes the subsequent highly powered clinical trials and includes more than four times the number of patients. The data establish SLIT as a viable alternative to allergen injection immunotherapy, with a significantly lower risk profile. There is support for the use of SLIT in children and additional support for its use in allergic rhinitis because of seasonal allergens and perennial disease because of house dust mite. The sublingual route appears safer and has a better side-effect profile compared to the subcutaneous route, although a standardized grading system for side effects is needed to permit more accurate and consistent reporting in the future. A recent study of SLIT using grass allergen tablets for seasonal pollinosis demonstrated long-term benefit for at least one year following 3 years of treatment, implying the induction of both clinical and immunological tolerance. Further long-term studies in adults and children are needed; also adequately powered head-to-head trials of sublingual vs. subcutaneous immunotherapy. Inclusion of standardized quality-of-life measures and

pharmacoeconomic evaluations as major outcomes will further define the place of SLIT in the treatment of allergic rhinoconjunctivitis.

Mechanism

Mucosal immunization application to allergic disease: Sublingual immunotherapy

Frati, F., Moingeon, P., Marcucci, F., Puccinelli, P., Sensi, L., Di Cara, G., Incorvaia, C. Allergy and Asthma Proceedings 2007; 28 (1): 35-39(5).

- Unique Characteristics of the Sublingual Mucosa
- Dendritic cells highest concentration in body
- Increased IgE
- Increased number of dendritic cells
- T-Cells 37 times more than in skin
- Effector Cells (eosinophils, mast cells, basophils) negligible in allergic patients

Sublingual immunotherapy (SLIT) is an effective and safe treatment for respiratory allergy, and its mechanism of action currently is investigated with increasing attention. Studies of pharmacokinetics showed that allergen extracts administered via the sublingual route are not directly absorbed by the oral mucosa but are long retained at mucosal level, where the allergen molecules are captured by dendritic cells and, following their migration in the draining lymph nodes, presented to T cells. This seems to be the pivotal factor underlying the mechanisms of action of SLIT, at least for the long-term effects, and for the short-term efficacy, observed with ultra rush or coseasonal treatment, a down-regulation of mast cells resulting in hypo-reactivity at the peak of the pollen season may be suggested. Regarding the clinically established long-lasting effects, the core mechanism is likely to consist of T regulatory (Treg) cell activation. In particular, Treg cells differentiate from naive T cells after application of soluble antigens to the mucosa, a crucial factor being the tolerogenic function of dendritic cells, and exert a suppressive effect on both Th1 and Th2 responses. Moreover, at least for the type 1 cells (Treg1), a first mechanism...production of IL-10 with consequent down-modulation of the immune response has been reported. Another characteristic of sublingual immunization is the absence of effector cells, viz., mast cells, basophils, and eosinophils, in the oral mucosa of allergic subjects, which account for the excellent tolerability of SLIT.

Regarding lymphocytes, the T cells are located mainly in perivascular spaces in the epithelial layer and they are represented ~37 times more in the oral mucosa than in the skin, whereas the B cells are not present in the epithelium and in the papillar layer of the mucosa. The role of T cells in orchestrating the immune response is well known. In particular, in tolerance to allergens they may exert suppressive but also regulatory activity. The latter is currently regarded as very important in the response to allergens. The cells with such activity are named Treg cells and include naturally occurring CD4+ and CD25+ T cells and cells induced by antigen exposure (e.g., Tr1 cells, Th3 cells, and CD8+ Treg cells). The presentation of allergens by dendritic cells is critical in inducing the differentiation of Treg cells, which in turn can down-regulate Th1 and Th2 immune responses directly by cell or by production of immunosuppressive cytokines such as TGF- β (typical of Th3 cells) or IL-10 (typical of Tr1 cells). An association between atopy and a deficit in Treg functions is well documented.

A last remark about the immunity in the oral mucosa regards the effector cells of allergic inflammation, i.e., eosinophils, mast cells, and basophils. These cells are abundantly found in sites targeted by allergy

such as the nose, the eyes, and the lungs, but it has been shown that in the oral mucosa of allergic mucosa in allergic subjects, they normally are absent or in negligible number.

A first mechanism may be suggested for the short-term efficacy of SLIT observed with ultra rush or coseasonal treatment in patients with pollen allergy as hypothesized by Bousquet, down-regulation of mast cells is more efficient with the high allergen doses administered in a short time and results in hypo-reactivity at the peak of the pollen season.

A second mechanism might depend on Treg activation, which is likely to underlie the long-lasting effects of characteristics of prolonged immunotherapy observed also with SLIT. In particular the differentiation in Treg of naive cells is stimulated by the application of soluble antigens to the mucosae, a crucial factor being the tolerogenic function of dendritic cells. Antigen-specific Treg cells have a suppressive effect on both Th1 and Th2 response and, at least for the type 1 cells (Treg1), down-modulate the immune response producing IL-10. A recent report on this issue showed that patients treated with prolonged SLIT with house-dust mite extract had a significant production of IL-10, which was absent in untreated patients with mite-induced rhinitis.

Local immunological mechanisms of Sublingual Immunotherapy

Allam, Jean-Pierre, Novak, Natalija *Current Opinion in Allergy and Clinical Immunology*. 11(6):571-578, December 2011.

Recent findings: To Date, SLIT is widely accepted by most allergist as an alternative option to conventional subcutaneous immunotherapy (SCIT). Although detailed immunological mechanisms remain to be elucidated, much scientific effort has been made to shed some light on local and systemic immunological responses to SLIT in mice as well as humans. Only a few studies focused on the detailed mechanisms following allergen application to the oral mucosa as part of the sophisticated mucosal immunological network. Within this network, the pro-tolerogenic properties of local antigen-presenting cells (ACCs) such as dendritic cells – which are able to enforce tolerogenic mechanisms and to induce T-cell immune response in nasal and bronchial mucosa but also on the systemic T-cell immune response.

Conclusion: Local DCs within the oral mucosa bind allergens during SLIT, leading to a shift from Th2 to Th1 immune response along with the induction of regulatory T cells and the induction of IgG antibodies. The local oral mucosal microenvironment with its pro-tolerogenic nature contributes to such immunological mechanisms. Future investigations need to focus on the benefit of adjuvant supplementation of SLIT and whether other regions than sublingual tissue in the oral cavity are more potent for allergen application.

Summary: Thus, much exiting data have been published providing a better understanding of the immunological features of SLIT, but far more investigations are necessary to uncover further exciting details on the key mechanisms of SLIT.

The immune privilege of the oral mucosa

Natalija Novak, Jrög Haberstok, Thomas Bieberand Jean-Pierre Allam *Trends in Molecular Medicine* Volume 14, Issue 5, May 2008, Pages 191–198

- Excellent description of the protolerogenic nature of the oral mucosa

Despite high bacterial colonization and frequent allergen contact, acute inflammatory and allergic reactions are rarely seen in the oral mucosa. Therefore we assert that immune tolerance predominates at this site and antigen presenting cells, such as dendritic cells and different T cell subtypes, serve as key players in oral mucosal tolerance induction.

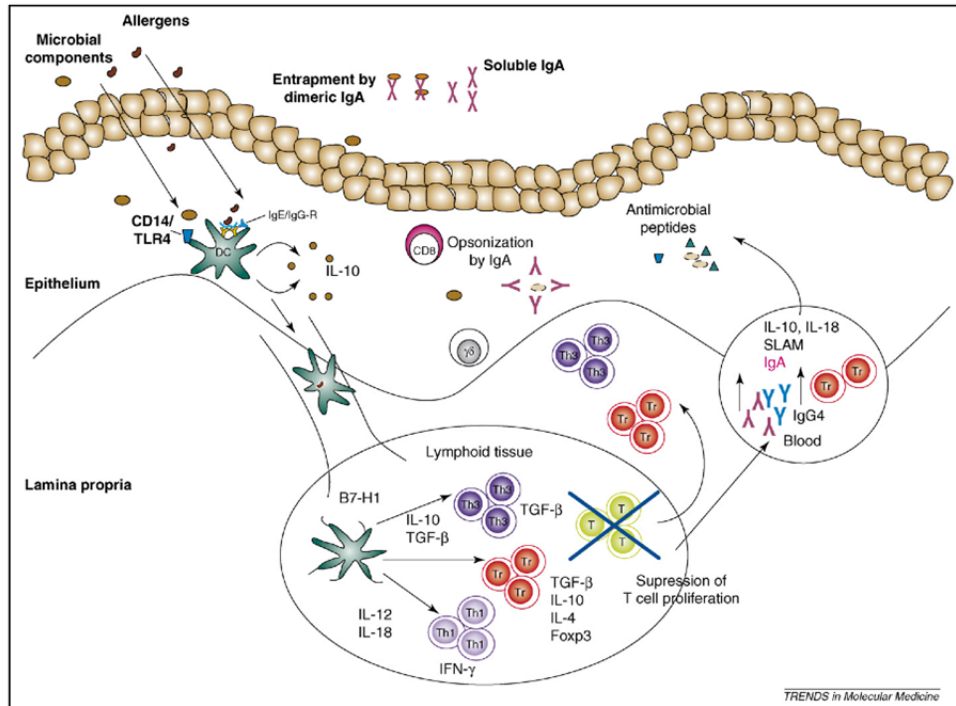


Figure 2. Inductive and regulatory protolerogenic mechanisms in the oral mucosa. The schematic depicts normal physiological tolerance induction after contact with microbial stimuli and allergens by IgA, innate immune responses mediated by antimicrobial peptides released within the oral mucosa and stimulation of pattern recognition receptors on antigen presenting cells. Allergens applied during sublingual immunotherapy (SLIT) are most likely to be taken up by the IgE receptor bearing antigen-specific dendritic cells (DCs). These allergens might co-activate IgE and IgG receptors and thereby induce stimulatory and inhibitory signals simultaneously. In addition, co-stimulation of pattern recognition receptors, such as Toll-like receptor (TLR4) and CD14, on oral mucosal DCs by microbial components or adjuvants used in the context of SLIT could increase the induction of tolerogenic mechanisms in the oral mucosa. DCs activated by allergens or microbial antigens release IL-10, migrate to the lymphoid tissue and upregulate co-inhibitory molecules such as B7-H1 on their cell surface. Within the lymphoid tissue they might induce TGF-β producing T cells (Th3), interferon-γ producing T cells (Th1) and T cells with characteristics of regulatory T cells (Tr), causing these cells to produce IL-4, IL-10 and TGF-β and to express forkhead box protein 3 (Foxp3). Furthermore, these DCs are capable of suppressing the proliferation of T cells. Enhancement of Foxp3⁺CD4⁺CD25⁺ Tr cells and IL-10 in the peripheral blood, as well as enhancement of IL-18 and the signalling lymphocytic activation molecule (SLAM) in peripheral blood mononuclear cells (PBMCs), are changes observable in the peripheral blood during SLIT that might indicate the induction of tolerance. Abbreviations: CD14/TLR4, CD14 associated with TLR4; DC, dendritic cell; Foxp3, forkhead box protein 3; IgA, immunoglobulin A; IgG-R, immunoglobulin G receptor; SLAM, signalling lymphocytic activation molecule; TGF-β, transforming growth factor β; Th1, T helper cell 1; Th3, T helper cell 3 (TGF-β producing regulatory T cell); TLR, Toll-like receptor; Tr, T reg (CD4⁺CD25⁺Foxp3⁺ regulatory T cell).

Existing knowledge on oral mucosa tolerance:

- *Dendritic cells play a central role in mucosal tolerance induction and are capable of taking up antigens in the oral mucosa and of acquiring tolerogenic properties mirrored by production of IL-10 and upregulation of co-inhibitory molecules such as B7-H1.*
- *Immune exclusion takes place by way of IgA.*
- *Induction of TGF-β-producing Th3 cells occurs with oral mucosal tolerance.*
- *High amount of IL-10 and TGF-β-producing T regs occurs during oral mucosal tolerance induction.*
- *There is an increase of IgG4, IgA, IL-10, IL-18 and SLAM in the peripheral blood during oral mucosal tolerance induction.*
- *There is lower proliferation of T cells.*

Safety

Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study

M. S. Khinchi, L. K. Poulsen, F. Carat, C. Andre, A. B. Hansen, H.-J. Mailing, *Allergy*, 2004; 59: 45-53

- Illustrates the specific AND partially aspecific effect of sublingual immunotherapy

Background: Both sublingual allergen-specific immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) have a documented clinical efficacy, but only few comparative studies have been performed.

Objective: To investigate the clinical efficacy of SLIT vs. SCIT and secondary to compare SLIT and SCIT with placebo and to evaluate the relative clinical efficacy in relation to systemic side-effects.

Methods: A 3-year randomized, placebo-controlled, double-blind, double-dummy study including 71 adult birch pollen hay fever patients treated for two consecutive years after a baseline year. Allocation to treatment groups was based on disease severity in the baseline season, gender and age.

Results: Clinical efficacy was estimated in 58 patients completing the first treatment year by subtracting baseline data and by calculating the ratio first treatment season vs baseline. SLIT diminished the median disease severity to one-half and SCIT to one-third of placebo treatment. No statistically significant difference between the two groups was observed. Both for symptoms and medication scores, actively treated patients showed statistically significant and clinically relevant efficacy compared with placebo. SLIT treatment only resulted in local mild side-effects, while SCIT resulted in few serious systemic side-effects.

Conclusion: Based on the limited number of patients the clinical efficacy of SLIT was not statistically different from SCIT, and both treatments are clinically effective compared with placebo in the treatment of birch pollen rhinoconjunctivitis. The lack of significant difference between the two treatments does not indicate equivalent efficacy, but to detect minor differences necessitates investigation of larger groups. Due to the advantageous safety profile, SLIT may be favored.

Prevention of New Sensitizations

Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients

Marogna, M., Spadolini, I., Massolo, A., Zanon, P., Berra, D., Chiodini, E., Canonica, G.W., Passalacqua, G. *Annals of Allergy* 2007; 98, 3:274-280.

Results: Those patients receiving SLIT for grass or birch had a significant clinical improvement and nasal eosinophil reduction vs baseline and vs patients who did not receive SLIT in the target season ($P < .01$), but also in the unrelated pollen season ($P < .05$). The patients receiving SLIT for grass and birch improved as well, and their improvement in clinical symptoms and inflammation was significantly greater than in patients treated with SLIT for the single allergens.

Conclusion: In patients sensitized to grass and birch, SLIT with the two allergens provided the best clinical results. Nevertheless, SLIT with birch only or grass only also provided a measurable improvement in the grass season and birch season, respectively.

The results of our comparative study suggest that, in the case of birch-grass sensitization, the SLIT with both allergens performs globally better than SLIT with the single allergens. In fact, the birch and grass SLIT provided a significantly greater improvement of symptoms plus medication score in both seasons compared with the single allergens, which were anyway effective in their target seasons. One challenging and unexpected result (Figs 2 to 5) was that patients treated with SLIT for birch or grass improved also in the grass and birch season, respectively. This fact was consistently reproducible also for bronchial hyper-reactivity and nasal eosinophils, which are reliable markers of allergic inflammation. Thus, an extended or carryover effect of the administration of a single allergen should be hypothesized. In this regard, we have no reasonable explanation for the observed effect because our study did not evaluate specific immunological parameters.

We can hypothesize that the SLIT-induced increase in interleukin 10 as previously reported plays a critical role, since interleukin 10 exerts its regulatory effect in a partially aspecific way. In addition, a role of cross-reactive proteins could be invoked to explain the nonallergen-specific effect. It is well known that profilins are partly shared by birch and grasses, although their clinical role seems not to be of great relevance with the considered allergens.

In conclusion, this open study suggests that the effect of SLIT with one allergen is extended also to the other allergens (birch or grass). Since this result could have clinical and economic implications, it needs more rigorous confirmations. First, the observation should be repeated in double-blind trials, with larger samples of patients. Second, it is important to know if the effect is present also with unrelated allergens (eg, pollens and mites). Finally, an immunological approach, including the evaluation of the behavior of T regulatory cells and cytokines, could help elucidate the clinical observation.

Long-lasting Effect

Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10 year prospective study

Di Rienzo, V., Canonica, G.W., and Passalacqua G. *Clinical and Experimental Allergy*, 2003 33:206-210

- Sublingual Immunotherapy shows true disease modification effects that persist even after treatment is stopped

Background: Subcutaneous immunotherapy for respiratory allergy has shown a long-lasting efficacy after its discontinuation, whereas this evidence is still lacking for sublingual immunotherapy, despite the fact that it is widely used.

Objective: We aimed to evaluate whether a long-lasting effect of SLIT occurs, in a prospective parallel group controlled study.

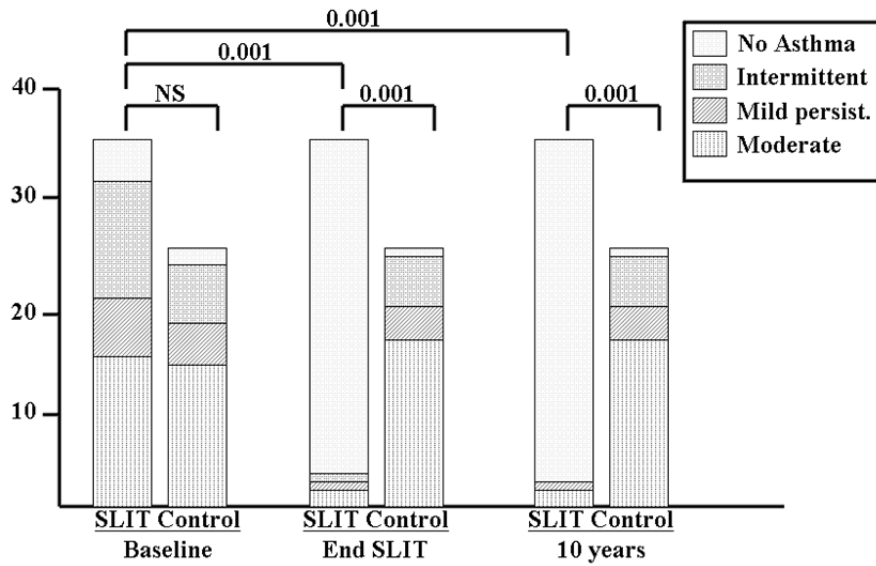
Methods: Sixty children (mean age 8.5 years) suffering from allergic asthma/rhinitis due to mites were subdivided into two matched groups: 25 underwent a 4- to 5 year course of SLIT with standardized extract and 25 received only drug therapy. The patients were evaluated at three time points (baseline, end of SLIT and 4 to 5 years after SLIT discontinuation) regarding presence of asthma, use of anti-asthma drugs, skin prick tests and specific IgE.

Results: We found that in the SLIT group, there was a significant difference vs. baseline for the presence of asthma (and the use of asthma medications), whereas no difference was observed in the control

group. The mean peak expiratory flow result was significantly higher in the active group than in the control group after 10 years. No change was seen as far as new sensitizations were concerned. Specific IgE showed a near-significant increase (baseline vs. 10 years, $P = 0.06$) only in the control group.

Conclusion: Our study demonstrates that sublingual immunotherapy is effective in children and that it maintains the clinical efficacy for 4 to 5 years after discontinuation.

Long-lasting effects



Number of patients taking anti-asthma medications

	Baseline	End SLIT	10 years	P
SLIT	31/35	4/35	3/35	NS
Control	23/25	24/25	24/25	
P	NS	0.001	0.001	

Long-term clinical and immunological effects of allergen immunotherapy

Eifan, Aarif O., Shamji, Mohamed H.; Durham, Stephen R. *Current Opinion in Allergy and Clinical Immunology*.11(6):586-593, December 2011.

- The long-term clinical effect is associated with allergen-specific IgG “blocking” antibodies

Purpose: The present review updates current finding on long-term clinical and immunological outcomes after cessation of allergen immunotherapy for respiratory disease.

Recent Findings: Recent studies have shown that allergen immunotherapy has sustained disease-modifying effects that persist for years after discontinuation. This is in contrast to the effects of antiallergic drugs that do not induce tolerance to offending allergens. Long-term effects of immunotherapy include a reduction in nasal symptoms, a decrease in the use of rescue medication and improvement in quality of life. These benefits are accompanied by immunological changes such as the induction of allergen-specific IgG antibodies with inhibitory activity for IgE-facilitated binding of allergen – IgE complexes to B cells. One study reported a reduction in the development of asthma in children with seasonal pollen-induced asthma.

Summary: Allergen immunotherapy induces clinical and immunological tolerance as defined by persistence of clinical benefit and associated long-term immunological parameters after discontinuation of treatment. These findings are largely confined to studies of subcutaneous and sublingual immunotherapy for seasonal pollinosis. Further studies are needed to address potential long-term clinical effects for other seasonal and perennial inhaled allergens in both children and adults, and to identify potential biomarkers of tolerance.

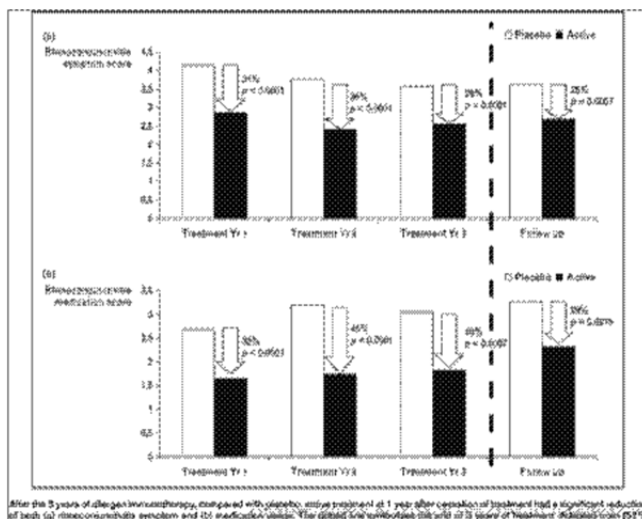
Duration

Update on sublingual immunotherapy

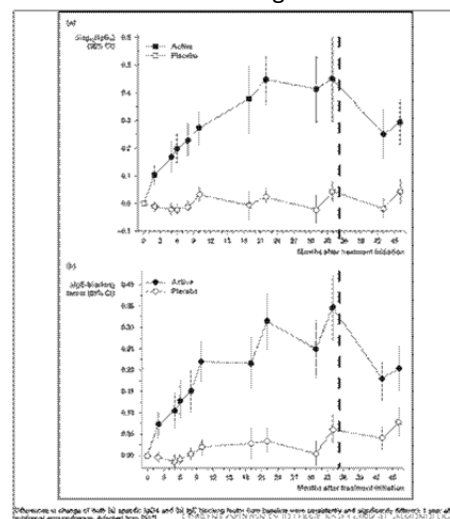
Potter, MD, FCP(SA), DCH(SA) *Annals of Allergy, Asthma & Immunology* 2006; 96(2): S22-25.

- Long-lasting tolerance is achieved after two to four years of SLIT, typically in patients with persistent perennial nasal allergies and also those with asthma.

Long-term clinical efficacy of allergen immunotherapy



Persistence immunological changes after cessation of allergen



An early phase of oral tolerance is observed within weeks of initiating SLIT. Patients who initially react to the sublingual drops with oral itching report that the itching goes away within a few weeks, and increasing oral doses are tolerated, without local clinical effects, before any relief of nasal or asthma symptoms or reduction in concomitant medicines for allergy relief is observed.

The next phase is an intermediate phase of short-lived tolerance. This phase was typically observed in patients who received preseasonal SLIT for pollen-induced allergic rhinitis. Within three months of initiating SLIT, a reduction in clinical symptoms is observed. A similar fairly rapid acquisition of significant protection and tolerance to latex allergens has been reported within three months of SLIT. There is no evidence that the clinical tolerance induced within such a short period is long lasting if the vaccine is not continued. A later phase of long-lasting tolerance is achieved after two to four years of SLIT, typically in patients with persistent (perennial) nasal allergies, but also for patients with asthma.

Multiple daily administrations of low-dose sublingual immunotherapy in Allergic rhinoconjunctivitis

Bordignon, V., Burastero, S., *Annals of Allergy, Asthma & Immunology* 2006;9:158-163.

- Frequency is important in sublingual administration of antigens

Background: Sublingual immunotherapy (SLIT) is an efficacious treatment for allergic rhinoconjunctivitis.

Objective: To investigate whether the number of daily administrations of SLIT can affect its efficacy.

Methods: In an open study, 64 patients with allergic seasonal rhinoconjunctivitis to grass or birch pollens were assigned to the following 2-year daily treatment schedules: “3-3” group, one drop three times daily for two years; “2-3” group, one drop twice daily in year one and one drop three times daily in year two; “1-3” group, one drop once daily in year one and one drop three times daily in year two, and control group, no treatment. One fifth of the allergen concentration recommended by the manufacturer as maintenance treatment was used throughout the study. Patients were monitored for skin reactivity to the allergen used for SLIT using an end point dilution technique for drug use.

Results: No treatment-related adverse effects were observed. Skin reactivity to allergen decreased compared with controls in the first treatment year only in the “3-3” group and in all treated patients in year two. Drug use decreased in the first treatment year in the “3-3” and “2-3” groups vs. controls. This outcome extended to “1-3” patients in treatment year two. Antihistamine use decreased significantly compared with baseline in year “3-3” and “2-3” patients and in all treated patients in year two. No changes were observed in controls.

Conclusion: The number of daily administrations seems to correlate with the efficacy of SLIT.

Compliance

Sublingual Immunotherapy: An Update

G, Lombardi C, Canonica GW. *Current Opinion in Allergy and Clinical Immunology* February 2004; 4:31-36

- Compliance with SLIT is very good
- SLIT - The adherence was 95% for pollen immunotherapy and 97% for mite immunotherapy

Purpose of review: Sublingual immunotherapy is now officially accepted as a viable alternative to the traditional subcutaneous route, and it is widely used especially in European countries. Despite the large amount of experimental evidence on the safety and efficacy of the method, some concerns still exist, and several aspects need to be clarified: magnitude of the efficacy, adherence, long-lasting effect and others. Recently published studies have provided answers to some of these points.

Recent findings: The most recent studies have shown that sublingual immunotherapy exerts a long-lasting effect up to 5 years after discontinuation and that it is able to prevent the onset of new sensitizations. Moreover, when systematically assessed, the adherence to treatment is quite satisfactory, despite the treatment being self-administered. In addition, evidence has been provided that sublingual immunotherapy is effective in treating allergic conjunctivitis, and a meta analysis has confirmed its efficacy in rhinitis. Moreover, some studies have addressed the possibility of simplifying the schedule of administration by shortening the build-up phase.

Summary: More and more new data on sublingual immunotherapy are rapidly appearing in the international literature. These data confirm the clinical value of this treatment and show that it is comparable to subcutaneous immunotherapy from several points of view.

“Three Shots and They’re Out”

2009 American Academy of Allergy Asthma & Immunology Annual Meeting. Study conducted by Allergy Partners & Greer March 17, 2009, *Yahoo finance*

- In human subcutaneous immunotherapy there are significant attrition rates
- 25% scheduled to begin SCIT
- 11% never showed up for their first allergy immunotherapy appointment
- 13% percent discontinued treatment within the first three sessions
- 60% percent of patients did not complete the recommended 3-year course of treatment

Research presented at the 2009 American Academy of Allergy Asthma & Immunology annual meeting highlighted poor compliance among allergy immunotherapy candidates. The research project, supported by Greer, was conducted by Allergy Partners, P.A., a large single-specialty allergy practice, and is the first to evaluate patterns of allergy immunotherapy care in a “real world” allergy practice setting.

The goal of the study was to evaluate patterns of care among patients who received allergy testing and subsequent allergy immunotherapy, commonly known as allergy shots. The study also sought to identify aspects of compliance with allergy immunotherapy, including average duration of treatment. The study reviewed computerized HIPAA-compliant claims data for more than 42,000 patients who received care at the Winston-Salem, N.C. and Greenville, S.C. Allergy Partners clinics from 2002-2008.

Investigators found that 71 percent of patients (29,987) who visited the two facilities during the six-year period received allergy testing. Following allergy testing and determination of patients' appropriateness for treatment, patients' agreement to initiate treatment, and scheduling and confirmation of their appointments, the clinics subsequently prepared antigen (i.e. immunotherapy prescription) for approximately 25 percent (7,452) of the patients. Researchers were surprised to find that 11 percent of patients for whom an immunotherapy prescription was prepared never showed up for their first allergy immunotherapy appointment. An additional 13 percent discontinued treatment within the first three sessions of allergy immunotherapy.

Sublingual Immunotherapy in Human Atopic Dermatitis

Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: A randomized, double-blind, placebo-controlled study

Pajno GB. *J Allergy Clin Immunol* 2007;120:164-70

- First double blind placebo controlled study using SLIT for atopic dermatitis
- Sublingual immunotherapy may represent an additional therapeutic tool for the treatment of extrinsic atopic dermatitis
- High dose SLIT; 2 patients had severe itching one hour after dose
- Significant improvement in patients with mild-moderate disease

Background: Atopic dermatitis often has an allergic component, and immunotherapy may therefore prove beneficial.

Objective: To assess the effect of sublingual immunotherapy (SLIT) in children with atopic dermatitis.

Methods: Children age 5 to 16 years with atopic dermatitis

(Scoring Atopic Dermatitis [SCORAD] > 7) and sensitization to dust mites alone, without food allergy or chronic asthma, were enrolled in a randomized, double-blind, placebo-controlled study and stratified according to disease severity. SLIT or placebo was given for 18 months in addition to standard therapy. SCORAD visual analog scale, and rescue medication consumption were recorded at 3-month intervals. Results: Fifty-six children were enrolled, and 28 were allocated to SLIT. Forty-eight completed the study, with 2 dropouts in the active and 6 in the placebo group. The difference from baseline in the SCORAD was significant ($P = .025$) between the 2 groups starting from month 9. Similarly, there was a significant reduction in the use of medications only in the active group. A trend toward significance was seen for the visual analog score only in the active group versus baseline ($P = .07$). A significant difference in the considered parameters was found only in patients with " mild-moderate disease, whereas severe patients had only a marginal benefit. SLIT had to be discontinued in 2 patients because of exacerbation of dermatitis.

Conclusion: Sublingual immunotherapy to dust mite improves mild-moderate atopic dermatitis. Clinical implications: Sublingual immunotherapy may represent an additional therapeutic tool for the treatment of extrinsic atopic dermatitis in properly selected children.

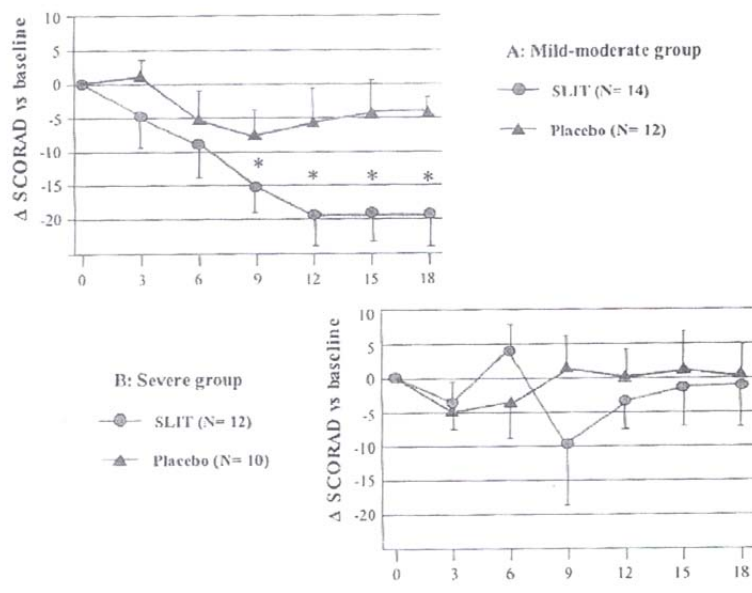


FIG 3. Change from baseline (Δ SCORAD) in the SLIT and placebo groups at the different time points. The patients are subdivided according to AD severity (A, mild-moderate; B, severe). *Significant differences.

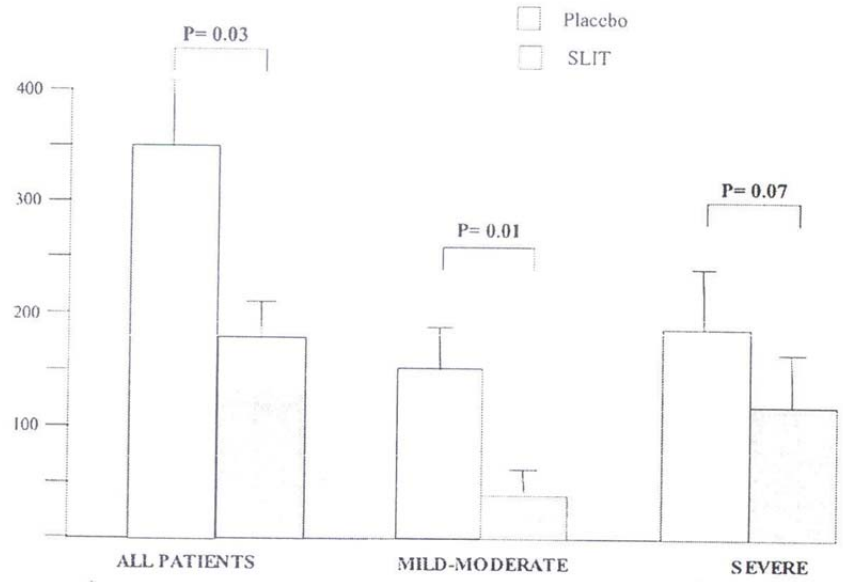


FIG 5. Total drug consumption (means, SEMs) in the whole population, in mild-moderate AD, and in severe AD.

Atopic Dermatitis

Bieber, T. *Ann Dermatol.* 2010 May; 22(2): 125–137.

- A comprehensive overview of human atopic dermatitis

It is well accepted that allergen-specific immunotherapy, which has been reported since 1911 in the management of allergic diseases, represents the only causative therapeutic approach. Unfortunately with regard to AD, only limited, and often contradictorily information is available. A recently published study, re-examining the efficacy of a subcutaneous immunotherapy (SCIT) in atopic patients sensitized to house dust mites, demonstrated effectiveness in reducing eczema and allergic sensitization to HDM97. The improvement of eczema was accompanied by a reduction of topical corticosteroids needed to treat eczema. Interestingly, because of its limited side effects, sublingual immunotherapy (SLIT) may represent an alternative to SCIT. Further studies to verify the benefit of SCIT and SLIT are currently running and we may experience a revival of immunotherapy in AD in the near future.

Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis?

Caroline Bussmann, Anette Böckenhoff PhD, Henning Henke, Thomas Werfel MD, Natalija Novak MD
The Journal of Allergy and Clinical Immunology Volume 118, Issue 6, Pages 1292-1298, December 2006

- Good review of studies done in human atopic dermatitis both SCIT and SLIT
- Exacerbations of AD can occur with SCIT and SLIT

House dust mite (HDM) allergens are perennial indoor allergens, which may play a role as allergic trigger factors in atopic dermatitis (AD). Facilitated by their high enzymatic activity, HDM allergens are capable of penetrating the impaired epidermal skin barrier in patients with AD, gaining access to immune cells. In this way, HDM allergens induce both allergic reactions of the immediate type and allergic reactions of the delayed type, which contribute to impairment of AD. Because allergen reduction achieved by encasing strategies does not always lead to significant improvement of clinical symptoms, specific immunotherapy (SIT) might represent an attractive therapeutic option for long-time treatment of this subgroup of patients with AD. However, systematic studies on the effectiveness of SIT in patients with AD are rare. Furthermore, data on the immunologic changes induced by SIT in patients with AD are not well studied. In this review, we provide an overview of the pathogenic impact of HDM allergens as an example for aeroallergens on the course of AD. In addition, we discuss prophylactic and therapeutic options for the treatment of HDM allergy in patients with AD, including a summary of the current data available on SIT as a potential therapeutic option for patients with AD.

In more than 85% of adult patients, AD is associated with IgE mediated sensitization mirrored by increased total IgE serum levels and allergen specific IgE against different aeroallergens or food allergens and positive skin prick tests, combined with respective clinical symptoms after allergen exposure. In this context, both inhalation of aeroallergens via the respiratory tract, and the application and exposure of these aeroallergens to the skin of these patients can lead to severe exacerbations of AD and cause severe flare-ups of skin lesions in some patients with moderate to severe AD. Further, the degree of sensitization to aeroallergens has been shown to be correlated with the severity of the disease in some studies.

Facilitated by their high enzymatic activity, HDM allergens are capable of penetrating the impaired epidermal skin barrier in patients with AD to get access to immune cells, such as mast cells or dendritic cells. In this way, HDM allergens induce both allergic reactions of the immediate type and allergic reactions of the delayed type, which contribute to flare-ups of eczema and impairment of the course of AD.

Specific immunotherapy against HDM sensitizations is not generally indicated for AD without concomitant allergic rhinoconjunctivitis or mild allergic asthma at present. One reason for this is the risk of exacerbations of eczema or potential relapses of AD in patients with latent AD or a history of AD under SIT.

Sublingual immunotherapy efficacy in patients with atopic dermatitis and house dust mites sensitivity: a prospective pilot study.

Cadario G, Galluccio AG, Pezza M, Appino A, Milani M, Pecora S, Mastrandrea F. *Curr Med Res Opin.* 2007 Oct;23(10):2503-6.

Background: Specific subcutaneous immunotherapy (SCIT) with house dust mite (HDM) preparation has recently been shown to improve eczema in patients with atopic dermatitis (AD). So far, there is less data regarding efficacy and safety of specific sublingual immunotherapy (SLIT) in patients with AD. Study aim: To evaluate in an open non-controlled, non-randomized pilot trial the effect of SLIT with HDM allergen extracts preparation (SLITone, ALK Abellò Italy) on SCORAD in adult patients with mild-moderate AD.

Patients and Methods: 86 Subjects (53 females and 33 males) between 3 and 60 years of age with AD and IgE-proved (Class > 2) HDM sensitization were enrolled after their informed consent in the trial. Exclusion criteria were severe asthma and treatment with systemic or high potent topical corticosteroids or immunosuppressant agents. Patients were treated with SLIT (Dermatophagoides pteronyssinus and Dermatophagoides farinae extracts: SLITone, ALK-Abellò) for at least 12 months. SCORAD was evaluated at baseline and after 12 months of treatment.

Results: Baseline SCORAD value, mean +/- SD, was 43.3 +/- 13.7 (range 15-84). After 1 year of SLIT, mean +/- SD, SCORAD value was reduced to 23.7 +/- 13.3 (range: 0-65) (p = 0.0001; unpaired t-test vs. baseline). This was a 46% reduction in SCORAD in comparison with baseline value. A significant improvement, defined as a SCORAD reduction of > 30%, was observed in 51 out of 86 patients (59%). In 5 patients (5.8%) SCORAD values did not change at the end of the observation period. In 30 patients (35%) the SCORAD reduction after SIT was <= 30% in comparison with baseline. Total and specific IgE serum levels were significantly (p = 0.001) reduced after SLIT. No severe adverse events were observed during the trial.

Conclusion: In this open non-controlled trial, SLIT with HDM extracts in patients with mild to moderate AD was effective in reducing the SCORAD after 1 year of SLIT treatment. In addition the treatment was very well tolerated. Treatment with SLIT, furthermore, has allowed a gradual and relevant reduction of concomitant therapies with topical corticosteroids or immunosuppressants. Present results require further controlled trials in order to confirm the potential clinical benefit of SLIT in this clinical setting.