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Sublingual swallow immunotherapy

Komarla Nagendra Prasad

Department of Allergy and Applied Immunology, Bengaluru Allergy Centre, Jayanagar, Bengaluru, Karnataka, India

Correspondence Address:

Komarla Nagendra Prasad

Bengaluru Allergy Centre, #55, Second cross, Gavipuram extension, Bangalore - 560 019, Karnataka
India

Abstract

Allergen Specific Immunotherapy (ASI) in the form of subcutaneous route (SCIT) used over a century and is currently under used for management of IgE mediated allergy disorders. SCIT Meta analysis showed very promising results and sustained effect for a long period from 7 years to 12 years on stopping the therapy. The adverse events are not common and application for day to day practice currently restricted among trained physicians. Allergy prone subjects adherence to SCIT is very less and drop outs are more either due to invasive injections, the long term dosage, cumbersome to wait at the clinic after the injection or due to local and systemic reactions. Alternate route suggested by WAO, ARIA and EAACI is Sublingual (SLIT) for better compliance and to increase the adherence of the therapy. SLIT Meta analysis showed its efficacy is equivalent to SCIT with mild to moderate tolerable adverse events without discontinuation of dosage schedules. SLIT becomes successful in the hands of trained physicians who initiate the effective dose for effective response which is crucial. The quality of standardised allergen extracts and the appropriate dose is to generate clinical response is very important. Selection of allergens for therapy by taking care of proteolysis which degrade in combination of heterogeneous allergens and time of administration is very critical. SLIT is friendly with children less than 6 years, SCIT restricted below 6 years. SLIT in the form of drops, tablets and Stripe is currently used and SLIT kept below the tongue before food for 2 to 5 minutes and swallow. The prescribed tailor made dosage consumed on daily basis at a regular time shows better results. At present the SLIT is a personal Medicine. SLIT is popular among European countries and US FDA is in the process of evaluation of clinical trials.

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Full Text

Introduction

Allergen Specific Immunotherapy (ASI) for Type I allergy disorders is well defined with indication and its use beyond century. ASI emerged much before the classical new generation of drugs which are fore front in its use in the current management of allergy disorders. ASI is currently under used since its therapeutic effect, limitations and merits is not

proportionately understood and or experienced by the competent clinician. The vulnerable allergy subject who demand instant relief. Understanding ongoing allergy march and nature of atopic, explains the passage of illness with remodeling of tissues leads to crippling of quality of life. The persistent chronic disorder made to understand management to generate optimum treatment. Short term management by pharmacotherapy, which is meant for relief of to-day and long term management with sustained effect for tomorrow by ASI, is very crucial for allergy disorder. Chronic disorders is best treated by knowing the nature of illness, course of illness, duration of illness and its influence on day to day life. ASI is programmed for therapy and is customized, tailor made on the basis of personal approach which is effective in allergy disorders expressed by most of the studies published till date.

Long term management is a laborious and unpalatable which is common feeling by majority of the subjects and gives room to commit for shortcut management and succumb to various different approach of treatment and ultimately land in confusion and frustration without total relief. Educating the subjects play a crucial role and make them to understand the illness by its existence and its course in his life time. Merits of treatment and target of treatment selected for its effectiveness made to understand the selection for right therapy.

ASI by subcutaneous route (SCIT) had its long history of existence and survived till date. SCIT travelled beyond century from research group, clinicians and ultimately reached the allergy prone subjects under gold standard therapeutic tool. SCIT showed resistance between the clinician and subjects with merits and demerits having local and systemic reactions made unacceptable by majority of the subjects and medical professionals restrict its use. Alternate routes were proposed and trial in different research centers by different routes such as oral, intranasal, intra bronchial and sublingual routes. Out of these, intranasal and sublingual swallow routes were shown promising. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA) and World Allergy Organisation (WAO) emerged with position papers after meta-analysis data to accept Sublingual swallow. Specific Immunotherapy is a disease modifying treatment which reduces symptoms of Allergic Rhinitis and Asthma (Abramson2003, Calderon 2007, Dahl 2007 and Penagos 2008). ASI, potentially effective in reducing Allergic Ocular symptoms (Durham 2007, Mortemosque 2003).

SLIT was first described in DBPC trial in 1986. Sixty trials published and reviewed by WAO position paper. Majority of these trails used house dust mites, grass, ragweed and parietaria pollens. All trails with various inclusion criteria such as rhinitis only, asthma only and asthma and rhinitis in children. 52 trials conclude significant effect versus placebo. 8 trials provided totally negative results. These studies had heterogeneity and questioned its judgment.

In general, SLIT is considered to be a better safety profile than SCIT, most of the reactions are transient and local without interruption of the treatment. [14] Randomised DBPC trials, position papers and meta-analysis have emphasized the efficacy and safety of SLIT [12],[7],[8],[40] . More than million doses have been administered in clinical trials [14] and beyond one billion doses administered world wide since 2000. Survey of members of American Academy of Allergy, Asthma and Immunology reported from 1990 to 2001, fatalities by SCIT at a rate of one in 2 to 2.5 million injections of SCIT [5] and reconfirmed by survey of North American allergist in 2008 reporting 10.2 systemic reactions per 10,000 injections and 3% were classified as 'life threatening anaphylaxis with severe airway compromise or upper air way obstruction with strider or hypotension with or without loss of consciousness' [6] . Siber et al., analysed prescription data from Germany over 2 years period and found that SLIT significantly persistency than SCIT [43] . SCIT and SLIT increase allergen tolerance by induction of CD4+, Th2 to Th1, IgE to IgG. Savolainen et al demonstrated that SLIT reduces the expression of IL 5 and enhances the expression of IL 10 in peripheral blood mononuclear cells (PBMC) stimulated with allergen [41] . Clinical effects of SLIT resemble those of SCIT and data available suggest that the mechanisms of action are similar. SLIT appears to elicit mucosal IgA response contributing tolerance induction [34] . Obvious difference between SCIT and SLIT relates to the allergen dose administered. Slit requires 90 to 365 times more allergen than SCIT to achieve similar level of efficacy [15] .

Sublingual uptake and processing of allergens have a number of specific features. SLIT regimens, the allergen is kept under tongue for two to five minutes and then swallowed. Biodistribution studies in mice and humans demonstrate that allergens bind to epithelial cells and cross the mucosa with in next 15 to 30 minutes before captured by antigen-presenting cells (APC) [27],[2] . Following migration to draining cervical lymph nodes and induct gamma and IL 10 producing Th1 cells and regulatory CD4+ T cells [34],[27],[28] . Specific features of local DCs, the oral immune system appears to elicit tolerance rather than anaphylaxis or rest of the adverse events. Murine and human oral tissues contain low number of mast cells and eosinophils¹. Mast cells are closer to the mucosal surface in lingual tissues than in oral tissues, which can induce lingual edema and is frequently reported as adverse events of SLIT [28] . A subcutaneous injection is associated with greater risk of direct contact with circulating pro-inflammatory basophils and Th2 lymphocytes. The allergen is captured by DCs whose effector immune responses are associated with the release of pro-inflammatory mediators [34] . Cox et al. reported that local, oral mucosal reactions occurred in 40-75% of SLIT during initial build up phase which did not lead to dose reduction or interruption of treatment [15] . They found that SLIT related serious adverse reactions/ 384 treatment years, mainly asthmatic reactions, abdominal pain/ vomiting, uvula edema and urticaria. World Allergy Organisation (WAO)

task force has issued recommendations on safety reporting in clinical SLIT trial [11] .

SLIT has demonstrated to prevent the onset of new sensitisation. In open, controlled trial, the rate of occurrence of new sensitisation was 5.8% in the active group and 38% in the controlled group. In children with rhinitis, SLIT demonstrated the capability of reducing the risk of asthma onset. These results were shown in large randomised open study involving more than 200 children followed up for three years. Two studies one in adult and one in children reported that the clinical benefits of SLIT is maintained up to 5 years after the discontinuation. SLIT in subjects with allergic rhinitis has been proven to be safe and successful in reducing allergic symptoms was well tolerated and showed safe with once daily dose and compared with conventional escalation regimen for SLIT [44] .

Meta-Analyses

The first meta-analysis of SLIT for allergic rhinitis included 22 trials and 979 patients upto September 2002. It concluded that SLIT was significantly effective than placebo (WAO) [46] . 25 trials for asthma (include open and blinded) involving more than 1000 adults and children, demonstrated significant effect of SLIT with considered reduction of symptoms, medication score with spirometry function and overall improvement [9] . SLIT meta-analysis for allergic rhinitis in pediatric patients (4 to 18 years) involved in 10 trials and 484 subjects showed significantly more effective than placebo in terms of symptom score and rescue medication score [36],[38] . SLIT in asthma in pediatric subjects include 9 DBPC trials with 441 subjects found significant effect of SLIT on both asthma symptom and rescue medication score. Observing these studies, they are heterogeneous trials with varying sample size, publication biases and discrepancies in data collection and studies provide suggestive evidence [33] .

There were 8 randomised open controlled trials, assessing the clinical efficacy of SLIT, compared with controlled group who are on drugs [16],[20],[21],[23],[24],[25],[26],[29] . Two demonstrated a significant reduction in non-specific bronchial hyper-responsiveness [23],[24],[25],[29] , one study evaluate the safety of non-up dosing regimen [21] , one study designed [26] to demonstrate with two non crossing allergens (birch and grass) is overall more effective than single allergen in both pollen seasons.

DBPC-RCTs of SLIT in other than respiratory allergy, namely food allergy [18],[19] , latex allergy [3],[32] , atopic dermatitis [35] , and hymenoptera venom allergy [42] studies favorable response to SLIT.

Eriqre et al., [18] found that SLIT increases the oral provocation threshold with hazelnut and Fernandez et al showed with peach [19] . Pajno et al., [35] showed that in subjects allergic to mites and with mild moderate atopic dermatitis, SLIT after 9 months significantly reduced the SCORAD score. Severino et al in 30 subjects with honey bee demonstrated 6 month SLIT with maintenance dose of 525 mcg venom significantly reduced the severity of local reactions to sting challenge [42] .

42 trials with a total of 3958 subjects having allergic conjunctivitis, 2011 had SLIT and 1947 had placebo and showed reduced symptoms of allergic conjunctivitis, redness, itchiness and watery eyes compared to placebo [10] .

Radulovic et al., reviewed SLIT searching Cochrane ENT group trials register, Central (2010, Issue 3), PubMed, EMBASE, CINAHL, Web of Science, Biosis Previews, Cambridge Scientific Abstracts, mRCT and additional sources. This review include randomized, double-blind, placebo controlled trials of sublingual immunotherapy in adults and children [5] . Sixty randomised controlled trials and found forty nine suitable for pooling in meta-analysis (2333 SLIT, 2256 placebo participants). Overall they found significant reduction in symptoms (SMD) 0.49; 95% confidence interval $P < 0.00001$ and medication requirements (SMD) 0.32; 95%, $P < 0.00001$ compared to placebo. None of these trials reported severe systemic reactions, anaphylaxis or use of adrenaline. This review reinforces the conclusion of Cochrane review 2013. The data establish SLIT as a viable alternative to allergen injection immunotherapy with low risk profile.

M. A. Calderon et al., reviewed safety profile [10] with SLIT 66 published studies representing 4378 subjects and approximately 1181000 doses, Cox et al., reported that local, oral mucosal reactions occurred in 40-75% of SLIT subjects especially during build up phase and one study SLIT related serious adverse reaction per 384 treatment years mainly consisted of asthma reactions, abdominal pain/vomiting, uvula edema and urticaria [14] .

SLIT use in children in allergic rhinitis sensitive to seasonal pollens and perennial house dust mites. SLIT appears safer and least side effects compared to SCIT. 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 [21] . Implying the induction of both clinical and immunological tolerance.

Comparing Scit and Slit

One double-dummy, double blind study without placebo group conducted grass pollen study showed clinical efficacy of SLIT equivalent to SCIT [39] . Another DBDDPC study with birch pollen compared SLIT and SCIT, symptoms were reduced about one-third in SLIT group and one-half in SCIT group with no significant difference evidence between treatments and there were 3 and 4 adverse reactions with SCIT and none in SLIT group [22] . Four open studies and one by Bernasr. et al., study with *alternaria tenuis* with rhinitis having significant difference in favor of SLIT [4] . A study having [43] subjects with rhinitis, sensitive to mite for immunological observation which was significantly in favor of SCIT [37],[31] . The open comparison 81 in mite showed that clinical improvement were more with SCIT especially asthma symptoms and SLIT controlled rhinitis symptoms well. Mauro et al., [30] compared SCIT and SLIT in 47 patients with birch allergy and found no difference between the two treatments. In seasonal symptom score although specific IgG4 significantly increased only with SCIT.

Controversial aspects in these published data are variable dose. The dose used with SLIT ranges between 2 and 375 times, the amount given with SCIT. Response to low and high dose generated positive and negative results. A clear dose response relationship has been formally demonstrated for grass extracts, where optimal dose identified as 15 to 25 mcg of major allergen per day which is roughly 50 times the monthly dose of SCIT. There is no consensus on whether the best regimen is pre-seasonal, co-seasonal or continuous administration. Majority of trials utilized a per-seasonal regimen but this cannot be immediately extrapolated to all extracts and to all patients. The maintenance phase without build up phase with few trials have used shown safe.

Other controversial aspects are common to both SCIT and SLIT. For instance the allergen and protein content of commercial extracts is highly variable between manufacturers, making the comparison amongst extracts and regimens difficult and representing a major cause of the heterogeneity of studies. Another problem related to the heterogeneity is that the DBPC trials use different methodological designs, variable outcomes and arbitrary selection criteria for patients. There has recently been a great deal of effort to recommend that studies with both SLIT and SCIT should use the same experimental design and that outcomes and patient selection are standardized. Another problem is the use of mixtures of different allergens, since the majority of patients are polysensitized and it is often necessary to prescribe immunotherapy with multiple extracts. There are a few older studies specifically assessing the effects of allergen mixtures, which showed controversial and sometimes with surprising results. A recent randomised DBPC trial showed that an immunological response is achieved with a single grass extract, but the same dose combined with 9 other pollen extracts produced only a limited response. In contrast, a SLIT study showed that the co-administration of grass and weed pollen extracts is more efficacious than a single extract used alone.

Two post-marketing surveys performed in adults and children consistently suggested that the use of multiple allergens for SLIT does not increase the rate of side-effects. Finally, there is as yet no universally accepted system for the classification/grading of adverse events due to ASI. To address this need, a WAO task force has recently proposed a new grading system which will provide uniformity of assessment and help to standardise the post marketing surveys on the safety of immunotherapy.

In the last 20 years there has been an impressive development in the field of ASI. SCIT still represents the standard modality of treatment and its indications, contraindications and optimal doses are well demonstrated. The most important novelty, from a clinical point of view, has been the introduction of SLIT, which is now accepted as a viable alternative to injection immunotherapy. It is true that some points need to be better detailed for SLIT, such as the ideal classical subject, the extent of the long-lasting effect, and the preventative role. Nevertheless, the clinical efficacy is well demonstrated and has been proven in more than 60 trials. It is important to remember that SLIT is effective and safe provided that a correct and detailed diagnosis has been made, and that both SCIT and SLIT must be prescribed and administered only by trained physicians. Despite the existence of several official documents, and the capacity to achieve a modification of the natural history of the disease, the perception is that for the number of subjects, who would benefit from the treatment, ASI is still under-utilized and prescriptions are still limited. In parallel to the clinical developments of SLIT, the mechanisms of specific desensitisation have been clarified with increasing detail. This has prompted the exploration of new opportunities, such as the use of bacterial and DNA adjuvant, peptides and recombinant/engineered allergens. Although these latter approaches are still at the beginning in humans, they represent the frontiers of scientific investigation for the immediate future.

Conclusion

The original systemic 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 [45]. Review by S. Radulovic et al., includes highly powered clinical trials and includes more than four times the number of subjects [40]. The data establish SLIT as a viable alternative to SCIT with a significantly lower risk profile. Use of SLIT in children and safer having better side-effects profile compared to the SCIT although there is no standardised grading system for side-effects. 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 with clear induction of clinical and immunological tolerance [17].

References

- 1 Allam JP, Stojanovski G, Friedrichs N, Peng W, Bieber T, Wenzel J *et al.* Distribution of Langerhans cells and mast cells within the human oral mucosa: New application sites of allergens in sublingual immunotherapy? *Allergy* 2008;63:720-27
- 2 Bagnasco M, Passalacqua G, Villa G, Augeri C, Flamigni G, Borini E, *et al.* Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers. *Clin Exp Allergy* 2001;31:54-60.
- 3 Bernardini R. Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study. *Curr Med Res Opin* 2006;22:1515-1522.
- 4 Bernardis P, Agnoletto M, Puccinelli P, Parmiani S, Pozzan M. Injective vs. sublingual immunotherapy in *Alternaria tenuis* allergic patients. *J Investig Allergol Clin Immunol* 1996; 6:55-62.
- 5 Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36.
- 6 Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol* 2010;104:530-35.
- 7 Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A *et al.* Allergic Rhinitis and its Impact on Asthma 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63 Suppl 86:8-160.
- 8 Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
- 9 Calamita Z, Saconato H, Bronhara Pela` A, Nagib Atallah A. Efficacy of sublingual immunotherapy in asthma. Systematic review of randomized clinical trials. *Allergy* 2006;61:1162-72.
- 10 Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham; Sublingual immunotherapy for treating allergic conjunctivitis (Review) *S Evidence Based Child health: A Cochrane Review Journal* 2012;7.3:1041-54.
- 11 Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling H-J, *et al.* Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for Respiratory Allergy: A Statement of a World Allergy Organization taskforce. *Allergy* 2007;62:317-24.
- 12 Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, *et al.* Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009 *Allergy* 2009;64 Suppl 91:1-59.
- 13 Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: Results of a GA2LEN meta-analysis. *Allergy* 2009;64:1570-79.
- 14 Cox LS, Larenas-Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: A comprehensive review. *J Allergy Clin Immunol* 2006;117:1021-35.
- 15 Cox L. Sublingual immunotherapy and allergic rhinitis. *Curr Allergy Asthma Rep* 2008;8:102-10.
- 16 D'Ambrosio FP, Ricciardi L, Isola S, Savi E, Parmiani S, Puccinelli P, *et al.* Rush sublingual immunotherapy in Parietaria allergic patients. *Allergol Immunopathol (Madr)* 1996;24:146-51.
- 17 Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, *et al.* Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010;125:131-138.e1-7.
- 18 Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R *et al.* Sublingual immunotherapy for hazelnut food allergy: A randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005;116:1073-79.
- 19 Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Alonso Dıaz de Durana MD, Garcıa BE, Gonzalez-Mancebo E, *et al.* Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. *Allergy* 2009;64:876-83.
- 20 Gozalo F, Martın S, Rico P, Alvarez E, Cortes C. Clinical efficacy and tolerance of two year *Lolium perenne* sublingual immunotherapy. *Allergol Immunopathol (Madr)* 1997;25:219-27.

- 21 Guerra L, Compalati E, Rogkakou A, Pecora S, Passalacqua G, Canonica G. Randomized open comparison of the safety of SLIT in a no-updosing and traditional updosing schedule in patients with Parietaria allergy. *Allergol Immunopathol (Madr)* 2006;34:82-83.
- 22 Khinchi S, Poulsen LK, Carat F, Andre'C, Malling HJ. Clinical efficacy of sublingual swallow and subcutaneous immunotherapy in patients with allergic rhinoconjunctivitis due to birch pollen. A double-blind double-dummy placebo-controlled study. *Allergy* 2004;59:45-53.
- 23 Lombardi C, Gargioni S, Venturi S, Zoccali P, Canonica GW, Passalacqua G. Controlled study of preseasonal immunotherapy with grass pollen extract in tablets: effect on bronchial hyperreactivity. *J Investig Allergol Clin Immunol* 2001;11:41-45.
- 24 Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: Clinical efficacy and more. *Allergy* 2004;59:1205-10.
- 25 Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: A 3-year randomized controlled study. *J Allergy Clin Immunol* 2005;115:1184-88.
- 26 Marogna M, Massolo A, Spadolini I, Zanon P, Berra D, Passalacqua G. Efficacy of sublingual immunotherapy with single or multiple allergens in polysensitized patients. *Ann Allergy Asthma Immunol* 2007;98:274-80.
- 27 Mascarell L, Lombardi V, Louise A, Saint-Lu N, Chabre H, Moussu H, *et al.* Oral dendritic cells mediate antigen-specific tolerance by stimulating TH1 and regulatory CD4+ T cells. *J Allergy Clin Immunol* 2008;122:603-609.
- 28 Mascarell L, Lombardi V, Zimmer A, Louise A, Tourdot S, Van Overtvelt L, *et al.* Mapping of the lingual immune system reveals the presence of both regulatory and effect CD4+ T cells. *Clin Exp Allergy* 2009;39:1910-19.
- 29 Marcucci F, Sensi L, Di Cara G, Incorvaia C, Frati F. Dose dependence of immunological response to sublingual immunotherapy. *Allergy* 2005;60:952-56.
- 30 Mauro M, Russello M, Incorvaia C, Gazzola GB, Di Cara G, Frati F. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: A randomized study. *Eur Ann Allergy Clin Immunol* 2007;39:119-22.
- 31 Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite sensitive patients with rhinitis and asthma: a placebocontrolled study. *Ann Allergy Asthma Immunol* 1999;82: 485-90.
- 32 Nettis E, Colanardi MC, Soccio AL, Marcandrea M, Pinto L, Ferrannini A, *et al.* Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: A 12-month study. *Br J Dermatol* 2007;156: 674-81.
- 33 Nieto A, Mazon A, Pamies R, Bruno M, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: An evaluation of meta-analyses. *J Allergy Clin Immunol* 2009;124:157-61.
- 34 Novak N, Bieber T, Allam J-P. Immunological mechanisms of sublingual allergen-specific immunotherapy. *Allergy* 2011;66:733-39.
- 35 Pajno GB, Caminiti L, Vita D, Barberio G, Salzano G, Lombardo F *et al.* Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: A randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007;120:164-70.
- 36 Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, *et al.* Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in children. Meta analysis of randomized controlled trials. *Ann Allergy Asthma Immunol* 2006;97:141-48.
- 37 Piazza I, Bizzarro N. Humoral response to subcutaneous, oral and nasal immunotherapy for allergic rhinitis due to dermatophagoides pteronyssinus. *Ann Allergy* 1993;71: 461-69.
- 38 Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, *et al.* Meta analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008;133:599-609.
- 39 Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual vs injective immunotherapy in grass pollen allergic patients: A double-blind double-dummy study. *Clin Exp Allergy* 1996;26:1253-61.
- 40 Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy. *Allergy* 2011;66:740-52.
- 41 Savolainen J, Jacobson L, Valovirta E. Sublingual immunotherapy in children modulates allergen-induced in vitro expression of cytokine mRNA in PBMC. *Allergy* 2006;61:1184-90.
- 42 Severino M, Cortellini G, Bonadonna P, Macchia D, Campi P, Spadolini I, *et al.* Sublingual immunotherapy for large local reactions. due to honeybee sting. Double-blind placebocontrolled trial. *J Allergy Clin Immunol* 2008;122: 44-48.
- 43 Sieber J, De Geest S, Shah-Hosseini K, Mo'sges R. Medication persistence with long-term, specific grass pollen immunotherapy measured by prescription renewal rates. *Curr Med Res Opin* 2011;27:855-61.
- 44 Sue Jean Mun MD *et al.*, Efficacy and safety of a once-daily sublingual immunotherapy without escalation regimen in house dust mite-induced allergic rhinitis. *Int Forum Allergy Rhinol* 2013;3:177-83.

- 45 Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis.Cochrane Database Syst Rev 2003; Art.No.:CD002893. DOI: 10.1002/14651858.
- 46 Wilson DR, Torres L, Durham SR. Sublingual immunotherapy for allergic rhinitis. Allergy 2005;60:3-8.

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