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Sublingual Immunotherapy: An Innovative Alternative for Allergies

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ABSTRACT

Sublingual Immunotherapy is a form of immunotherapy that involves placing the allergen extract under the tongue. An allergist gives patient small doses of an allergen under the tongue to boost the tolerance to the substance and reduce its symptoms. At present, the only forms of SLIT approved by the FDA are tablets for ragweed, northern pasture grasses like timothy, and dust mites. The safety and efficacy of allergy drops is yet being established by the FDA, and they are only used without label in the United States. The possible advantages of sublingual treatment are those of no use of injections, comparatively few regular doctor visits, possibility of home dosing after the first treatment, also a lower risk of serious reactions. Parents of young children often prefer sublingual immunotherapy as their child does not have to have regular injections. The main disadvantage of this form of treatment is its cost as more allergen needs to be swallowed than injected, this results in the cost per allergen being more expensive than that of injected treatments.

Keywords: Sublingual immunotherapy, allergies, SLIT, SCIT, AIT, allergen.

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INTRODUCTION [1]

Sublingual Immunotherapy (SLIT): It has been used in the US since the late19th century. The oldest description dates back to the year1900. In the last 30 years, excellent quality research allowed this treatment modality to be clearly considered as a very useful, effective and safe alternative for the administration of immunotherapy. Properly designed studies and review studies confirm SLIT's safety and effectiveness. Safety is one of the sparking features of SLIT. It is a very well-known fact that Subcutaneous Injection Immunotherapy (SCIT) can show reactions as either local arm reactions or systemic reactions, it can either be mild or severe. Many cases of transience have been reported in the literature after SCIT administration and even though the rate of transience cases appears to be decreasing overtime the spectrum of this possibility is always present to any practitioner that administers injectable immunotherapy. SLIT is not free from problems. There are several reactions after SLIT administration, usually known as Adverse Events (AEs). In most of the cases, the incidence of these AEs is relatively small. There have been no mortality cases related to SLIT administration. Very few cases of severe reactions after SLIT administration have been reported where patients developed asthma attacks requiring hospital care. Most of the reports about SLIT have been based on its administration for monosensitized patients.

Mechanism of sublingual immunotherapy [2, 5]

- Allergen immunotherapy tends to provide an opportunity to study antigen-specific tolerance in humans.
- Subcutaneous immunotherapy (SCIT) decreases the allergic Th2-mediated inflammation and improves the antigen-specific IgG, probably by inducing the regulatory T cells (T regs), immune deviation (Th2 to Th1) or apoptosis of effector memory Th2 cells.
- The oral mucosa is a natural site for immune tolerance (Langerhans cells, FcR1, IL-10, IDO [indoleamine 2,3-dioxygenase]).
- Sublingual immunotherapy (SLIT) is useful in optimal doses; SLIT has been showing long-term remission after discontinuation and may protect from new sensitizations, it features consistent with the induction of tolerance.
- SLIT induces modest systemic changes which are consistent with SCIT, but additional local mechanisms

in the oral mucosa and/or regional lymph nodes are likely more important.

- Sublingual immunotherapy is associated with:
  - Retention of allergen in sublingual mucosa for many hours.
  - An early increase of antigen-specific IgE and blunting of seasonal IgE.
  - Persistent enhancement in antigen-specific IgG4 and IgE blocking activity that parallel long-term clinical benefits of both SCIT and SLIT.
  - Inhibition of eosinophils and reduction in the number of adhesion molecules in target organs.
  - An early (at 4-12 weeks) increased peripheral phenotypic Tregs and delay in (at 12 months) immune deviation in favor of Th1 responses.
  - Identification of CD25+FOXP+phenotypic T reg cells in the sublingual mucosa.
  - Change in the dendritic cell markers (e.g., increases in expression of complement component C1Q) that correlate with clinical response to the treatment and merit the further study.
- Biomarkers that are predictive of or surrogates for clinical response to immunotherapy are not currently available for the routine use.
  - Molecular diagnosis of IgE sensitivities will help in patient selection for immunotherapy.
  - Serum IgG–associated functional blocking activity and basophil activation tests merit the further study.
  - Studies of peripheral T cell and dendritic cell signatures have yielded important information, yet these tests are currently impractical for routine clinical use.

TREATMENT [4]

An allergist must first use allergy testing to confirm patient's sensitivities. Once this is determined, an allergen extract is prepared in a drop form or a tablet is prescribed by the allergist to the patient. The patient is directed to keep it under his/her tongue for one to two minutes and then swallow it. The process is repeated from between three days a week to as often as daily with the recommendations that the therapy is to be continued for three to five years to develop a long lasting immunity. For grass and ragweed allergies, the patient typically takes the tablet before and during the allergy season. For the dust mite allergy, the patient takes the tablet year-round. The length of a patient's treatment is based on which tablets he/she is taking and input from the allergist. One must see an allergist to find expert care and relief for their allergies or asthma. SLIT is delivered by means of 2 methods. With sublingual spit, in this method the vaccine is kept under the tongue for a short period and then spat out. This method was used in some of the earlier studies; however majority of the studies used the sublingual swallow method. In this method the vaccine is kept under the tongue for 1 to 2 minutes and then finally swallowed.

Clinical efficacy of sublingual immunotherapy [2]

- As of June 2013, there were 77 randomized, double–blind, placebo-controlled (RDBPC) trials of SLIT, out of which 62 were conducted with grass or house dust mite (HDM) extracts. Most of these studies were heterogeneous for allergen dose duration, and also for patient selection. All statements on efficacy of SLIT refer to the products which have demonstrated efficacy in appropriate studies.
- 17 trials, out of which one was completely negative, were published after the previous WAO position paper.
- The literature suggests that, overall, SLIT is clinically very effective in rhino conjunctivitis and asthma, although differences exist among the allergens.
- The available meta-analyses are definitely in favor of SLIT (rhinitis and conjunctivitis in adults; asthma and rhinitis in children), although the results are limited by the heterogeneity of the studies in terms of their doses, duration, and patient selection.
- Clinical efficacy and dose dependency of SLIT have been demonstrated for rhino conjunctivitis due to grass pollen in adequately powered, well-designed RDBPCs.
- Some open but controlled trials suggested that the clinical efficacy of SLIT is similar to that of injection immunotherapy.
- Dose-finding trials and large number of studies with properly defined outcomes and sample sizes are needed for other relevant individual allergens.

SAFETY [2,3]

Sublingual immunotherapy (SLIT) seems to be better tolerated than subcutaneous immunotherapy (SCIT). SLIT should be prescribed only by physicians with appropriate allergy training and expertise. Special instructions should be provided to patients regarding the management of adverse reactions, unwanted interruptions in treatment, and situations when SLIT should be withheld. SLIT mostly causes adverse events like local reactions (e.g., oro mucosal pruritus) that occur during the beginning of treatment and resolve within a few days or weeks without any medical assistance (e.g., dose adjustment, medication). Some rare cases of SLIT-related anaphylaxis have been reported but there have been no fatalities .The major risk factors for the occurrence of SLIT severe adverse events (SAEs) have not yet been established, although there are some suggestion that patients who have had prior systemic reactions to SCIT may be at increased risk. There is a definite need for a generally accepted system of reporting allergen immunotherapy (AIT) adverse reactions that is applicable to both clinical practice and research.

- A systematic classification system for grading for AIT systemic reactions has been developed.
- Also a classification system for grading SLIT local reactions has been developed.
- The consistent use of Systemic Reaction and SLIT Local Reaction Grading Systems is recommended.

Advantages of SLIT for the Administration of Immunotherapy [1]

Since SLIT is very effective and extremely safe it can be considered the ideal modality for home-based immunotherapy. It can also be used in patients who are not good candidate for SCIT as is the case with young children, very old patients, and patients with high risk. For the patients who are scared of needles oral vaccines are ideal. SLIT also has an advantage that there is no need for treatment interruption for vacations or relocations. It is very easy to restart SLIT treatment if it is interrupted. Glycerin is

considered a potent protein stabilizer. When it is used as the diluent for mixing SLIT, the potency of allergens is maintained for a long time; and hence these drops do not need refrigeration. SLIT is a non-injectable route; therefore the side effects like local arm reactions are nonexistent which are sometimes painful and many a times interfere with injectable dose advancement. SLIT may also offer an economical advantage: The patients who do not have medical insurance coverage or those who have insurance but with high copays can easily be treated with SLIT instead of SCIT. Hence the patient also saves time as there is no need to go to the office, also there is no need to wait 30 minutes after injections. These factors imply to a potential for more patient compliance. One of the reports suggests that adherence to SLIT could be more than 90% .When an individual's age, health, physical location, or economics interfere with transportation to the office, SLIT should definitely be considered. In special circumstances where SCIT can be problematic or even controversial there is a role for SLIT, like when treating very young, asthmatic, or pregnant patients.

SIDE EFFECTS [6]

The most common uncomfortable side effects of sublingual immunotherapy are:

- Oral itchiness (pruritus)
- Lip itchiness
- Oral swelling,
- Tongue swelling
- Throat irritation

The Future of Immunotherapy in the Community Care Setting [1,2]

- **The importance of primary care**:
  - The rate of prevalence of allergic diseases is increasing rapidly worldwide, hence the point of first contact for most allergy patients is primary care.
- **Allergy education**
  - Allergy teaching should become a core part of undergraduate and postgraduate curriculum.
  - The primary care teams, require further training in the detection, diagnosis, management (including prevention), and treatment of allergic disorders.
  - Different programs need to be developed for a better patient-physician partnership.
- **Delivery of SLIT in the community setting**
  - Primary care physicians (PCP) and general practitioners (GPs) should be aware of how to select the appropriate treatment for a patient's illness and must be trained to make a comprehensive assessment and to recognize the treatment failure (inadequate therapy, improperly administered therapy, inadequate control) and exacerbations of illness.
  - The PCPs/GPs that are interested in treating the allergic diseases with allergen immunotherapy (AIT) should be trained in all aspects of SLIT, including the assessment of patients and administration of SLIT. Major emphasis should be kept on identification and management of side effects that includes local and systemic reactions.
  - Before SLIT therapy is given from allergists to primary care, careful research to identify the risks, benefits, and cost-effectiveness of treatment will be required. This will be a compulsory requirement for the commissioners, and without it, implementation is unlikely.
- **Collaboration between primary care team and allergist** :
  - In order to control the allergic diseases, it is mandatory to encourage the cooperation and collaboration between primary health care clinicians (including physicians, nurses, and others) and relevant specialists.
  - Primary health care clinicians must be able to administer SLIT with the mentorship of a trained allergist and must maintain regular liaisons with the allergist.
  - In collaboration, the allergist and the PCP/GP will plan the SLIT, administer it to the patient, and arrange follow up as and when needed; they will also jointly decide when to discontinue therapy.
  - However, the decision whether or not to initiate SLIT (as for SCIT) should be made by the allergist.

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