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## *REVIEW ARTICLE*

# Sublingual Immunotherapy (SLIT): An Emerging Therapy ? – A Review

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Asthma is a substantial health problem among children and adults worldwide, with increasing prevalence rates in many countries.[1] Allergic rhinitis is also a global health problem affecting at least 10-50 % of the population.[2] The prevalence of the disease is increasing in industrialized as well as industrializing countries. Epidemiological studies have shown that 80% of asthmatics have co-existent rhinitis.[2] Asthma in Bangladesh appears to be also a substantial public health problem: an estimated 7 million people including 4 million children suffer from asthma related symptoms.[3]

Among chronic illnesses, allergic rhinitis and asthma are the leading causes of absenteeism[4]. With two million annual lost school days attributed to allergic rhinitis[5]. While pharmacotherapy reduces symptoms of allergic rhinitis, immunotherapy (IT) is the only treatment offering potential long-term immune modification. Conventional subcutaneous immunotherapy (SCIT) requires frequent injections, and often results in patient noncompliance due to inconvenience or intolerance. In the 1980's, SCIT was deemed responsible for several deaths, causing the British Committee for the Safety of Medicine to raise concerns about its safety.[6]

Due to SCIT safety concerns, multiple non-injection IT routes have been investigated. Sublingual immunotherapy (SLIT) has been the most promising of the non-injection IT routes and has now been in use in Europe for over 20 years.[7]

Sublingual Immunotherapy is method of allergy treatment that uses an allergen solution given under the tongue, which reduces sensitivity to allergens. Sublingual immunotherapy, or SLIT, has a very good safety profile and is given at home in adults and children.[8]

The basis of sublingual immunotherapy is treatment of the underlying allergic sensitivity. Allergic symptoms improve as the allergic sensitivity improved. As a safe and effective method of treating the underlying disease, sublingual immunotherapy is capable of modifying the natural progression of allergic disease which can begin with allergic food sensitivities & eczema in young children and progress though allergic rhinitis and asthma in older children & adults.[8]

It has long been known that oral administration of an allergen favours the development of tolerance. Current understanding is that regulatory T cells secreting TGF-â are involved in this type of tolerance. Administration of high-dose allergen immunotherapy by means of sub-cutaneous injection also induces the development of regulatory T cells, with evidence that the secretion of both IL-10 and TGF-â is important in the mechanism of tolerance. Because many patients receiving SLIT show immunologic changes similar to those observed in patients receiving SCIT, such as suppression of the immediate and late-phase skin test responses, increased levels of allergen-specific IgG4, and in some studies suppression of allergen-induced lymphocyte

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proliferation, it is not unreasonable to suggest that stimulation of regulatory T cells underlies the response to immunotherapy by both routes.[9]

Low-dose sublingual immunotherapy (SLIT) for respiratory allergy was firstly described in a controlled trial in 1986[10] and it appeared as a promising therapeutic option, especially for the favourable safety profile. The original rationale of SLIT was that of achieving a prompt and rapid absorption of the vaccine through the oral mucosa. It then became the most used noninjection route for immunotherapy in Europe. After a review of the literature existing in 1998, a panel of experts of the World Health Organization concluded that SLIT is a viable alternative to SCIT[11]. This statement was confirmed in a position paper of the European Academy of Allergology and Clinical Immunology[12] and in the ARIA (allergic rhinitis and its impact on asthma) document[13] that extended the indications of SLIT to children.

The history of SLIT is chronologically short and encompasses a period of only 20 years. The sublingual approach was initially proposed empirically, without knowledge of the bio-distribution of allergens and of the possible mechanism of action. As a consequence, the practical aspects of SLIT (i.e., allergen dose, frequency of administration, build-up modality) were selected by investigators on the basis of personal experience, often translating into SLIT, the protocols used for SCIT. The result is significant variability in administration schedules, dosages, and duration of SLIT courses. Nonetheless, the clinical trials in the latter 20th and early 21st century began to address this variability, and there is a trend toward more uniform SLIT protocols, similar to the previous development for SCIT. Because of regulatory issues SLIT is not used worldwide but is employed in clinical practice in Europe and other countries and regions including South Africa and Latin America.[14]

SLIT is currently marketed by several European and Indian manufacturers and the administration schedules and amount of allergen(s) largely vary, depending on the producer. Almost all the SLIT vaccines commercialized in Europe are standardized either biologically or immunologically[14]. The allergen extracts are labelled in units that differ from one manufacturer to another. Some of the more common labelling units are allergen units (AU), index of reactivity (IR), biological units (BU) standard unit (STU). The content in microgram of the major allergens is available for many extracts, and thus has allowed a quantitative approach to determine the optimal SLIT dose. In general the maintenance dose of allergens is 5 to 300 times higher with SLIT compared to SCIT. The term "high-dose SLIT" is sometimes used to indicate this dose difference.

The vaccine of SLIT is available in two principle pharmaceutical forms.

a) Buffered solution to be delivered by drop-counters, droppers, predosed actuators or disposable single dose vials.

b) Tablets with appropriate composition facilitating slow (1-2 minutes) dissolution In the mouth upon contract with saliva.

For the build-up or the updosing phase vials or blisters of tablet at increasing concentration are provided.

SLIT can be delivered by means of two methods. With sublingual spit, the vaccine is kept under the tongue, for a short period and then spat out. This method was used in some earlier studies but the majority of the studies used sublingual swallow method. In this method the vaccine is kept under the tongue for one to two minutes and swallowed. In a study that investigated the pharmacokinetics of the two techniques and the author concluded that the contact with the oral mucosa was a crucial step and the sublingual swallow method was the more appropriate and advantageous way to administer the allergen because the sublingual spit method led to a partial loss of allergen[15]. The vaccine or solution is usually administered in the morning with the patient in fasting state, but may be administered at any time of the day.

SLIT traditionally involves a build up phase (with gradually increasing doses) and maintenance phase with maximum dose. This approach is similar to SCIT but more accelerated. The build up phase is usually 4 to 6 weeks. The vaccine is prepared in separate vials at increasing concentrations. The treated subject starts the lowest concentration and gradually increases using the different doses preparations, until the maintenance dose is reached. The relative safety of SLIT doses not

strictly limit the maximum dose and this contributes to the variability of the maintenance doses used in clinical trails[16]. The suggested maintenance interval varies among manufacturer and investigators.

SLIT can be administered either pre seasonally (start prior to the season and stop at the beginning at the season), pre-co seasonally (start prior to the season and stop at the end of the season) or continuously. Pre-seasonal or pre-co seasonal schedules are commonly used for pollen allergy. In this case the treatment is commenced about two months before the expected pollen season. On the other hand for nearly perennial or perennial allergens, a continuous treatment (all year round is preferred).

The most used regimen is once daily or alternate day or once weekly or twice weekly administrations have been utilized. The studies reporting SLIT include doses that vary by 30,000 fold, frequency of dosing vary from daily to weekly and duration of treatment varying from two months to five years. There are very few comparative studies[17].

SLIT appears efficacious for IgE-mediated respiratory allergy. SLIT is specific for the allergen and not the disease. The major issue to be determined before initiating SLIT, or any allergen immunotherapy, is the causal importance of a specific allergen or allergens. The allergy diagnosis is made by clinical history, physical examination, skin testing and or serum specific IgE assays. SLIT is self managed by the patient at home, thus detailed instructions, schedule of administration, and possible side-effect discussions are mandatory. The Manufacturers usually provide written instruction with SLIT but it is common practice for most allergists to see the patients before he/she starts the treatment, to provide additional information and verify understanding. A contact physician for telephone reporting of adverse events should be provided.[18]

As per guidelines, SLIT is indicated in patients with rhinitis or asthma or both, especially those who refuse injections or previously experienced severe adverse reactions to SCIT. Although there is no formal evidence of increased risk, SLIT is usually not recommended for patients with severe/uncontrolled asthma. The clinical efficacy of SLIT in mild, intermittent rhinitis is less defined. Ideally, SLIT should be used in an integrated treatment plan, including avoidance measures and appropriate pharmaceutical therapy. SLIT is self-administered and usually managed at home, thus, concerns about compliance & monitoring. Adherence with SCIT is documented since it is given in the presence of physician. Some studies have attempted to quantify the adherence to SLIT therapy by means of unscheduled telephone interviews.[19]

SLIT may be associated with minor adverse reactions. By far the most common are local symptoms in the oral cavity; however, abdominal complaints, urticaria, and asthma have been reported, although all are uncommon. Anaphylactic reactions accompanied by hypotension and fatal reactions have not been reported. It should be recognized, however, that there has been little reported use of SLIT in patients with severe asthma, and multiple allergen SLIT has not been reported[20].

The cumulative dose of allergen given via sublingual route is greater than SCIT, and therefore, the cost of vaccine is greater. The cost of vaccine is offset by the reduced need for medical and nursing time, so the global cost of SLIT may be less than SCIT.[21]

Specific immunotherapy is a cornerstone in the management of respiratory allergy since it is allergen specific, immune modulating, and affects disease progression. SLIT, introduce about 20 years ago is potentially a significant advance offering an excellent safety and acceptance profile. But many questions remain unanswered regarding SLIT including effective dose and schedule, timing, mechanism and safety in high risk groups. Until the optimal effective dose and dosing schedule is established a cost benefit analysis of SLIT cannot be made. Currently there is no CPT (current procedural terminology of American Medical Association) code for SLIT. One barrier to endorsement of SLIT is the absence of FDA approved product for SLIT. Physicians prescribing SLIT should provide specific instruction for managing the different variables that might be anticipated with this home based therapy, such as gaps in the treatment and clinical situations for which the treatment should be withheld.

Mechanism to monitor patients' adherence and adverse treatment should be carefully considered before this treatment is prescribed.[22]

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