Current Concepts and Update for Sublingual Immunotherapy

Sandra Y. Lin

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Abstract Recent reports of the prevalence of allergic rhinitis in the United States range from 20 to 40 % of the population. Typical symptoms can include nasal obstruction, rhinorrhea, sneezing, and conjunctivitis. Inhalant allergens, such as plant pollens, can cause seasonal symptoms, while perennial symptoms can be induced by dust mites, cockroaches, and certain molds. Allergen specific immunotherapy (SIT) is typically recommended for patients whose allergic rhinoconjunctivitis symptoms cannot be controlled by medications and environmental controls, cannot tolerate their medications, or desire an alternative to pharmacotherapy. While currently the only FDA approved form of SIT in the United States involves subcutaneous injection, sublingual immunotherapy is an alternative “off-label” form of allergen desensitization. This review article examines the efficacy and safety of sublingual immunotherapy for the treatment of allergic rhinitis.

Keywords Sublingual immunotherapy · Allergy immunotherapy · Specific immunotherapy · Oral immunotherapy · Allergy desensitization

Introduction

Allergic rhinitis is estimated to affect 20–40 % of the United States’ population [1–5], and therefore, is a widespread clinical problem. Typical manifestations of symptoms include rhinitis, rhinorrhea, nasal obstruction, and conjunctivitis.

Seasonal symptoms are provoked typically by plant pollens, while year-round or perennial symptoms are caused by such allergens as pet dander, cockroaches, dust mites, and certain molds. The treatment of allergic rhinitis includes avoidance of provoking allergens, pharmacotherapy, and immunotherapy [4, 5]. Allergen specific immunotherapy (SIT) is typically recommended for patients whose allergic rhinoconjunctivitis symptoms cannot be controlled by medication and environmental controls, cannot tolerate their medications, or desire an alternative to pharmacotherapy. SIT involves repetitive controlled dosing of the allergen in the allergic individual in order to produce immunologic changes with the goal of improving tolerance and thereby decreasing symptoms and medication usage. Currently, in the United States at the time of preparation of this manuscript the only form of FDA approved SIT involves subcutaneous injections of immunotherapy (SCIT). Typically SCIT is administered with injections in a physician’s office, usually starting with weekly injections and requires an observation period of 20–30 min in the office for systemic reactions after injection.

In the mid 1980s, concerns over safety, convenience, and patient tolerability regarding SCIT led to renewed interest in alternative forms of immunotherapy. In 1986, the British Committee for the Safety of Medicine questioned the risk–benefit ratio of SCIT after several deaths from SCIT [6]. Although the investigation eventually concluded that the deaths were results of avoidable human error, this report greatly increased interest in alternative routes of immunotherapy. Interest in sublingual immunotherapy (SLIT) has steadily increased after the first modern published report of dust mite allergen SLIT in 1986 [7]. Since the early reports over two decades ago, investigators have published data regarding the safety and efficacy of SLIT, primarily in Europe. As data supporting the clinical use of SLIT has increased, the World Health Organization

S. Y. Lin (✉)
Department of Otolaryngology-Head and Neck Surgery,
The Johns Hopkins School of Medicine, 601 N. Caroline Street,
#6254, Baltimore, MD 21287, USA
e-mail: Slin30@jhmi.edu

concluded in 1998 that SLIT was an acceptable means of immunotherapy [8]. Further publications by the European Academy of Allergy and Immunology and the Allergic Rhinitis and Its Impact on Asthma (ARIA) support the use of SLIT in allergen desensitization in children and adults in their treatment guideline documents [9].

Sublingual immunotherapy involves placement of the allergen under the tongue for local absorption to desensitize the allergic individual over a period of time in similar manner to SCIT in order to reduce allergic symptoms. In other parts of the world, sublingual forms of immunotherapy have gained favor and popular acceptance in the forms of aqueous SLIT and SLIT tablets. Sublingual tablet immunotherapy has been approved by the European regulatory authorities. Currently, in the United States there are no FDA approved sublingual forms of immunotherapy. However, some studies and physicians in the United States are exploring off-label use of subcutaneous aqueous allergens for sublingual desensitization. Potential advantages of sublingual immunotherapy include ease of administration, the ability to treat young children who cannot tolerate repeated injections, home administration versus in-office injection therapy, and to increase access to immunotherapy to those who live in medically underserved areas. This review article examines the mechanisms of action, safety, and efficacy of sublingual immunotherapy for the treatment of allergic rhinitis.

Sublingual Immunotherapy: Mechanisms of Action

Previous literature has addressed the immunologic changes, local and systemic, that occur with the administrations of SLIT. Sublingual immunotherapy dosing involves the administration of the allergen under the tongue where it is kept for several minutes. The interaction of the sublingual mucosa and allergen is thought to be important in the mechanism of action of SLIT. Previous studies of radio-labelled SLIT have found evidence of radioactivity in the oral cavity for 2–20 h after initial administration of SLIT [10]; this is thought to be due to the local uptake of antigen by local dendritic cells [11•]. It is thought that the allergen in contact with the oral mucosa is taken up and processed by dendritic cells within 30–60 min, and then presented to T cells in local lymph tissue and in the cervical lymph nodes. These T cells then migrate systemically to produce increasing systemic allergen tolerance [12].

Sublingual immunotherapy is thought to increase systemic tolerance towards allergens in a similar manner to SCIT, by modulating allergen specific T cell response from a T helper 2 to T helper 1 profile. The serologic changes seen after administration of SLIT are similar to those seen after administration of SCIT, although the clinical

significance of these serologic changes is unclear. Both forms of SIT induce changes in skin testing, increases in allergen specific IgG4, and decrease in antigen specific IgE [13–15]. This suggests a similar mechanism underlies both routes of immunotherapy. In addition, SLIT appears to generate a local IgA response [12].

Safety of Sublingual Therapy

Sublingual immunotherapy, like all forms of SIT, has the potential to provoke untoward allergic reactions as a side effect. The reactions of SLIT fall broadly into two categories, local reactions and systemic reactions. Local reactions occur at the site of allergen immunotherapy administration, and in the case of SLIT, this is the oral cavity. Systemic reactions are those reactions that occur distant from the site of allergen administration. Systemic reactions to immunotherapy can include any organ system; examples include urticaria, rhinitis, asthma, and gastrointestinal upset. The most severe systemic reactions to immunotherapy include life-threatening reactions and anaphylaxis.

Prior studies have attempted to answer questions about the safety of SLIT, particularly in comparison to SCIT. In a study which examined over 1 million doses of SLIT, there were 14 serious adverse events reported, which included asthma, swelling of the uvula, abdominal pain, vomiting, and urticaria [16]. In comparison to SCIT, this report found the rate of systemic reaction was 0.6 % for SCIT versus 0.056 % SLIT; deaths 1 per 2.5 million for SCIT, versus no reported deaths for SLIT. Sublingual immunotherapy local reactions were found in 40–75 %, particularly in the early phases of SLIT.

A recent paper by Calderon et al. [11•] reviews the reports of anaphylaxis caused by SLIT. These authors found 11 nonfatal cases of SLIT related anaphylaxis reported in the medical literature. The authors found that these reports met the World Allergy Organization criteria for anaphylaxis after immunotherapy. Two of these reports included SLIT for latex allergy, and the remainder were reports of treatment for inhalant allergies. Six of these reports were adults, and five were children. Six out of 11 experienced hypotension and shock. However, these authors were of the opinion these reports of anaphylaxis with SLIT represented non-standard practices of SLIT, involving rush protocols, overdose, interruptions in dosing regimen, and those patients who had previous serious adverse reactions to SCIT. Reports of anaphylaxis from the first dose of sublingual tablets have led to the recommendation in Europe that the first dose of a sublingual tablet be administered in a physician's office capable of recognizing and treating serious systemic reactions [17, 18].

Although the current literature supports a favorable safety profile of SLIT, and in Europe where there has been the greatest experience with this form of therapy dosing continues at home, there are certain practical safeguards that can further reduce the risk of adverse reactions. Examples include proper labeling of patient vials with more than one patient identifier to avoid distributing the wrong vial to a patient, or the use of bar code scanning and labeling of vials. In order to decrease the chance for human error in mixing, mixing should be performed in a quiet environment where there are no outside distractions. Patients must be thoroughly educated in proper dosing at home, and consideration given to giving the first dose in the office. Patients receiving allergen SIT should be instructed in the signs and symptoms of anaphylaxis. Training on an epinephrine auto injection device should be offered to the patient, as well as a prescription for the device. These types of precautions and comprehensive patient education may provide increased safety for patients receiving SLIT.

Efficacy of Sublingual Immunotherapy

The efficacy of SLIT has been the subject of several recent large scale reviews and meta-analyses. The first large scale Cochrane meta-analysis was published by Wilson entitled “Sublingual Immunotherapy for Allergic Rhinitis” in 2003, which examined 979 subjects pooled from 22 randomized double-blind placebo controlled studies of SLIT [19]. Wilson’s meta-analysis included both pediatric and adult subjects. This meta-analysis found significant reduction in symptom and medication scores with SLIT, and concluded that SLIT was effective for allergic rhinitis. The authors did comment, however, on the large heterogeneity in studies as far as dosages/treatment schedules and safety data reporting, which appears to be a continuing issue in comparing ongoing published studies. This review was updated in 2011 [20], and 60 randomized controlled trials of SLIT met the authors’ inclusion criteria in the updated review. This update found significant reductions in symptoms, and medication use when comparing SLIT to placebo. No severe systemic reactions were found in this review. The 2011 review found the efficacy greatest for studies with house dust mites. The authors found aqueous and tablet forms to have similar effectiveness.

Several recent reviews of SLIT have focused on particular clinical outcomes. In 2006, a systematic review of the efficacy of SLIT in asthma was performed by Calamita et al. [21]. Randomized controlled clinical adult and pediatric trials from 1974 to 2005 were included; 1,706 patient from 25 studies met study inclusion criteria. The authors found that SLIT was beneficial for asthma

treatment when looking at symptoms, medication use, lung function, and bronchial provocation. While the effects while statistically significant in this systematic review, the effects were small in scale. A 2011 systematic review of SLIT focused on the efficacy in treating allergic conjunctivitis symptoms; the authors concluded that SLIT was effective in reducing ocular symptoms of allergy [22].

Other systematic reviews of sublingual immunotherapy have focused on a particular allergen. Grass allergen sublingual immunotherapy was the focus of a systematic review by Di Bona et al. [23]. The authors found grass allergen sublingual immunotherapy significantly reduced symptoms with a modest clinical improvement. In 2009, Compalati performed a meta-analysis of the efficacy of dust mite sublingual immunotherapy [24], and concluded that symptoms were significantly reduced with use.

SLIT Efficacy in the Pediatric Population

As sublingual immunotherapy has been considered to be a favorable alternative to subcutaneous immunotherapy for children, based on convenience and ease of administration without multiple injections, this age group has frequently been the subject of SLIT studies. In 2003, Wilson et al. [19] did a subgroup analysis with a small number of pediatric studies using sublingual immunotherapy for allergic rhinitis and did not find a significant treatment effect for symptoms of allergic rhinitis or medication usage; however, a subsequent systematic review demonstrated effectiveness of SLIT in children. Penagos et al. [25] performed a meta-analysis of nine studies on the efficacy of sublingual immunotherapy in allergic pediatric patients with asthma and found significant decreases in asthma symptoms and medication usage. Sopo et al. [26] evaluated the clinical efficacy of sublingual immunotherapy in children with inhalant allergies and systematically reviewed eight studies. No significant clinical results were found using sublingual immunotherapy in children with respiratory allergies due to seasonal allergens or rhinoconjunctivitis due to house dust mites, although low to moderate clinical effects were found with the use of sublingual immunotherapy in children with mild to moderate persistent asthma due to house dust mites. Olaguibel et al. [27] also performed a meta-analysis with seven studies on the efficacy of sublingual immunotherapy on asthma, rhinitis, and conjunctivitis symptoms in children with allergic rhinitis or asthma. They found statistically significant reductions in asthma and medication scores, but not for rhinitis or conjunctivitis symptoms. Calderon et al. [22] pooled nine studies that included participants aged 4 to 17 years and showed significant reduction in allergic conjunctivitis symptoms in children treated with sublingual immunotherapy.

SLIT Efficacy in Disease Modifications and Prevention

Previous studies have sought to provide information on the long-term effects of SLIT for allergies and asthma as far as disease modification and prevention. Disease modification in asthma has been addressed in two studies [28, 29]. Niu et al. [28] found that SLIT with dust mites in children significantly decreased the severity of asthma over 6 months of treatment when compared with controls. In a study of 216 children undergoing sublingual immunotherapy with dust mites, trees, and grass, Marogna et al. [29] found a significantly lower percentage of children with mild persistent asthma at the conclusion of the study.

The prevention of asthma has been reported in a sublingual immunotherapy study that followed patients for 3 years [30], and also in a separate 8-year study [31]. Novembre et al. [30] found that grass pollen sublingual immunotherapy in children significantly decreased the development of asthma over 3 years; controls in this study developed asthma 3.8 times more frequently. However, in a separate 8-year study, 2 years of sublingual immunotherapy had no asthma preventative effect [31].

Prevention of new allergy sensitivities with the use of SLIT had also been discussed in the scientific literature. Marogna found that treatment with multi-antigen sublingual immunotherapy (dust mites, birch, weeds, and grass mix) significantly decreased the development of new skin sensitizations [32]. He reported in a subsequent study that the percent of children with new allergen skin sensitivities was significantly decreased after 3 years [29]. However, in a different study with 8-year follow-up, there was no preventative effect on the development of new sensitivities 2 years after *Parietaria* sublingual immunotherapy [31].

Efficacy of SLIT Versus SCIT

Several published prospective studies have compared the efficacy of sublingual to subcutaneous immunotherapy [32–41], and these are detailed in Table 1: Prospective Studies of SLIT versus SCIT. These studies were published from 1993 to 2011, with dust mite the most common allergen studied (60 %). The studies all have small number of subjects with the exception of Tahamiler et al. [38]. While the majority of these studies find both SLIT and SCIT efficacious, there is no clear agreement among the studies as to which form of treatment is more effective.

Sublingual Immunotherapy Dosing

The majority of scientific literature has been published in Europe, and this literature may serve as a basis to establish effective dosing for U.S. physicians who practice

sublingual immunotherapy. However, there are limitations when comparing European allergens to United States allergens [42•]. While in the U.S. the FDA establishes for each standardized allergen an in vitro potency test which all manufacturers must use to compare their extracts; this is not true in Europe. In Europe, each allergen manufacturer has its own in-house reference standards rather than a single European standard. Another difference is that the in vivo potency in the U.S. is quantified by intradermal testing methods, while in Europe, prick testing is utilized. A study by Larenas-Linnemann et al. [43•] sought to compare European SLIT maintenance solution to U.S. standardized extracts approved for SCIT. The extracts were analyzed for protein content, relative potency, and major allergen content; U.S. extracts were found to have relative potency up to ten times greater than European SLIT maintenance formulations for the same allergen. Therefore, due to differences in U.S. versus Europe allergen standardization and potency, some caution must be exercised when attempting to translate European dosing to the United States.

Despite the potential difficulties in translating European dosing to the United States, the scientific literature consistently demonstrates that higher doses of antigen are necessary for sublingual immunotherapy versus subcutaneous immunotherapy. The majority of European antigen manufacturers' recommendations for monthly maintenance SLIT dose range between 5 and 45 times the dose recommended for SCIT maintenance treatment with their products [44]. A review of SLIT studies from 2006 found cumulative SLIT monthly dosing to range up to 500 times the customary SCIT dose, with the mean of 87 and median of 49 times the usual SCIT dose [16].

Fortunately, some recent U.S. studies of sublingual immunotherapy are shedding some insight into effective dosing with allergens manufactured in the U.S. Greer Laboratories conducted a study evaluating the efficacy of sublingual immunotherapy for short ragweed utilizing their liquid short ragweed antigen product currently labeled for subcutaneous injection use [45]. The study demonstrated a reduction in rhinoconjunctivitis symptoms and anti-allergy medication use scores for both the 4.8 and 48 Amb a 1 Unit doses versus placebo. The reduction only reached statistical significance only at the higher dose.

Recent U.S. studies have also examined the efficacy of sublingual grass tablets. The first study was conducted in the pediatric population [46]. This study showed a significant reduction in total combined symptom and medication scores. This study replicated the previous findings in similar studies conducted with the product at European centers. The maintenance dose utilized in this study was approximately 15 mcg of Phl p 5 Timothy grass antigen. A study in the adult population [47] performed in the U.S. of grass

Table 1 Prospective studies of SLIT versus SCIT

References	Allergen	Number of subjects	Results
Piazza and Bizzaro [32]	Dust mite	57	Only SCIT induced significant clinical improvement
Quirino et al. [33]	Grass mix	20	Both equally effective for improving symptoms and decreasing medication use
Bernardis et al. [34]	<i>Alternaria</i>	23	Both reduce symptoms Statistically significant difference in favor of SLIT
Mungan et al. [35]	Dust mite	36	SCIT significantly improves asthma and rhinitis SLIT significantly improves rhinitis but not asthma Both significantly improve medication scores
Khinchi et al. [36]	Birch	71	Both significantly improve symptom and medication scores SLIT better safety profile
Mauro et al. [37]	Birch	47	No significant differences between SCIT or SLIT for symptom/medication improvement SLIT better safety profile
Tahamiler et al. [38]	Dust mite	193	Both induced significant improvement during treatment and 3-year follow up SCIT had greater benefit over 6 years
Eifan et al. [39]	Dust mite	48	Both significantly improve rhinitis, asthma, and medication scores SLIT better safety profile
Yukselen et al. [40]	Dust mite	30	Both reduced symptom/medications scores, but only significant improvement with SCIT
Keles et al. [41]	Dust mite	51	SCIT plus SCIT better outcomes than SCIT or SLIT alone

mix tablets demonstrated that the 300 IR tablets significantly improved combined symptom medication scores when compared to placebo.

Dosing Frequency, Escalation, Duration

While Cox et al.'s [16] review of published SLIT studies found dosing frequency from once a week to daily, it appears that most recent algorithms utilize daily dosing. There is also variation in the duration of dosage escalation, but the overall trend is towards escalation much more quickly than in SCIT protocols, or no escalation period at all [48]. Sambugaro et al. [49] published an induction phase comparison in 2003. The randomized, open study included three different induction schedules (8-, 15-, and 20-day inductions, respectively) in comparison to a control group. After induction, all groups had a once-daily maintenance phase for total treatment duration of 2 years. There was no significant difference in the rate of adverse events among groups. The tablet-based sublingual immunotherapy products available in Europe do not utilize dose escalation, but start at the maintenance dose with the first dose and the tablet is dosed daily. As far as duration of dosing in order to achieve persistent benefit beyond discontinuation of therapy, a recent prospective study compared dosing of dust mite SLIT given for 3, 4, or 5 years [50]. The authors found that receiving SLIT for 3 years had benefit in clinical scores for 7 years, while those treated for 4 or 5 years had benefit for 8 years. New sensitivities were least likely to occur in those treated with SLIT for the longest period of time.

Dosing: Perennial, or Co-seasonal

Dosing of SLIT co-seasonally or perennially has been a topic of study. In different trials, the antigen has been delivered perennially, pre-seasonal and co-seasonal. A recent publication investigated the efficacy of co-seasonal and perennial sublingual immunotherapy [51]. The authors performed an independent patient data meta-analysis of three open, prospective observational studies on SLIT with 1,052 subjects using standardized allergen extracts in patients with allergic rhinoconjunctivitis with and without asthma to compare the effectiveness of perennial and co-seasonal treatments, as well as ultra-rush and standard titrations. Symptom improvement was demonstrated in all treatment groups, with no significant difference between perennial, co-seasonal, ultra-rush, and standard titration protocols. This study demonstrates that multiple options may be available and effective for sublingual dosing that can be tailored to the needs of individual patients.

Single Versus Multiple Antigen Dosing

The majority of SIT studies, both sublingual and subcutaneous, are studies of treatment with a single antigen. However, in the United States, SIT is typically given as multiple antigen immunotherapy, with treatment of all allergic sensitivities demonstrated by history and allergy testing. Two sublingual studies have compared single versus multi-antigen immunotherapy [52, 53]. The first of these articles compared Timothy grass monotherapy to Timothy grass

multi-antigen therapy (Timothy grass plus nine other allergens) [52]. While nasal challenge with Timothy grass yielded significantly better results when comparing Timothy monotherapy to placebo, there was no difference in Timothy grass multi-antigen SLIT versus placebo. In another paper, three groups were compared: sublingual birch, sublingual birch plus grass, and pharmacotherapy [53]. The multi-antigen treatment group had significantly greater improvement in clinical symptoms when compared to the single antigen group. The data from these two studies demonstrate inconsistent result, and insufficient data exists to comment definitively on the effectiveness of single versus multiple antigen sublingual immunotherapy.

Conclusions

Sublingual immunotherapy has been shown in multiple studies and several large scale meta-analyses to be efficacious in the treatment of allergic rhinitis in the adult and pediatric population. Studies demonstrate immunologic changes in SLIT that are similar to SCIT, suggesting a similar mechanism of action. SLIT enjoys a good safety profile which allows for the convenience of dosing in the home and in individuals unable to tolerate injections such a young children, although there have been a few reports of anaphylaxis. The safety profile of SLIT appears to be more favorable than that of SCIT. As the majority of literature has been published in Europe, multiple factors have made the translation of dosing to the United States difficult. Future studies will be helpful in clarifying optimal dosing and dosing schedules in the United States. There is a need for future studies to compare single to multiple antigen SLIT, to determine the long term effects of SLIT, as well as studies that directly compare the efficacy of SLIT versus SCIT head to head.

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