Sublingual Immunotherapy: Controversies and Issues

1. Introduction

Immunotherapy or, more precisely, allergen-specific immunotherapy is a unique treatment designed to reduce or eliminate allergy symptoms by inducing tolerance to an offending allergen. Immunotherapy was first proposed as a specific treatment for allergy more than 100 years ago and came into use in the United States during the 1920s. Since then, immunotherapy has been studied, developed, improved and standardized. Over the past 70-plus years, subcutaneous immunotherapy (SCIT), also commonly referred to as “allergy shots” or “allergy injections,” has been adopted by allergy specialists in the U.S. with millions of doses of SCIT administered annually.

SCIT is approved by the FDA for subcutaneous injection of approved allergy extracts. Allergy serum approved for SCIT is formulated into one or more sets of treatment vials for each patient. The allergy specialist factors in knowledge of the local aerobiology and correlates the patient’s clinical history, examination, and allergy test results in order to formulate an individualized serum for treatment.

Through many high-quality, controlled studies, SCIT has proven to be both effective and long-lasting in the induction of tolerance to allergens, even well beyond the term of treatment for allergic rhinitis/conjunctivitis, allergic asthma, and insect-venom hypersensitivity. In fact, SCIT may even prevent the development of asthma in some patients with respiratory allergy. However, SCIT also has the potential for serious side effects, which can include anaphylaxis. Therefore, SCIT requires administration in a medical office under a supervising physician prepared to treat potential reactions.

Despite the proven effectiveness of SCIT, physicians have long sought a more convenient method of administering immunotherapy with a lower potential for serious side effects. Thus, sublingual immunotherapy (SLIT) was studied as an alternative approach, in which the allergen preparation is administered orally or beneath the tongue. The convenience of this self-administered treatment and its low potential for severe side effects have helped SLIT gain popularity in several countries.

SLIT is currently approved for use in Europe, but the treatment is not FDA-approved for use in the U.S. This might be explained in part by differences in aerobiology between the two regions, as well as by a disparity between patterns of hypersensitivity in U.S. and European populations. FDA clinical trials in the U.S. as of this publication have not received approval for use of SLIT in this country, indicating that there are still some issues that need to be resolved before it is recommended for the treatment of allergy.

In 2005, the American Academy of Allergy Asthma and Immunology (AAAAI) and the American College of Allergy Asthma and Immunology (ACAAI) reviewed 102 publications on SLIT. They concluded that although there is substantial evidence that SLIT is an effective treatment, many questions have been left unanswered, such as: effective dose, treatment schedules, and duration of treatment, among others. These professional organizations concluded that until these questions are answered, a cost benefits analysis cannot be determined. (Cox et al, JACI 2006; 117:1021-35)

Although the efficacy of SLIT has been supported by several meta-analyses of published studies, in a recent publication, Nieto et al carefully evaluated the five previously published meta-analyses through 2008 and found discrepancies, inconsistencies, and a lack of robustness. As a result, the authors
immunotherapy (STIT)

In contrast, SLIT was considered experimental until the 1990s, in the treatment of insect-sting anaphylaxis. For a number of patients suffering from respiratory allergy, SLIT has been effective in up to 85% of patients with respiratory allergy and up to 95% effective for those suffering from IgE-mediated respiratory allergy. (JACI 2009;124:157-161)

2. Differences between SLIT and SCIT

Since the 1930s, SCIT has been considered the benchmark for immunotherapy based on a number of controlled studies covering a broad variety of common aeroallergens. Clinical trials performed in the U.S. have found SCIT to be effective in up to 85% of patients with respiratory allergy and up to 95% effective for those suffering from IgE-mediated insect-sting anaphylaxis. For a number of patients suffering from respiratory allergy, SCIT has been effective when pharmacological treatment has proved inadequate.

In contrast, SLIT was considered experimental until the 1990s, when high-quality studies revealed its effectiveness when higher doses were administered. In Europe, a number of controlled studies found SLIT to be an effective treatment method for allergic rhinitis and allergic asthma when a single allergen is administered (mono-therapy). For example, a grass-sensitive patient could receive SLIT containing grass allergen during the grass pollen season. In addition, extensive research and development has resulted in a stable, high-dose, high-quality oral allergen preparation in the form of a dissolving tablet (grass allergen). This form of sublingual treatment is referred to as sublingual tablet immunotherapy (STIT).

The dose of allergen used for SCIT and SLIT are notably different. For example, SCIT requires a much smaller administered dose of allergens than SLIT to achieve good clinical results. Further, it has been found that multiple allergens can be administered at the same time with SCIT, which especially benefits patients with multiple allergen sensitivities (poly-sensitized patients). This latter issue has a great impact on immunotherapy in the U.S., since many Americans are sensitive to multiple, different allergens. In the U.S., local allergy seasons (e.g., tree, grass, weed and mold) often overlap, exposing these poly-sensitized individuals to many different allergens concomitantly.

It should be noted that the most successful controlled studies indicated that the total required dose of allergen used in SLIT/STIT can be 10 to 100 times higher than the concentration of the same allergen used in SCIT. In addition, SLIT/STIT has been found to work best in studies involving the administration of a single allergen or a group of closely related allergens (e.g., five grass pollens). Patients sensitized to a single allergen (mono-sensitized patients) seem to benefit best from SLIT.

SLIT/STIT is self-administered by placing the allergen drops/tablet under the tongue for a few minutes and then swallowing the remainder. This is repeated daily or a few times per week, beginning some months prior to the onset of the allergy season and continuing throughout the season. Since SLIT is given orally, it is easily administered at home, and the incidence of severe allergic reactions is rare.

In contrast, SCIT requires regularly supervised allergy injections and has the potential for serious reactions.

In Europe, many patients are mono-sensitized or primarily sensitized to a single group of related allergens, and these allergens are often released during a discrete pollen season. For example, the allergy season involving the release of grass pollen may be distinct without significant overlap of confounding allergens. Patients sensitized to grass would have symptoms during the grass season and would therefore be candidates for SLIT/STIT. SLIT/STIT studies have demonstrated success using mono-therapy for the following allergens: grass pollen, dust mite, cat dander and birch, among others.

Although treatment with SLIT/STIT has been found to offer significant relief with various allergens as a mono-therapy, it has not conclusively demonstrated similar success with concomitant administration of multiple unrelated allergens. The best results seen so far with recently conducted FDA-monitored, controlled trials in the U.S. appeared to occur when a single allergen was used in a sublingual tablet (STIT) rather than in an aqueous solution or SLIT. (Blais, M, Maloney, J, Nolte, H, et al. Efficacy and Safety of Grass Allergy Immunotherapy Tablet (AIT) in a North American Pediatric Population. J Allergy Clin Immunol 2010; 125)

3. Mechanism behind SLIT

During a course of SLIT, the administered allergens are taken up by dendritic cells (antigen-presenting cells) lining the oral mucosa. Sublingual dendritic cells secrete interleukin (IL 10), which causes inhibition of the inflammatory or allergic response. Antigen-specific T-helper (TH) cells locally increase IgA production and simultaneously suppress IgG and IgM. These allergens are presented to T-cells mostly located in the regional lymph nodes. Since the allergen is administered orally, side effects are largely limited to the oral or gastrointestinal mucosa, and systemic side effects are very rare.

Over
**SLIT clinical trials**

**a. SCIT vs. SLIT.** In a 6-year study comparing subcutaneous immunotherapy (SCIT) to sublingual immunotherapy (SLIT), Tahamiler et al (2008) enrolled 193 patients with allergic rhinitis due to dust mite allergy. Half the participants received SCIT, while the other half received SLIT for 3 years, followed by 3 more years of follow-up. Prick tests showed a greater reduction in sensitivity with SCIT. No systemic reactions occurred in either group. However, side effects with SLIT included oral pruritus (48%), rhinitis (31%), and gastrointestinal symptoms (12%). SLIT studies generally revealed a 30% reduction in symptoms. It would appear that SLIT is most effective for patients suffering from mild to moderate symptoms. Further, the investigators felt that SCIT was more effective than SLIT for treatment in perennial allergic rhinitis due to dust mites. (Tahamiler et al. ORL 2008;70:144-50)

**b. In Europe, grass sublingual tablets (STIT) were compared to placebo in a multi-site controlled trial.** A total of 634 adults were treated for grass pollen-induced allergic rhinitis with a sublingual tablet (Grazax®), which contains a single grass allergen (timothy). Daily treatment consisted of a sublingual tablet containing 15mcg of Phl p 5 or placebo. Symptom scores improved by 30% and medication scores by 38% as compared to placebo. This was statistically significant, and the same treatment was subsequently employed in a U.S. study, but failed to achieve similar results. (Dahl, R, Kapp, A, Colombo, G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006; 118:434)

**c. In 2007, a multi-site study of grass-sensitive allergic rhinitis/conjunctivitis patients was undertaken in the U.S. using the same Grazax® produced by ALK/Schering Plough.** Unlike the prior European study, no measurable clinical benefit was noted. Possible reasons for this failure included the presence of confounding aeroallergen due to overlapping seasons, poor grass pollen season, and a poly-sensitized patient population included in the study. Ultimately, the study was not adequately controlled for the above variables. (Press release may be accessed at www.forbes.com/feeds/afx/2007/11/16/afx4348325.html)

**d. The above study was redesigned and completed in 2009 with both an adult and pediatric participation.** With more than 400 patients participating over multiple sites, STIT (Grazax®) achieved statistical significance for combined daily symptom and medication use reduction as compared to a placebo. No serious side effects were reported. Although this study was successful for mono-therapy in a tightly controlled study, the question is raised whether this treatment will be effective for poly-sensitized American patients exposed to simultaneous aeroallergen seasons. (Blaiss, M, Maloney, J, Nolte, H, et al. Efficacy and Safety of Grass Allergy Immunotherapy Tablet (AIT) in a North American Pediatric Population. J Allergy Clin Immunol 2010; 125, 2, supplement, Feb 2010, AB558)

**e. When multiple grass allergens were combined in a single tablet (STIT) from 5 related grass pollens and administered to grass sensitized patients during the season, statistical improvement was noted compared to placebo.** Treatment was well tolerated without significant serious side effects. (Didier, A, Malling, HJ, Worm, M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. JACI 2007; 120:1338)

**f. In another SLIT study, patients were evaluated one year after completion of treatment following 3 years of active grass tablet treatment or placebo.** Actively treated patients continued to demonstrate a reduction in allergy symptoms scores and medication scores. Therefore, there is evidence that sublingual tablet immunotherapy can produce lasting relief from allergy symptoms. (Durham, SR, Emminger, W, Kapp, A, 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)

**g. Liquid sublingual immunotherapy extracts.** Glycerinated aqueous allergen extracts (produced by Greer Labs) were used in clinical trials in the U.S. with ragweed and dust mite allergen.

Using ragweed, a dose-dependent benefit in symptom scores was noted for both the medium and high dose group, but they did not reach statistical significance in this parameter.

A subsequent, larger, phase III Greer-sponsored study was performed with more than 400 subjects. The company issued a news release that the study failed to reach its primary clinical endpoints of revealing clinical statistically significant benefits over placebo. (Skoner, D, Gentile, D, Busg, RK, et al. Sublingual Immunotherapy in Patients with Allergic Rhinoconjunctivitis Caused By Ragweed Pollen. J Allergy Clin Immunol 2010; 125) (Press release viewable at www.greerlabs.com/research_dev/rdev.slit_updates.php)
time, administration of an allergen to a sensitized individual can induce tolerance, thus decreasing allergy symptoms. The underlying mechanism in oral immunotherapy responsible for this acquired tolerance is associated with the gastrointestinal immune system, which is made up of physical barriers, gut-associated lymphoid tissue (GALT), and secretory IgA. This natural defense mechanism normally facilitates tolerance toward food antigens. SLIT/STIT has been adapted to this system by administration of aeroallergens via the oral mucosa, resulting in tolerance to non-food allergens.

Systemic tolerance to the administered allergens develops slowly as T-helper cell activity decreases, which is likely a result of increased T-suppressor cell activity. Over time, sublingual therapy can cause a decrease in antigen-specific IgE (e.g., decreased allergen skin test reactivity and RAST activity), as well as an increase in allergen-specific IgG1 and IgG4 “blocking antibodies,” indicating the down-regulation of the allergic response.

Another marker of the immunologic response to sublingual immunotherapy is the blunting of the normal seasonal increase of allergen-specific IgE. For example, grass-specific IgE, which rises during the grass season in a sensitive patient, will show less of an increase when the patient is on oral immunotherapy for grass. Similar findings are observed for those treated with SCIT.

It is important to note that many studies have demonstrated that both clinical and immunologic responses are dose-dependent, and that an insufficient dose of allergen will fail to achieve the desired clinical results.

4. SLIT/STIT studies

More than 100 controlled clinical studies have been carried out using SLIT/STIT as mono-therapy with either birch pollen, grass pollen (timothy), dust mite, ragweed pollen, and cat allergens. Although significant efficacy was found in many studies, results were not always reproducible in all geographic regions (e.g., in the U.S.).

Kinetic studies revealed that the optimum total dose of allergy extract for significant clinical response was often 10-100 times that used in SCIT. Higher doses are best achieved when individual allergens are not diluted by mixing different allergens together. A number of studies have found that the best clinical results appear to occur when high-dose sublingual tablets were used with a single allergen.

Recent studies (Roder et al. JACI 2007;119:892) performed in the U.S. have not produced the same significant clinical findings as observed in European trials. These differences are likely due in part to regional differences in aerobiology. Further, many different Aeroallergens may be released in certain U.S. regions concurrently, thus affecting the response to therapy in a poly-sensitized patient. In contrast, certain Aeroallergens such as grass may be released without the presence of confounding allergens during the season in certain European regions, leading to successful SLIT mono-therapy. Further, multiple Aeroallergen exposures in individuals with multiple sensitivities to various Aeroallergens could obscure the benefits of mono-therapy. These factors might offer an explanation why mono-therapy with SLIT/STIT in U.S. clinical trials has not yet been granted FDA approval.

5. SLIT: Pros and Cons

Pros:
- SLIT/STIT causes fewer systemic side effects than SCIT. Serious systemic side effects with SLIT/STIT are rare, but a few have been documented.
- Greater convenience due to self-administration, no need for a waiting period in a medical office, and no discomfort of injection.
- Possible quicker onset of efficacy, usually within 3-4 months, whereas SCIT may take 6-9 months.

Cons:
- No FDA-approved product available at this time.
- Number of available future FDA-approved allergens may be limited.
- SLIT may not be effective for the poly-sensitized patient.
- Compliance-related issues due to self-administration.
- May not be as effective as SCIT for certain allergens.
- Costs may be quite high and are not yet covered by insurance companies or Medicare.

6. SCIT: Pros and Cons

Pros:
- Most studied and best understood form of immunotherapy with an outstanding record of efficacy for both mono-sensitized and poly-sensitized patients in the U.S.
- High success rates.
- Compliance monitored by a physician.
- Much smaller doses needed to achieve optimum results.
- Common side effects can usually be managed by reducing the dose.
- SCIT extracts are FDA-approved, and many are standardized. Dosing schedules are also standardized by regulating agencies, and written national guidelines for SCIT treatment are published by the major professional allergy organizations.
- Almost all common Aeroallergen sensitizers—including molds and common tree pollens—are currently available as FDA-approved extracts.
- Multiple allergens can be administered simultaneously and work well for most patients.
- Cost is often offset by insurance coverage and patients experience savings in decreased need for medications.

Cons:
- Weekly shots during the build-up period require a significant time commitment.
- Potential discomfort of injection.
- Travel to office and post-injection waiting time.
• Potential for serious systemic reactions (e.g., anaphylaxis).

7. **SLIT side effects**

**Very common (affect more than 1 in 10 people)**
- Itching of the mouth or tongue
- Swelling (angioedema) of oral mucosa or tongue
- Sneezing
- Itching in the ears
- Throat irritation and soreness

**Common (affect between 1 in 10 and 1 in 100 people)**
- Itchy eyes
- Conjunctivitis
- Runny or blocked nose
- Swelling in the mouth or throat
- Throat tightness
- Cough
- Asthma
- Tingling or numb sensations in the mouth
- Blistering in the mouth
- Swollen or painful tongue
- Headache
- Indigestion
- Nausea
- General pruritus
- Fatigue

**Uncommon (affect between 1 in 100 and 1 in 1000 people)**
- Dizziness
- Eye swelling
- Upper airway infection
- Mouth ulcers or sores
- Dry mouth and throat
- Vomiting
- Diarrhea
- Abdominal pain
- Swollen glands
- Shortness of breath, wheezing or asthma attack
- Voice changes/hoarseness
- Difficulty or pain when swallowing
- Nettle-type rash (hives or urticaria)
- Chest pain or tightness
- Severe swelling of the face, mouth, tongue and throat (angioedema)
- Fever or feeling hot

**Very rare**
- Anaphylaxis

8. **Safety of SLIT**

A review of the published literature of controlled studies involving thousands of patients reveals that SLIT/STIT is relatively safe for the majority of patients.

Although sublingual immunotherapy appears to be relatively safe, a few case reports have appeared in the literature that link SLIT to anaphylaxis or other serious reactions. While no fatalities have been reported, 7 acute systemic reactions were documented among 43 patients receiving SLIT. None required hospitalization. (Rodriguez-Perez, et al. *Annals of Allergy Asthma*, 2008;101:304-10)

In one published report (Anaphylaxis to Sublingual Immunotherapy. Dunsky et al, *AllergyNet* 2006: 61: 1235-1244), a 31-year-old woman with a history of allergic rhinitis, asthma, and food allergy developed hives, angioedema, wheezing, and vertigo on the second day of treatment with SLIT. When she restarted SLIT, a similar reaction occurred, which was even more severe than the original event. Others have also reported similar severe reactions. (Antico et al, *Allergy* 2006; 61:1236-7, Eifan. AO et al Allergy 207:62:567-8, and Blazowski L., *Allergy* 2008:63:374-381)

Further, some authors have reported significant side effects presenting as angioedema of the lips and/or oral cavity with the potential of airway obstruction (Dahl et al. *JACI* 2006; 118: 434-40). Although most severe reactions to SLIT are rare, they are real and patients need to be informed of the risks and adequately prepared for such reactions.

Since severe reactions can occur, it would be prudent to initiate SLIT in a physician’s office prepared to treat anaphylaxis. In addition, patients should carefully review an informed consent document prior to initiating SLIT/STIT treatment.
informing them of the remote possibility of the potential for a severe reaction as well as the issues regarding “off-label” SLIT (See Section 13 below). Patients must be educated to quickly recognize a severe reaction and be prepared to take action—either with an EpiPen™ or similar device. Advising patients that SLIT has no potential for severe side effects is misleading.

9. **Practical issues related to SLIT**

   **Types of oral or sublingual immunotherapy:**
   - Oral or sublingual immunotherapy (SLIT) comes in several forms including:
     - Sublingual aqueous extract of allergen placed under the tongue and subsequently swallowed.
     - Sublingual tablets (STIT) where the allergen is contained within a rapidly dissolving tablet that is held under the tongue for a minute or two and then swallowed.
     - Enteric coated or microencapsulated allergen preparations, which dissolve in the small intestine.
   - Allergens used in sublingual immunotherapy include:
     - Grass pollen, birch pollen, dust mite, cat dander, and ragweed pollen. At this point, more controlled studies will need to be undertaken to provide convincing evidence that all allergens administered via SLIT are effective.

10. **Cost**
    
    Grazax® tablets are currently sold in Canada for about $10 a tablet at retail prices; therefore, four or five months of therapy could exceed $1000 for a single high-quality allergen preparation.

11. **Duration of effect**
    
    Both SLIT/STIT and SCIT appear to induce long-lasting tolerance following completion of treatment. It is not clear which treatment is superior with regard to this issue.

12. **FDA approval**
    
    The FDA approval process for any new treatment program is long, complicated and expensive. However, it brings together some of the best clinical investigators in the country using a carefully constructed double-blinded protocol, which is developed by the manufacturer, FDA scientists, and the clinical investigators involved in the study. The level of monitoring during these studies is incredibly intense, leaving little doubt of the accuracy of the performance of the study. These Phase III clinical trials are usually large, involving 20 to 30 experienced clinical investigators, each of whom enrolls 15 to 30 carefully screened patients according to a well-defined protocol. The FDA reviews the study design, the quality of materials used, the study design, workbooks, diaries, and tests and insists on intense monitoring at every phase of the study protocol. The statistical results of these tightly controlled studies are then scrutinized by the FDA, and if statistically significant benefits can be demonstrated without significant side effects, the treatment is usually approved. This rigorous process lends robustness to the results, which prevents ineffective or problematic treatment programs from entering the U.S. marketplace. This process, in which the FDA is intimately involved at every level, offers the public the best protection available that the treatment approved has achieved a high probability that it will be safe and effective when used in the population studied. The process prevents the errors that are seen when off-label treatments are used on patients that are based on studies performed with less rigorous standards, which is often the case in non-FDA-approved clinical trials. In addition, it is not advisable to assume that SLIT therapy performed on a local population in Europe with its own unique aerobiology and patient sensitivity will predict similar results in our local population with significant differences in sensitivity and aerobiology. Therefore, off-label use of medication, which has not passed through the FDA review process, cannot be considered a result of evidence-based medicine for use in the U.S. and therefore should be reserved for experimental use.

13. **"Off-label" SLIT**
    
    The FDA has not approved SLIT treatment in the U.S. as of the date of this publication. However, some physicians offer SLIT as an off-label treatment.

    Off-label refers to the administration of an FDA-approved product or treatment in a manner for which it was not intended or for treatment of a disease for which it was not approved.

    Off-label treatments are legal, giving physicians an opportunity to literally experiment with medications that may offer some promise of relief in patients that have not responded to approved medications or cannot tolerate approved medications. A prudent physician will weigh all issues and inform the patient of the potential benefits and risks and offer reasons for recommending the off-label use of a medication. Further, it is generally recognized that off-label use of medication is not a typical therapeutic approach and not recommended as an accepted standard of treatment when an alternative FDA-approved treatment is available.
SLIT, currently offered to patients in the U.S., is an off-label use of an allergy extract intended for injection, rather than sublingual administration. The injectable serum is formulated by a physician or his staff for sublingual administration without FDA testing and approval. Further, Medicare and most insurers do not cover treatment costs. Since off-label use of SLIT is unregulated, there is no oversight by any insurer or regulating agencies. In fact, there are no nationally-recognized standards for the preparation and use of off-label SLIT by any of the major allergy organizations* or government agencies with regard to antigen concentration, selection of allergens, mixing of allergens, or dosing schedules.

Off-label SLIT program standards can vary greatly from one physician to another. Since there are no approved guidelines, this situation can lead to great variation in both preparation and dosing. Consequently, a lack of standardization can lead to unpredictable results, including treatment failures. It has already been demonstrated that low-dose therapy results in inferior clinical outcomes.

As a result of these issues, most board-certified allergists, allergy training programs, and major professional allergy organizations do not recommend off-label SLIT as an accepted treatment for respiratory allergy at this time. Once the FDA has approved a sublingual therapy program product for the treatment of respiratory allergy, it will be a welcome addition and will find its place throughout the community of physicians specializing in allergy.

*The AAAAI and ACAAI

14. All sublingual preparations are not equal in dose, quality or stability.

Some physicians who are dispensing off-label SLIT may mix unrelated antigens together in the same vial or dispenser, resulting in a diluted final concentration of allergens. This may lead to an ineffective treatment program.

SLIT as an off-label treatment in the U.S. is being promoted by some physicians as a superior alternative to SCIT. This view is not supported by most board-certified allergists or their professional organizations. Patients told that off-label SLIT is equal to or superior to SCIT are simply being misinformed. Strong promotion of SLIT in the U.S. may, in some cases, lead to over-preservation of this unregulated treatment. The paradox of this situation is that patients may end up paying more money for a less effective or ineffective allergy treatment program than the FDA-approved SCIT as the treatment of choice.

15. SLIT: The bottom line

Many SLIT studies indicate significant benefits for patients with respiratory allergy, while other studies fail to demonstrate effectiveness during clinical trials. This variation in effectiveness of SLIT has been attributed to a number of issues, especially the differences in the dose of allergen used in different studies. In general, the higher the dose of allergen, the better the clinical results. (Cox L., et al, JACI, 2007, 120:1466-1467)

Higher doses of allergen mostly indicate that SLIT has the potential for effective treatment of allergic rhinitis and perhaps allergic asthma. Hundreds of studies now support SLIT as an effective treatment when used as a mono-therapy with higher doses of allergen administered. Yet several questions need to be answered before SLIT can be used outside of the research setting in the United States. The FDA will want objective proof of efficacy in both the mono-sensitized and poly-sensitized patient as well as standardization of an effective dosing schedule of a specific standardized SLIT formulation prior to approval. It’s not yet clear whether the starting/maintenance doses will be the same for all of the various allergens, nor if the outcome will be beneficial when a poly-sensitized patient is exposed to different antigens during overlapping allergy seasons. Once these questions have been addressed, the cost-effectiveness of SLIT will also need to be established.

Since some physicians are recommending SLIT as an off-label treatment in this country prior to comprehensive study and approval by the FDA, the following concerns regarding the potential efficacy and safety issues regarding off-label use were raised by the executive committee of the AAAAI in the following statement:

In a letter to the editor of the Journal of Allergy and Clinical Immunology, The AAAAI executive committee raised a number of concerns regarding off-label SLIT use in the U.S.: (Greenberger et al, JACI, 2007, 120:1466-1467)

- “It is difficult and ill-advised to vouch for the appropriateness of the use of non-FDA-approved products or off-label indications with currently available extracts. It is likely that many patients who would or might respond to SLIT would have achieved greater reductions in symptoms and medications with SCIT.”
- “If patients with seasonal allergic rhinitis choose to receive SLIT because they are informed that SCIT has disadvantages, this practice is a disservice…”
- “In the absence of FDA-approved products and the modest or inconsistent effectiveness of SLIT, we believe that the patient would not be receiving optimal treatment when SLIT is used instead of SCIT.”

As of this date, the FDA has not approved any of the SLIT therapy that has been studied in controlled FDA approved trials here in the U.S. However, it appears that eventually, an effective SLIT product and dosing schedule will be approved. Such a treatment will be much-welcomed and surely will find its optimum place among the many treatments available for allergy management. However, until the FDA approves a specific SLIT product, the use of various off-label formulations of SLIT cannot be recommended as an alternative to SCIT.

Caveat emptor (buyer beware). Over time, some individuals receiving non-standardized, off-label SLIT may find that their treatment is no more effective than placebo. In such cases, the patient would have been better served to have received FDA-approved SCIT for their allergy treatment with its long and successful track record.

In the final analysis, it is our opinion that although off-label SLIT may be convienent, it is not FDA-approved as an effective treatment for allergy and therefore should not be a recommended treatment by those claiming expertise in allergy. On the other hand, American allergists eagerly look forward to the availability of an effective and reliable SLIT product that has achieved FDA approval.