

Efficacy comparison of multiple-antigen subcutaneous injection immunotherapy and multiple-antigen sublingual immunotherapy

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Abstract

We performed an observational study to determine whether allergen-specific sublingual immunotherapy (SLIT) is as effective as allergen-specific subcutaneous injection immunotherapy (SCIT). Our study population was comprised of 66 patients who had been taking SLIT. Of this group, 36 patients had switched to SLIT after having been treated with SCIT (group I), while the remaining 30 patients had received SLIT only (group II). A questionnaire was used to evaluate the results of treatment. In group I, 33 patients (92%) gave SLIT a favorable rating; 27 of these patients (75%) said it was just as effective as SCIT, and 6 (17%) said it was actually superior (the remaining 3 patients [8%] said that SCIT was better). In group II, 27 of 30 patients (90%) said they had attained symptom relief with SLIT; 21 (70%) said that the relief had been very significant. Overall, 60 of the 66 patients (91%) expressed various degrees of satisfaction with SLIT. We believe that our SLIT protocol, which is based on established guidelines for SCIT administration, is an effective, safe, well-tolerated, and easy-to-use regimen. Future prospective studies of larger groups are clearly indicated.

Introduction

Antigen-specific immunotherapy is a well-established treatment for allergy. Antigen mixtures are typically administered by injection into the subcutaneous tissues. While subcutaneous injection immunotherapy (SCIT) is the standard of practice throughout most of the world, any patient who undergoes this therapy is at risk of experiencing a severe reaction. Reactions can occur during either

the buildup or the maintenance phase of treatment.^{1,2} The potential for complications is greater in brittle patients, such as those with severe asthma; when asthma is not well controlled, SCIT administration may be dangerous because any of the shots might trigger an episode of serious bronchospasm.³

There are other circumstances in which the administration of SCIT is potentially hazardous. For example, patients who take a beta blocker may be less responsive to the emergency medications used to treat anaphylaxis if such a reaction were to occur.³ Given the prevalence of allergic conditions and beta blocker use, such a potentially perilous circumstance would not be unusual. Other, less serious, medical concerns may preclude SCIT, including needle phobia, complaints of recurring local pain from injections, and problems with lymphatic drainage in postmastectomy patients. Finally, several nonmedical considerations may also interfere with a patient's ability to safely and successfully undergo SCIT, including issues of cost, time, transportation, commitment, etc.

Administering immunotherapy via a sublingual route may provide a solution to these problems. Not only is SLIT easy to administer, it has been shown to be safe in both adults and children,^{4,7} and it has been accepted by the World Health Organization⁵ and endorsed by the Allergic Rhinitis and Its Impact on Asthma (ARIA) investigators.⁸ Although SLIT is commonly used in Europe, it is not well established in the United States.

Its safety and convenience notwithstanding, SLIT must still be *effective* in order to serve as a viable alternative to SCIT. In this article, we describe our observational study of the efficacy of our SLIT protocol, which is based on established guidelines for SCIT administration, in a series of patients in a private-practice setting.

Patients and methods

Our data were obtained from a survey questionnaire administered to patients who were undergoing allergen-specific

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SLIT at the solo practice of one of the authors (D.S.). The questionnaire was based on published instruments^{9,10} and adapted to our practice. In obtaining informed consent, we asked patients for permission to disseminate the clinical information we obtained from their questionnaire responses. Patient privacy was maintained at all times in accordance with the mandates of the Health Insurance Portability and Accountability Act (HIPAA).

Patients. After reviewing all the responses, we identified 66 questionnaires that were suitable for analysis. These surveys provided clinical information in addition to demographic data (table 1). In this observational study, the patient groups were not predetermined; rather, they evolved as we responded to patients' needs and preferences. Ultimately, the patients were divided into two groups:

- Group I was made up of 36 patients who were initially treated with SCIT and subsequently switched to SLIT. Reasons for making this change included relocation far from the practice, inability to leave work during office hours, painful local reactions at the injection site, and inability to make weekly copayments.

- Group II was comprised of 30 patients who were treated only with SLIT. This group included more children than did group I, as well as patients who lived far from the office, those who did not want to receive injections, those who did not have time for office visits, and those who could not make weekly copayments.

The patients in this study had been undergoing SLIT for a period of between 3 and 30 months. A total of 58 patients had been receiving treatment for at least 6 months.

Group I transition strategy. The 36 patients in group I who were switched from SCIT began their SLIT regimen with the same concentration of extracts that they had received during their final SCIT dose. Because doses were escalated in small increments (1 drop per week), we anticipated that their transition would be accomplished safely, and it was.

Response to adverse events. In the event of an adverse reaction, we decided to use the same strategy that we would use for a SCIT-induced complication. First, we would reduce the antigen dose to a level that the patient had previously tolerated; we would decide later whether to resume escalation or to maintain this dose. During the initial counseling, we specifically informed patients of this possibility, and we instructed them to contact the office if any problem occurred. (Although severe allergic reactions from SLIT are not expected, all allergy practices should be prepared to deal with such reactions.³)

Outcome measures. Patients in both groups were asked to rate the quality of their treatment on a scale of 1 (complete relief) to 5 (no improvement). Group I patients were

Table 1. Sex and age distribution

Sex	Age (yr)				Subtotal
	≤12	13-21	22-55	≥56	
Group I					
Male	0	3	8	2	13
Female	2	2	14	5	23
Subtotal	2	5	22	7	36
Group II					
Male	5	2	6	1	14
Female	4	2	8	2	16
Subtotal	9	4	4	3	30
Total	11	9	36	10	66

asked to rate SLIT as either *more effective* than SCIT, *just as effective* as SCIT, or *not as effective* as SCIT.

Diagnostic tests. All SLIT patients underwent five-fold intradermal dilution skin testing.^{11,12} Standardized antigens were used for testing and treatment whenever they were available; otherwise, weight/volume antigen extracts (ALK-Abelló, Inc.; Round Rock, Tex.) were used.

Treatment protocol

Preparation of treatment bottles. After we identify the endpoint (i.e., the first reactive wheal in the skin test) for a patient's reactive allergens, we prepare SLIT treatment bottles. The solutions are formulated according to published guidelines¹² with one modification—a 50% increase in both the volume of antigens and the total volume. The resulting 7.5 ml of antigen-diluent mix is easily contained in a 10-ml glass dropper bottle (ALK-Abelló).

The antigens in the SLIT solution are mixed the same way that the antigens in the SCIT solution are mixed. A 50% glycerin solution is used as a diluent. Because glycerin maintains antigen stability and therefore preserves its potency, the SLIT solutions do not require refrigeration (unlike the SCIT vials, which contain no more than 10% glycerin and do require refrigeration).¹³ The volume of each drop is 0.033 ml. In our protocol, 7.5 ml is enough for 6 weeks of treatment.

Administration schedule. Before undergoing any treatment, all patients receive oral and written counseling by an allergy nurse, who provides information about the treatment protocol and its potential complications.

In our protocol, SLIT is administered once daily. The drops are held under the tongue for 20 to 30 seconds and then swallowed.¹⁴ Patients start with 1 drop of the endpoint dose identified by intradermal dilution skin testing. The number of daily drops is increased by 1 every week

Table 2. SLIT escalation protocol*

Bottle A		Bottle B		Bottle C	
Wk	Endpoint (EP)	Wk	EP + 1 (5 × EP)	Wk	EP + 2 (25 × EP)
1	1 drop/day	6	1 drop/day	11	1 drop/day
2	2 drops/day	7	2 drops/day	12	2 drops/day
3	3 drops/day	8	3 drops/day	13	3 drops/day
4	4 drops/day	9	4 drops/day	14	4 drops/day
5	5 drops/day	10	5 drops/day	15	5 drops/day

*SLIT treatment starts at 1 drop from the EP concentration. Escalation continues, as tolerated, raising concentrations five-fold with each subsequent treatment bottle until drawing antigen (if the patient has tolerated it) from the manufacturer's concentrate vial.

to a maximum of 5 drops per day during week 5. Patients then switch to the next bottle (EP + 1), which is five times more concentrated. Again, patients start with 1 drop per day during week 6 and escalate the dose as tolerated to 5 drops per day during week 10. Each subsequent treatment bottle is made five-fold more concentrated, and the cycle is repeated. The treatment dose is advanced until the patient reaches the maximum possible dose (5 drops from the bottle made from concentrates) or the maximum tolerated dose (table 2).

When patients on maintenance dosing receive a new bottle, only a quick reprogression is required. They start with 1 drop on day 1 and increase the dose by 1 drop per day until they reach the number of drops of the maintenance dose (5 drops on day 5 for uneventful dose escalation).

(During the early days of our study, patients were required to be in the office when taking the first dose from each new bottle. However, we relaxed this rule once we became assured of the safety of this treatment modality. Eventually, we required patients to be in the office only for the first drop of the first treatment bottle, and we continue this practice to this day.)

Amount of antigen delivered. According to our protocol, the first sublingual dose is smaller (0.033 ml) than the subcutaneous dose (0.05 ml). However, because it is taken every day, the weekly dose of SLIT is larger (0.23 ml). (The amount of antigen administered over the successive weeks, using one antigen as an example, is shown in table 3, where we compare the doses of antigen given by SCIT and SLIT in the case of a hypothetical patient allergic to *Dermatophagoides pteronyssinus* whose endpoint is on the #3 dilution. The lot of standardized dust mite *D pteronyssinus* at 10,000 AU/ml used in this example contains 68 µg/ml of Der 1 and 71 µg/ml of Der 2 antigens. The concentration of antigen in both the SCIT and SLIT initial treatment vial/bottle is the same—80 AU/ml—but note that the amount of antigen administered by SLIT by the end of week 10 [464.0 AU] is more than 10 times the amount of antigen administered by SCIT at the end of the

same week [40.0 AU], and more than double the amount of antigen administered by SCIT at the end of the second vial on week 20 [200.0 AU].)

Results

Group I ratings. Of the 36 patients who switched from SCIT to SLIT, 27 (75%) said it was *just as effective* as SCIT, and 6 (17%) said it was *actually more effective* (table 4). Only 3 patients (8%) said SLIT was *not as effective*. In all, 33 patients (92%) were satisfied with their switch to SLIT.

On the 5-point scale, 23 patients (64%) gave SLIT a grade of 1 or 2, while only 5 patients (14%) gave it a grade of 4 or 5. Only 3 patients (8%) said it was not effective at all (table 5).

Group II ratings. Of the 30 patients who were treated only with SLIT, 21 (70%) gave it a grade of 1 or 2, and 5 (17%) gave it a grade of 4 or 5 (table 5). Three patients (10%) said that SLIT had not been effective at all. A review of the charts of these 3 patients revealed that they had been treated for only a relatively short time: 1 patient for 6 months and the other 2 patients for 4 months.

Adverse events. No severe complications occurred during the study period. Ten minor adverse events occurred in 9 of the 66 patients (14%). Three patients complained of pruritus—of the lips in 2 cases and the face in 1. Two patients had a transient skin rash; 1 of them also developed a sensation of throat tightness, but it did not require an office evaluation. Two patients reported headaches, 1 patient felt drowsy after taking SLIT, and 1 patient complained about the taste of the drops.

The adverse events in 6 of these patients were managed by lowering the dose of immunotherapy to the previously tolerated level and administering standard allergy medication as needed. No medications other than an antihistamine or a leukotriene receptor antagonist were needed, and there was no interruption of treatment.

One of the patients who had developed headaches did not improve after reducing the number of SLIT drops.

Table 3. Comparison of the amounts of single antigen delivered weekly for the treatment of allergy to house dust mite (*Dermatophagoides pteronyssinus*) with SCIT and SLIT**SCIT, beginning at #3 endpoint (EP) and advancing to the end of the next vial (EP + 1 vial)**

EP vial (D pter #3 at 80 AU/ml*)			EP + 1 vial (D pter #2 at 400 AU/ml)		
Wk	Volume (ml)	Antigen (AU)	Wk	Volume (ml)	Antigen (AU)
1	0.05	4.0	11	0.05	20.0
2	0.10	8.0	12	0.10	40.0
3	0.15	12.0	13	0.15	60.0
4	0.20	16.0	14	0.20	80.0
5	0.25	20.0	15	0.25	100.0
6	0.30	24.0	16	0.30	120.0
7	0.35	28.0	17	0.35	140.0
8	0.40	32.0	18	0.40	160.0
9	0.45	36.0	19	0.45	180.0
10	0.50	40.0	20	0.50	200.0

SLIT, beginning at #3 EP and advancing to the end of the next bottle (EP + 1 bottle)

EP bottle (D pter #3 at 80 AU/ml)			EP + 1 bottle (D pter #2 at 400 AU/ml)		
Wk	Volume (ml)	Antigen (AU)	Wk	Volume (ml)	Antigen (AU)
1	0.23	18.40	6	0.23	92.40
2	0.46	36.96	7	0.46	184.00
3	0.69	55.44	8	0.69	276.00
4	0.92	73.92	9	0.92	368.00
5	1.16	92.40	10	1.16	464.00

*AU = allergenic (allergy) units.

After reformulation to the next weaker dilution failed to solve the problem, the patient resumed SCIT (which had previously been well tolerated), and the headaches disappeared. The remaining 2 patients discontinued immunotherapy.

Discussion

To the best of our knowledge, this is the first contemporary attempt to standardize sublingual treatment. We endeavored to devise a protocol for SLIT administration that is safe, well tolerated, easy to understand and, most important, effective. We were pleasantly surprised, then, to find that not only did most patients in group I find SLIT and SCIT equally efficacious, but that a substantial percentage (17%) believed that SLIT was actually superior to SCIT. Certainly, this is a small sample upon which to base a conclusion, but it is an observation that should stimulate further research. Overall self-rated efficacy was good or excellent.

Several protocols for SLIT administration have been

published in the literature. We decided on daily administration¹⁵ to optimize patient compliance. Daily administration also allows for the delivery of a higher total dose while minimizing the risk of adverse oral reactions secondary to the administration of multiple doses.¹⁶

We knew that year-round administration of SCIT at the maximum tolerated dose is efficacious and leads to long-term relief of allergy symptoms.¹⁷ Therefore, we assumed that administering SLIT in a similar fashion would lead to similar results. We chose quantitative testing with five-fold intradermal dilution skin testing as a

Table 4. Evaluation of the efficacy of SLIT compared with SCIT by the patients in group I (n = 36)

	No. of patients (%)
More effective than SCIT	6 (17)
Equally effective as SCIT	27 (75)
Less effective than SCIT	3 (8)

Table 5. Patients' ratings of the effectiveness of SLIT on a scale of 1 (complete relief) to 5 (no improvement)

	n (%)				
Grade	1	2	3	4	5
Group I (n = 36)	9 (25)	14 (39)	8 (22)	2 (6)	3 (8)
Group II (n = 30)	10 (33)	11 (37)	4 (13)	2 (7)	3 (10)
Total (N = 66)	19 (29)	25 (38)	12 (18)	4 (6)	6 (9)

very conservative method of identifying starting treatment doses for SLIT.¹⁸ This approach was validated by the high degree of efficacy and the very low incidence of adverse events we observed.

One potential disadvantage of SLIT is that there is no local reaction at the injection site to alert the physician to the possibility of a systemic reaction. However, knowing that the potential for a serious adverse reaction to SLIT is low (as was confirmed in our series), we were prepared to use the adverse event itself as a warning to decrease the immunotherapy dose. Also, because our protocol provided for a well-controlled dose escalation, we expected that if an adverse event were to occur, we would be able to diagnose it in a timely fashion. In fact, complications in this series were mild and were safely managed by dosage adjustment, with almost no need for interrupting treatment.

The results of our observational study strongly suggest that a larger, blinded study is indicated. Ideally, such a study would be a prospective investigation that would include a SCIT-only group, a SLIT-only group, and a group that had switched from SCIT to SLIT. Outcomes would be measured with validated instruments, such as the one proposed by Juniper and Guyatt,⁹ or with other, better known, instruments (e.g., SNOT-20).¹⁰ Such a study should include not only subjective parameters but objective measurements of nasal resistance, peak airflow, and lung capacity.

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