

Allergy immunotherapy for inhalant allergens: Strategies to improve efficacy

Harold S. Nelson, M.D.

ABSTRACT

Background: Allergy immunotherapy (AIT), both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), is an effective and safe treatment for allergic rhinitis and allergic asthma due to inhalant allergens. However, there are many variables in how it is administered.

Objective: To review the evidence that suggests the optimum practices to enhance the efficacy of AIT.

Methods: Articles that reported the results of various approaches to the practice of AIT and evidence-based guidelines were consulted for guidance on what approaches would enhance the efficacy of AIT.

Results: Evidence is presented that supports optimum dosing for SCIT, a discussion of dosing with liquid SLIT, the management of the patient who is polyallergic, considerations in mixing allergen extracts, advantages and disadvantages of different up-dosing regimens with SCIT, the optimum duration of AIT, the comparative efficacy of SCIT and SLIT, and improving adherence to AIT. Also reviewed were two approaches, the use of adjuvants and of alternative routes of administration of currently available extracts, which may be useful in the future after further studies have defined their effectiveness.

Conclusion: Although there is still controversy about some aspects of AIT, there is literature to support approaches that enhance the efficacy of both SCIT and SLIT.

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Allergy immunotherapy (AIT) has been shown in meta-analyses to reduce the symptoms and medication requirements for both allergic rhinitis and allergic asthma when administered subcutaneously (subcutaneous immunotherapy [SCIT])¹ or sublingually (sublingual immunotherapy [SLIT]).^{1,2} AIT, in addition, modifies the immunologic abnormalities that underlie the susceptibility to allergic sensitization, which results in a response to the administered allergen closer to that observed in those who are not allergic.³ This normalization of the immune response is reflected, clinically, in a reduced risk of patients with allergic rhinitis to develop asthma^{4,5} and in persisting clinical improvement that can persist for years after the discontinuation of treatment.⁶ Despite the benefits that AIT offers, it is not without its drawbacks. Both approaches to AIT involve long courses of treatment to achieve persisting benefit, and the rate that patients do not complete the treatment is high.⁷ Furthermore, particularly with SCIT, there are concerns with regard to the occurrence of systemic reactions (SR). With the currently available allergen preparations, these drawbacks cannot be eliminated.

However, there are variables in the manner in which AIT is practiced that may increase or decrease its efficacy. This article reviewed the evidence, when available, that suggests the optimum practices to enhance the efficacy of AIT.

IMPROVING THE EFFICACY OF AIT

There are a number of steps in the preparation and administration of AIT treatment that may affect the clinical outcome (see Table 1).

Dosing

Among the variables in the practice of AIT, one that shows great variability and yet is of crucial importance to its efficacy is that of dosing. Reliable determination of proper dosing requires performance of randomized, double-blind, placebo controlled (RDBPC) trials. Expressing the effective dose in universally understandable units presents a problem. In the United States, for those extracts that are standardized, the U.S. Food and Drug Administration (FDA) has defined expressions of potency that reflect either the overall allergenic potency determined by titrated intradermal skin testing (for grasses and house-dust mites [HDM]) or the content of the major allergen (for cat and ragweed). This potency is then expressed in allergy units, bioequivalent allergy units, or FDA Amb a 1 units plus the weight/volume of extracted material (for short ragweed). For the nonstandardized extracts, potency is expressed as weight/volume or protein nitrogen units,

From the Division of Allergy/Immunology, Department of Medicine, National Jewish Health, Denver, Colorado

H.S. Nelson formerly served as an adviser to Merck and ALK

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Address correspondence to Harold S. Nelson, M.D., Division of Allergy/Immunology, Department of Medicine, National Jewish Health, 1400 Jackson St. Denver, CO 80206

E-mail address: nelsonh@njhealth.org

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Table 1 Variables that affect the efficacy of allergy immunotherapy

1. Dosing
2. Management of the patient with polyallergy
3. Mixing allergen extracts
4. Use of adjuvants
5. Administration regimens (standard, cluster, rush)
6. Preseasonal vs perennial administration
7. Duration of treatment
8. Efficacy of subcutaneous immunotherapy vs sublingual immunotherapy
9. Adherence
10. Alternative routes of administration of currently available extracts (intralymphatic, epicutaneous)

Table 2 Effective and suboptimal doses for subcutaneous immunotherapy

Allergen	Study	Effective Dose	Suboptimal Dose
House-dust mites	Haugaard <i>et al.</i> ⁹	7.0 µg Der p I	0.7 µg Der p 1
	Olsen <i>et al.</i> ¹⁰	7.0 µg Der p I, 10.0 µg Der f I	
Cat dander	Varney <i>et al.</i> ¹¹	15 µg Fel d I	
	Ewbank <i>et al.</i> ¹²	15 µg Fel d 1	3 µg Fel d 1
	Nanda <i>et al.</i> ¹³	15 µg Fel d 1	3 µg Fel d 1
Dog dander	Lent <i>et al.</i> ¹⁴	15 µg Can f 1	3 µg Can f 1
Grass	Dolz <i>et al.</i> ¹⁵	15 µg Dac q 5 + Lol p 5 + Phl p 5	
	Frew <i>et al.</i> ¹⁶	20 µg Phl p 5	2 µg Phl p 5
Short ragweed	Van Meter <i>et al.</i> ¹⁷	11. µg Amb a I	
	Creticos <i>et al.</i> ¹⁸	12.4 µg Amb a I	0.6 µg Amb a 1
	Furin <i>et al.</i> ¹⁹	24 µg Amb a 1	2 µg Amb a 1
Birch	Khinchi <i>et al.</i> ²⁰	3.28 µg Bet v 1	
	Pauli <i>et al.</i> ²¹	15 µg Bet v 1	
<i>Alternaria</i>	Horst <i>et al.</i> ²²	1.6 µg Alt a 1	
	Kuna <i>et al.</i> ²³	8 µg Alt a 1	

neither of which correlates well with allergenic potency. In Europe, each extract manufacturer standardizes their extracts against internal standards and uses different expressions of potency (*e.g.*, Standardized Quality (SQ), Index of Reactivity (IR)).⁸ At present, the only solution to this use of many nonconvertible expressions of potency is to express extract dosing in terms of the amount of one or more of the major allergens administered at maintenance dosing. Some representative RDBPC SCIT trials that reported doses that have produced clinically significant improvement and, in some cases, doses that have proven less or totally ineffective as well are listed in Table 2.

SCIT Dosing. To apply this information on optimum dosing to treating patients, it is necessary to know the major allergen content of the available extracts. Although this information is not readily available, many extract manufacturers have the ability to measure major allergen content. Information from one company on the mean and range of major allergen

content of FDA standardized and some nonstandardized U.S. extracts are provided in Table 3. This knowledge of the effective doses and of the range of major allergen content in U.S. extracts were used to formulate the recommendations for dosing in the Immunotherapy Practice Parameter Third Update²⁸ (Practice Parameters) (Table 4). However, there are multiple proteins in each allergen extract that elicit immunoglobulin E responses in some patients and often several that sensitize >50% of patients, as, for instance, Can f 1, Can f 4, and Can f 5 of dog²⁹ and Der p 1, Der p 2, Der p 4, Der p 5, and Der p 23 of *Dermatophagoides pteronyssinus*.³⁰ Furthermore, the allergen profile of extracts varies with the type of natural material from which it is extracted.²⁹ Therefore, it must be appreciated that these are only rough guidelines to dosing, with more-complete information on allergen content, it is hoped, to come in the future.

How do the prescribing patterns of U.S. allergists compare with the recommendations in the Practice Parameters?²⁸ An online survey of members of the

Table 3 Representative values for major allergen content of U.S. standardized extracts*

Allergen Extract	Expressed Potency of Concentrate	Major Allergen	Mean Content Major Allergen, $\mu\text{g/mL}^*$	Minimum Content Major Allergen $\mu\text{g/mL}^{\#}$	Maximum Content Major Allergen $\mu\text{g/mL}^{\#}$
Timothy	100,000 BAU/mL	Phl p 5	620	354	1336
Kentucky bluegrass	100,000 BAU/mL	Poa p 5	270	190	330
Bermuda grass	10,000 BAU/mL	Cyn d 1	200	125	449
Short ragweed	1:10 w/v	Amb a 1	500	335	763
<i>Dermatophagoides pteronyssius</i>	10,000 AU/mL	Der p 1; Der p 2	62; 63	38; 28	98; 104
<i>Dermatophagoides farinae</i>	10,000 AU/mL	Der f 1; Der f 2	73; 85	21; 51	140; 140
Cat dander	10,000 BAU/mL	Fel d 1	40	26	44
Dog dander	w/v or PNU	Can f 1	5.4	0.5	7.2
AP dog [§]	w/v	Can f 1	140 [§]	90 [§]	225 [§]
<i>Alternaria alternata</i> [¶]	1:10 w/v and 1:20 w/v	Alt a 1	1.4	<0.01	6.1
<i>Alternaria alternata</i>	1:5 w/v to 1:20 w/v	Alt a 1	0.98	0.04	2.75
<i>Aspergillus fumigatus</i> [¶]	1:10 w/v and 1:20 w/v	Asp f 1	16.3	4.0	64
German cockroach**	1:10 w/v and 1:20 w/v	Bla g 1	44		

BAU = Bioequivalent allergy unit; AU = allergy unit; PNU = protein nitrogen units; AP = acetone precipitated.

*Based on multiple lots of extracts manufactured by a single manufacturer between 2001 and 2011 (data provided by G. Plunket, Ph.D., ALK-Abello' Inc. Round Rock, Texas).

[#]Based on multiple lots of extract from multiple U.S. companies (data provided by G. Plunket, Ph.D., ALK-Abello' Inc. Round Rock, Texas).

[§]Hollister-Stier Laboratories, Spokane, Washington (assays performed by Hollister-Stier Laboratories, Spokane, Washington).

[¶]From Ref. 24.

^{||}From Ref. 25.

**From Refs. 26 and 27.

American Academy of Allergy, Asthma and Immunology (AAAAI) resulted in 1201 responses, 90% from North American allergists. When queried with regard to maintenance dosing for four standardized allergens, the responses indicated that the physicians dosed below the Practice Parameter²⁸ recommended range, from 9.7% for grass extract up to 19% for cat extract.³¹ It is clear that FDA standardized extracts vary greatly in their major allergen content, with pollen extracts regularly being more potent than those from HDMs and cats. There is even greater variability in the major allergen content of nonstandardized extracts. The nonstandardized pollen extracts tend to fall within a similar range of potency as the standardized pollens, but most dog extracts and extracts of fungi and cockroaches are quite low in major allergen content (Table 3), which makes their use for effective AIT questionable. There are two exceptions: (1) an acetone-precipitated dog extract is much higher in content of the major allergen of dog, Can d 1, than other dog extracts tested^{14,32}; and (2) low doses of Alt a 1 that have been effective in a RDBPC

trial, which suggests that effective doses may be attainable with some U.S. *Alternaria* extracts.²²

SLIT Dosing. The development programs for tablets for SLIT included studies that determined the safe upper doses for timothy³³ and short ragweed,³⁴ and, then, within the tolerated range, the most effective dose was determined for timothy (15 μg Phl p 5)³⁵ a 5-grass mix (25- μg group 5 allergens),³⁶ short ragweed (12 μg Amb a 1),³⁷ and HDMs (15 μg group 1 and 15 μg group 2 in one tablet,³⁸ and 16 μg group 1 and 58 μg group 2 in the other tablet³⁹). Therefore, there is no ambiguity with regard to proper dosing with SLIT tablets.

Almost no dose-ranging studies have been performed with SLIT liquid preparations and, because of the difference in volume in which they are dispensed (tablet, no diluent; and drops up to 0.5 mL), it cannot be assumed that an effective dose by tablet will be equally effective in a liquid vehicle. Doses for liquid

Table 4 Recommended dosing based on major allergen content of U.S. extracts

Extract	Major Allergen	Effective Dose, μ g	Mean Major Allergen Content U.S. Extracts	Recommended Dose Based on Mean Major Allergen Content	Recommended Dose Immunotherapy*
<i>Dermatophagoides pteronyssinus</i>	Der p 1	7	62 μ g/mL 10,000 AU	1129 BAU	500–2000 AU
<i>Dermatophagoides farinae</i>	Der f 1	10	73 μ g/mL 10,000 AU	1370 BAU	500–2000 AU
Cat hair or pelt	Fel d 1	15	40 μ g/mL 10,000 BAU	3750 BAU	1000–4000 BAU
Timothy Grass	Phl p 5	20	620 μ g/mL 100,000 BAU	3175 BAU	1000–4000 BAU
Bermuda grass	Cyn d 1	N.D.	200 μ g/mL 10,000 BAU	N.D.	300–1500 BAU
Short ragweed	Amb a 1	12	525 μ g/mL 1:10 (100,000 BAU)	2286 BAU	1000–4000 BAU
Dog dander	Can f 1	15	AP dog 140 μ g/mL 1:100 w/v	0.1 mL 1:100 w/v	15 μ g Can f 1

BAU = Bioequivalent allergy unit; AU = allergy unit; N.D. = not done.

*From Ref. 28.

SLIT that are offered commercially in Europe show great variability and often are lacking suitable studies to prove that they are effective.⁴⁰ An analysis of the potency of four allergen extracts from each of three European companies showed a great variation in allergen content (Table 5). In this table, the monthly SLIT dose recommended by the manufacturer is expressed as a multiple of the monthly maintenance SCIT dose recommended in the Practice Parameters.²⁸ Large RDBPC trials that used SLIT liquid also showed a wide range of dosing (Table 6). In most studies, only one dose was administered, which made it difficult to determine whether the doses reported to be effective were also necessary. It was shown that daily SLIT administration produced greater improvement than a larger total dose given only three times weekly.⁴⁷ Accordingly, only studies with daily dosing are included in Table 6.

In summary, effective SCIT doses have been determined for the FDA standardized and some nonstandardized U.S. extracts.²⁸ Guidelines for using this information are presented in Table 4. Tablets for grass, ragweed, and HDMs are FDA approved, with a single dose that was demonstrated to be safe and effective in numerous large trials.¹ Appropriate studies are lacking to determine optimum dosing of most liquid extracts administered sublingually. Commercially available SLIT liquid preparations in Europe differ markedly in allergen content and often have no supporting evidence of clinical efficacy. Studies that report effective doses have been published with a number of allergen extracts, but the doses used in some of these studies are quite high, which make them very expensive to use.

MANAGEMENT OF PATIENTS WHO ARE POLYALLERGIC

Patients who are sensitized to multiple allergens respond just as well to AIT with a single allergen as do patients monosensitized with the same allergen.⁴⁸ More controversial is the approach to SCIT in the patients who have multiple clinically relevant allergies. In Europe, the common practice is to treat with only the one or possibly two allergens that are considered clinically most important.⁴⁹ In the United States, the common practice is to use, in SCIT, a mixture of all clinically relevant allergens. This practice is supported by several old, small, yet quite convincing studies.⁵⁰

With SLIT, the monoallergen tablets preclude mixtures; however, it has been shown that two tablets can be taken simultaneous after 2 weeks of taking one tablet in the morning and the other in the evening.⁵¹ Although that study was designed only to show safety not efficacy, an earlier study in which patients sensitized to grass and birch who received SLIT with liquid extracts of both grass and birch had clinical improvement during the relevant pollen season equal to patients who receive SLIT with a single allergen.⁵² Similar clinical results plus promotion of Forkhead box P3 (Fox p 3)⁺ regulatory T cells were observed with dual administration of timothy and HDM extracts.⁵³ SLIT with more than two allergens has been addressed in only one study.⁵⁴ The response to timothy mixed with nine other pollen extracts was not as good as when the same dose of timothy was given combined only with diluent, even though the dose and dilution of timothy were the same in both groups. Until there is evidence for the effectiveness of mixtures of more than

Table 5 Monthly dosing of commercial European SLIT solutions relative to monthly recommended dosing for SCIT in the immunotherapy Practice Parameters Third Update*

Extract Manufacturer	<i>Dermatophagoides pteronyssinus</i>	Cat Dander	Timothy	Ragweed
Company 1				
Monthly dose	1440 AU	4.8 Fel d 1-FDA units	41,550 BAU [#]	378 Amb a 1-FDA units
Multiples of recommended SCIT dose	1	1	21	42
Company 2				
Monthly dose	3180 AU	50.4 Fel d 1-FDA units	113,250 BAU	615 Amb a 1-FDA units
Multiples of recommended SCIT dose	3	13	57	68
Stallergenes Greer Antony, France				
Monthly dose	15,870 AU [#]	117 Fel d 1-FDA units	187,200 BAU [#]	2,136 Amb a 1 FDA units [#]
Multiples of recommended SCIT dose	16	31	94	237

SLIT = Sublingual immunotherapy; SCIT = subcutaneous immunotherapy; FDA = U.S. Food and Drug Administration.

*From Ref. 40.

[#]Have studies showing efficacy.

two allergens administered sublingually, it is recommended that this practice be avoided.

If SCIT with a multiallergen mixture is to be used, then there are certain considerations in addition to dosing. The first is to consider cross-allergenicity to avoid administering an excess amount of one cross-reacting group of allergens. This applies particularly to the northern pasture grasses; the weed families; and certain groups of related trees, such as cedars and junipers and cottonwood, poplar, and aspen. It is recommended, in each of these instances, that either the locally predominant species be used or a mixture be prepared of several cross-reacting extracts and the mixture then be dosed as if it were a single allergen.⁵⁵ The second consideration is that fungal and cockroach extracts have been shown to have strong proteolytic activity that can degrade extracts of pollens, danders, and HDMs.^{56,57} This proteolytic activity can also cause autodigestion of the relevant allergens in the cockroach and fungal extracts, so only 50% glycerin extracts of these classes of allergens should be used.²⁶ Although 50% glycerin may be at least partially protective against this proteolytic activity, it is generally recommended that fungal and cockroach extracts not be combined with pollen, animal dander, or HDM extracts^{56,57} and that fungal and cockroach extracts not be combined.⁵⁸

In summary, there is disagreement with regard to the efficacy of multiallergen SCIT, but U.S. allergists regularly use this approach, with support from some old,

but well-conducted studies.⁵⁰ If multiallergen SCIT is elected, then consideration should be given to cross-reactive allergens to avoid allergen imbalance, and mixture of fungi and insect extracts with high proteolytic activity with pollen, dander, or mite extracts is to be avoided. There, as yet, is no evidence to support the use of combinations of more than two allergens by SLIT.

USE OF ADJUVANTS IN AIT

There is not yet enough evidence to support the use of adjuvants in AIT. Early approaches to stimulating toll-like receptors with Cytosine-phosphodiester-guanine (CpG) motifs bound to an allergen were abandoned.⁵⁹ Extracts that contain a toll-like receptor agonist, Monophosphoryl Lipid A (MPL), are available in Europe but not in the United States.⁶⁰ There, however, are some intriguing studies that indicate that the use of adjuvants could become appropriate, at least in selected patients. In a retrospective analysis of vitamin D levels in children who participated in an AIT (SCIT) study, those children with higher serum 25(OH)D levels experienced more significant reduction in asthma symptom score and had greater corticosteroid dose reduction.⁶¹ The better response to AIT correlated with having 25(OH)D levels in the normal range (≥ 30 ng/mL). These same investigators then conducted a study in 100 children who were receiving daily SLIT grass plus placebo, 1000 IU vitamin D, or the probiotic *Lactobacillus rhamnosus* GG compared with an untreated

Table 6 Studies that demonstrate effective daily doses with liquid SLIT

Study, y	No. Performed	Preparation (dosing vs monthly SCIT)	Duration	Primary Outcome	Secondary Outcome	TRAE
Studies with ragweed Skoner <i>et al.</i> , ⁴¹ 2010	115/18–50 y	Short ragweed liquid extract that contained 4.8 µg Amb a 1 or 48 µg Amb a 1; (12X and 120X)	1-Day 3–4 step up-dosing; 8–10 wk pre-seasonal	Daily symptom score; 15% N.S.	Medication score: $p = 0.048$; ANCOV: $p = 0.05$ high dose	Oral-mucosal adverse effects placebo 0%, medium dose 13%, high dose 11%
Creticos <i>et al.</i> , ⁴² 2014	429/adults	Short ragweed liquid; 50 µg Amb a 1 (125X)	8–16 wk pre-seasonal	TCS during peak ragweed pollen season 20%	None	TRAEs; active, 12%; placebo, 3%; no SRs reported
Studies performed with grass Ott <i>et al.</i> , ⁴³ 2009	183/8–65 y	5-grass liquid daily (equivalent to 21 µg Phl p 5) (25X)	During pollen season only for 3 y	S/M score significantly reduced all 3 seasons and $p = 0.052$ 1 y after stopping	IgG4 increased in active group; IgE increased, then declined	No severe SRs or anaphylactic reactions
Wahn <i>et al.</i> , ⁴⁴ 2012	207/4–12 y	6-Grass liquid; 40 µg group 5 daily(48X)	Jan through Aug	S/M score AUC reduced 21% vs placebo	IgG4 increased in active group	TRAEs active, 76%; placebo 33%
Studies performed with other allergens Pfaar <i>et al.</i> , ⁴⁵ 2019	357/adults	Birch liquid; 100 µg Bet v 1 daily (214X)	3–6 mo pre-seasonal	32% Reduction in S/M score vs placebo	VAS and RQLQ favored active	2 serious TRAEs in the active group
Wang <i>et al.</i> , ⁴⁶ 2014	484/16–50 y	300 IR daily that contained 28 µg Der p 1; 50 µg Der f 1 (275X)	1 Year	No difference in mild asthma; in moderate asthma well and totally controlled asthma significantly better in the active group	In moderate asthma only, ACQ and ICS reduction significantly better in active group	No serious TRAEs

SLIT = Sublingual immunotherapy; SCIT = subcutaneous immunotherapy; TRAE = treatment-related adverse effect; N.S. = not significant; ANCOVA = Analysis of Covariance; SR = systemic reactions; TCS = total combined score; S/M = symptom/medication; IgG4 = immunoglobulin G4; AUC = area under the curve; VAS = visual analog scale; RQLQ = rhinitis quality of life questionnaire; IR = index of reactivity; ACQ = asthma control questionnaire; ICS = inhaled corticosteroids.

control.⁶² The trend for the symptom/medication scores (higher scores associated with less well-controlled allergic rhinitis (AR)) was control > SLIT–placebo > SLIT–vitamin D > SLIT–probiotic, was highly significant by using the Kruskal Wallis test ($p < 0.001$). The greatest difference was between the controls and the three groups treated with SLIT.

Subsequently, two studies have been reported from China. In one study, patients with HDM induced AR received 6 months of HDM SCIT alone, with added probiotic (*Clostridium butyricum*), *C. butyricum* alone, or placebo.⁶³ The *C. butyricum* alone and placebo were without effect, HDM SCIT alone produced improvement in symptom/medication scores that were lost within a month of stopping SCIT. The combination of SCIT plus *C. butyricum* produced greater improvement in symptom/medication scores, plus suppression of T-helper type 2 cytokines and skin-prick test, and increased frequency of regulatory B cells. All these favorable responses persisted 6 months after SCIT was discontinued. In the other study, patients with AR and HDM sensitivity, who, as a whole, had insufficient serum levels of vitamin D, when administered HDM SCIT or 2000 IU vitamin D daily had improved AR symptoms, reduced serum levels of specific immunoglobulin E and T-helper type 2 cytokines, and increased interleukin 10 in peripheral B cells.⁶⁴ However, improvements in all these outcomes were greatest in patients who received both SCIT and vitamin D. If these results are confirmed by further studies, then they suggest a role for both vitamin D supplementation in patients with insufficient serum levels and a search for probiotics with appropriate adjuvant activity.

ADMINISTRATION REGIMENS

The customary practice with SCIT is to build up to a maintenance dose with a series of weekly injections. The starting dose and the rapidity of build-up differ among patients and practitioners. An example is the schedule in the Practice Parameters²⁸ that starts at 0.05 mL of a 1:1000 v/v dilution of the maintenance vial and proceeds to 0.5 of the maintenance vial (1:1 v/v), with 30 incremental increases. However, in patients without risk factors for an SR, the dose can begin at 0.05 mL of a 1:100 v/v dilution of the maintenance vial and increase to 0.5 mL of the maintenance concentration in 18 incremental injections, which saves considerable cost and inconvenience for the patient.^{12–14}

Two approaches to even more rapidly achieving maintenance are available: (1) rush, in which multiple injections are given on a single or consecutive days, and (2) cluster, in which, initially, more than one injection is given per visit, but the visits are not on consecutive days. The advantage of both is in more rapidly attaining the maintenance dose and in achieving

clinical improvement,^{65,66} and, perhaps, better patient adherence to AIT. Rush protocols have always been associated with an increased risk for SRs, even with premedication.^{67,68} Cluster, also, is suggested to be associated with an increased risk for SRs.^{69,70} In the national surveillance study on allergen immunotherapy, practices that used cluster reported an increased risk of SRs, including grade 3 and grade 4.⁶⁹ A high rate of SRs (10.6%), including both grade 3 and 4 reactions was reported from a single clinical practice (Table 7).⁷⁰ However, an even larger private practice reported no increase in the rate of SRs with cluster compared with conventional build-up⁷¹ and retrospective and prospective studies from Europe that compared head-to-head cluster and conventional regimens showed earlier improvement in clinical symptoms without increased rate or severity of SRs with cluster (Table 7).^{65,66,72}

In conclusion, rush immunotherapy is associated with a high risk of SRs, even with premedication. It should be reserved for special circumstances that justify the increased risk. Cluster, however, has not been documented in any prospective study as carrying an increased risk of SRs. It has, however, the advantage of fewer overall injection visits and more-rapid achievement of symptom improvement. It should be considered a safe alternative to conventional dosing. These considerations do not apply to SLIT, when dosing is routinely initiated with the maintenance dose.

PRECLOSEASONAL VERSUS PERENNIAL ADMINISTRATION

Although SCIT was initially used preseasonally, a number of advantages to administering SCIT perennially were perceived: perennial treatment made unnecessary the series of weekly preseasonal injections, distributed the patient load better throughout the year, made contact with patients to begin preseasonal injections unnecessary, and, because most patients were on multiple allergen injections, they would be receiving injections most, if not all the year, anyway, to cover the varying seasons for each allergen.

Because SLIT presently involves the administration of only one or two allergens and no build-up is required with the SLIT tablets, the question of precloseasonal versus perennial administration again arises, especially in view of the considerable cost saving between roughly 6 instead of 12 months of treatment. The question is made further relevant because one of the approved grass SLIT tablets (5-grass tablet) was developed as a precloseasonal treatment,⁷³ whereas the other (timothy tablet), once initiated, was continued on a perennial basis.⁷⁴ Although there has been no head-to-head study of the two grass SLIT tablets, 3 years of treatment with each resulted in persisting improvement for 2 years after

Table 7 SRs with cluster immunotherapy

Study	No. Subjects	Premedication	SRs, %			
			Per Injection	Per Patient	Grade 3	Grade 4
Copenhaver <i>et al.</i> ⁷⁰						
Cluster	441	Most	Not reported	10.9	10.6	2.1
Winslow <i>et al.</i> ⁷¹						
Conventional	9229		0.01	2.8	13	3
Cluster	2576	Prednisone , AH, and LTRA	0.06	2.5	11	1
Quiralte <i>et al.</i> ⁷²						
Conventional	319		0.7	4.4	0	0
Cluster	339	Not stated	0.2	1.5	0	0
Tabar <i>et al.</i> ⁶⁵						
Conventional	119		0.22		0	0
Cluster	120	Not stated	No difference		0	0
Zhang <i>et al.</i> ⁶⁶						
Conventional	48		0.9	6.8	0	0
Cluster	48	Not stated	1.0	6.7	0	0

SR = Systemic reaction; AH = antihistamines; LTRA = Leukotriene receptor antagonists.

treatment discontinuation.^{73,74} A relevant 2-year study was conducted in 60 children sensitive only to grass with allergic rhinitis and with or without asthma.⁷⁵ Both groups received preseasonal treatment with SLIT grass tablets before the first pollen season, then one group was on placebo until the next course of pre-seasonal treatment, whereas the other was on continuous treatment through the next grass pollen season. In the second grass pollen season, there were no significant differences between the two regimens in total symptom score, medication, asthma scores, pulmonary function tests, or fractional exhaled nitric oxide levels. However, in an RDBPC study of grass SCIT, there was no difference in efficacy the first year but, in the second pollen season, symptom/medication scores were reduced 59% with continuous versus 45% with pre-seasonal SCIT ($p=0.063$) and, in the third pollen season, reduction in symptom/medication scores were 73% and 56%, respectively ($p = 0.012$).⁷⁶ Whether the difference between these two study results is due to differences in subjects, route of administration, or duration of treatment is unclear. In conclusion, perennial treatment is favored for SCIT. For SLIT, it is not clear whether there is an advantage for perennial as opposed to pre-seasonal treatment for seasonal allergies.

Duration of AIT

The recommended duration for AIT, both SCIT^{6,77,78} and SLIT,^{73,74,79} is usually 3 to 5 years. Two studies compared the results of 3 versus 5 years of SCIT treatment. In one study, there was an additional 30% improvement in rhinitis scores with 2 additional years of treatment,⁸⁰ but the other study, in children with asthma, found little additional benefit from the 2 extra

years in reduction in inhaled corticosteroid dose, rhinitis, or asthma symptoms, quality of life, or methacholine sensitivity.⁸¹ An open study of SLIT with HDM extract found similar clinical improvement after 3, 4, or 5 years of treatment but a more rapid relapse (after a mean of 7 years) with 3 years of treatment than after 4 or 5 years (relapse after a mean of 8 years).⁷⁹ Their recommendation, for the conditions of their study, was to treat for 4 years.⁷⁹

A recent study addressed the question of whether 3 years was sufficient but perhaps not necessary.⁸² Subjects with grass allergy were treated with approved doses of timothy SCIT, timothy SLIT tablet, or placebo for 2 years, then followed up for 1 year to see if improvement persisted. The primary outcome, symptoms on allergen nasal challenge, improved significantly compared with placebo in both active groups after 2 years, but the improvement was no longer significant 1 year off treatment. The results of these studies indicate that a minimum duration of treatment should be 3 years. If a patient is virtually asymptomatic after 3 years, it may be appropriate to stop AIT, but if these are still bothersome symptoms after 3 years, 1 or 2 more years of treatment may be worthwhile.

Comparison of SCIT and SLIT

Until some recent studies, there were no high-quality head-to-head comparisons of the efficacy of SCIT and SLIT. In the absence of adequate studies, investigators have compared the findings in separate meta-analyses, which reported on the degree of reduction of symptoms and medication use.⁸³ In 51 studies in subjects with allergic rhinitis, reduction in symptom scores and medication use was -0.73 and -0.57 standard mean

difference (SMDs), respectively, with SCIT, whereas it was -0.49 and -0.32 SMDs in 49 studies with SLIT.¹ Although these figures indicate that SCIT is more effective, there are too many variables in methods to allow a definitive conclusion. Recently, there were two direct comparisons of approved doses of timothy SCIT and SLIT by using the response to nasal allergen challenge as the primary outcome.

In the first comparison, improvement with SCIT was significantly better than SLIT at 3 months but not later, whereas it was significantly better than in controls for all 15 months.⁸⁴ SLIT, however, trended toward improvement but was never significantly better than control. In the second study, after 1 year, SCIT was significantly better than both SLIT and placebo; after 2 years of treatment, the improvement with SCIT over SLIT was no longer significant, but it remained significant over placebo.⁸² SLIT, however, was not significantly better than placebo after 1 year of treatment but was after 2 years of treatment.⁸⁴ Thus, two studies that used approved doses of timothy indicate an early advantage of SCIT over SLIT. Whether the clinical improvement with SLIT would catch up over a longer period, awaits further and longer studies.

Adherence

Both SCIT and SLIT have been reported to have poor long-term adherence. In a study that used a pharmacy data base in the Netherlands, it was determined that only 23% prescribed SCIT and 7% prescribed SLIT were adherent for 3 years.⁷ There are a number of reasons for poor adherence, some of which, such as cost and inconvenience, cannot be corrected. However, one study showed a markedly improved adherence to SLIT by increasing the frequency with which the patients were seen in the clinic.⁸⁵ Adherence to the 2-year treatment was 82% with clinic visits every 3 months, 68% with visits every 6 months, and only 30% with yearly visits.

In accord with the Practice Parameters,²⁸ there are no absolute age limitations on administering AIT. A review of the experience with SLIT in children 3–6 years of age, followed up for 2 years with clinic visits every 3 months revealed a discontinuation rate in the first year of 52% in the 3 year olds, 18% in the 4 year olds, and 13% in the 5 year olds.⁸⁶ After 2 years, these rates were 70, 32, and 26%, respectively. The recommendation to prevent poor adherence with SLIT was that it should be started after the age of 4 years. In summary, overall adherence to AIT is poor. It is better with SCIT than with SLIT, probably because of the reinforcement provided by the frequent clinic visits to receive injections.

Alternative Use of Currently Available Extracts

Use of the currently available allergen extracts by alternative routes is not recommended, but there are

published reports that indicate that this may be a way to reduce the inconvenience of SCIT and SLIT, and reduce the risk of SCIT. There were three studies of epicutaneous immunotherapy by the same Swiss group.⁸⁷ In these studies allergen is applied weekly to the skin on patches, after tape stripping of the site to increase penetration. The investigators examined the number of patches, the duration that patches are left in contact with the skin, and the amount of allergen extract applied. With the most recent report, 6 weekly patches, each left in place for 8 hours, produced a 48% decrease in symptoms during the first grass pollen season and 40% the second season without further treatment.⁸⁷ With the most recent regimen, SRs and eczematous reactions at the patch application site occurred in only 4% of patients and 18% of patches, respectively.

In the initial study of intralymphatic immunotherapy, 3 monthly injections of small amounts of allergen extract into the inguinal lymph nodes produced benefit comparable with that obtained with 3 years of SCIT and with fewer SRs.⁸⁸ Although there have been several small studies that support the original report of efficacy,^{89,90} one double-blinded study failed to show any improvement compared with placebo⁹¹; however, in this study, injections were made at 2-week intervals rather than the 4-week intervals of the original report.⁸⁸ Although SRs, all mild, occurred in only 6 of 66 subjects in the original report, a recent report of multiallergen intralymphatic immunotherapy (ILIT) reported SRs in 4 of 11 subjects, including one grade 2 and one grade 3 in the Mueller classification.⁹² In summary, epicutaneous immunotherapy seems very promising, although final recommendations on the variables of administration are still awaited. Intralymphatic immunotherapy, however, awaits a large study to confirm the original favorable results.

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