Clinical Management Review

The Art of Immunotherapy

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Learning objectives:

1. Recognize the respiratory allergies for which allergen immunotherapy (AIT) is effective and the indications for prescribing AIT.
2. Prescribe effective doses of AIT for the treatment of allergic conditions.
3. Manage AIT to achieve the utmost in safety and efficacy.

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Selection of a patient with rhinitis/conjunctivitis or asthma for allergy immunotherapy (AIT) requires several decisions. First, does the patient's sensitization, pattern of exposure to an allergen, and degree of exposure to that allergen reasonably suggest a causal relationship? Does the level and duration of symptoms warrant the cost and inconvenience of immunotherapy, or is the patient motivated by the disease-modifying potential of AIT? If AIT is selected, is the choice to be greater safety and convenience with sublingual immunotherapy (SLIT) tablets, but with treatment probably limited to 2 or 3 allergens, or for subcutaneous immunotherapy where multiple allergen therapy is the rule and efficacy may be somewhat greater, at least initially, or does the physician go off-label into the unknowns of liquid SLIT? Are there extracts of sufficient potency to achieve likely effective doses? How does the physician deal with large local or systemic reactions, with gaps in treatment, with pollen seasons, and the use of premedication or cautionary prescription of epinephrine autoinjectors? How can adherence to AIT be improved? These and other questions are addressed in this paper. © 2023 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2024;12:1-10)

Key words: *Allergic asthma; Allergic rhinitis/conjunctivitis; Allergy immunotherapy; AIT; Patient selection; Subcutaneous; SCIT; Sublingual; SLIT; Dosing; Multiallergic*

In 2012, a group of experts representing the American Academy of Allergy, Asthma & Immunology (AAAAI) and the European Academy of Allergy and Clinical Immunology (EAACI) recommended that immunotherapy, which they defined as "the class of therapies that aim to induce immune tolerance to allergens," be called "allergy immunotherapy" or AIT, because "immunotherapy can include both allergen-specific and nonspecific approaches."[1] Certainly, allergen-specific forms of immunotherapy are the more common, but nonspecific approaches such as type A cytosine-phosphate-guanine[2] and bacterial lysates[3] have also shown efficacy without an allergen.

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Abbreviations used
AAAAI- American Academy of Allergy, Asthma & Immunology
ACAAI- American College of Allergy, Asthma & Immunology
ACE- Angiotensin converting enzyme
AIT- Allergy immunotherapy
AU- Allergy units
CRD- Component resolved diagnosis
EAACI- European Academy of Allergy and Clinical Immunology
EOE- Eosinophilic esophagitis
FDA- Food and Drug Administration
HDM- House dust mite
ICS- Inhaled corticosteroid
MC- Mountain Cedar
RDBPC- Randomized, double-blind, placebo-controlled studies
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy
SPT- Skin prick tests
SQ-U- Standard quality unit
SR- Systemic reaction

ALLERGIC CONDITIONS RESPONSIVE TO AIT

Subcutaneous immunotherapy (SCIT) has been found, in systematic reviews and meta-analyses, to be effective in allergic rhinitis,[4] allergic asthma,[5] Hymenoptera venom sensitivity,[6] and atopic dermatitis.[7] Sublingual immunotherapy (SLIT) has proven efficacy in allergic rhinitis[4] and atopic dermatitis.[7] The strength of evidence for SLIT in allergic asthma is not as strong as it is for SCIT,[8,9] but there are supporting studies for a house dust mite (HDM) SLIT tablet reducing inhaled corticosteroid (ICS) dose while improving asthma control[10] and reducing exacerbations after ICS withdrawal.[11] The HDM SLIT tablet has been recommended in EAACI guidelines for the treatment of controlled or partially controlled HDM-driven allergic asthma in adults, whereas, because tablets have not been approved for children, HDM SLIT drops were recommended for children with controlled HDM-driven allergic asthma.[12] There are only a few studies supporting the use of SLIT for Hymenoptera venom sensitivity[13] and use of SLIT for that indication was not recommended.[14] Currently oral, sublingual, and transdermal AIT for food allergy are under investigation.[15]

For the remainder of this paper, the discussion will be limited to the use of AIT for respiratory allergy, as treatments of the other allergic conditions differ and deserve separate discussions.

SELECTION OF PATIENTS WITH RESPIRATORY ALLERGIES FOR AIT

AIT may be considered in patients with allergic rhinitis and/or allergic asthma who demonstrate IgE sensitization by *in vivo* or *in vitro* testing to allergen(s) to which they are exposed in significant quantities and where the patient's pattern of symptoms corresponds to the pattern of exposure to the allergen. The allergic respiratory symptoms should be of sufficient severity and duration to justify the inconvenience and cost of the treatment. AIT is particularly indicated if the patient's symptoms respond incompletely to pharmacotherapy or if the latter causes unacceptable side effects. Studies showing disease modification by AIT suggest that even with good control by medication, patients may choose AIT for the remission that follows a successful course of treatment[16] or the reduced risk of a patient with allergic rhinitis developing asthma.[17]

EAACI guidelines, in 2018, listed conditions in patients that they felt absolutely contraindicated the use of AIT, including uncontrolled or severe asthma, active systemic autoimmune disorders, active malignant neoplasms, and initiation during pregnancy, whereas conditions in which benefits must outweigh risks in a particular patient were partially controlled asthma, β-blocker therapy, severe cardiovascular disease, systemic autoimmune disorders in remission, severe psychiatric disorders, history of poor adherence, primary and secondary immune deficiencies, and history of a serious systemic reaction (SR) to AIT.[18] All these recommendations for absolute and relative contraindications were based on what was deemed to be weak evidence, largely case reports and case studies. The US practice parameters third update generally concurred in the absolute contraindications, although autoimmune conditions were considered only a relative contraindication, and they stated that AIT should be initiated only if the patient's asthma is stable with pharmacotherapy.[19]

Although pregnancy is generally considered a contraindication for placing a woman on AIT, the patient receiving AIT may continue on her current dose if that dose is considered therapeutically beneficial. The danger of AIT in pregnancy is from SRs because AIT does not appear to adversely affect the pregnancy or the fetus.[20] The relative contraindication for placing patients on AIT who are receiving β-adrenergic blocking agents or angiotensin converting enzyme (ACE) inhibitors is less tenable with the recent publication of a prospective study in 1342 individuals placed on SCIT with Hymenoptera venom.[21] SRs during venom immunotherapy occurred in 5.6% of those receiving a β-blocker or ACE inhibitor compared with 7.4% of those not taking these drugs, and the severity of the SRs was not affected by taking either of the drugs.

The Food and Drug Administration (FDA), in approving the SLIT tablets, added as contraindications: (1) any history of a severe SR or any severe local reaction after taking any SLIT, and (2) any history of eosinophilic esophagitis (EOE).[22,23] The last of these reflects the unusual, but real, occurrence of EOE attributable to SLIT, liquid, or tablet.[24]

THE SELECTION OF SCIT OR SLIT

Although there are many similarities between SCIT and SLIT, perhaps most importantly, their ability to modify the underlying immunologic abnormalities toward the immune response seen in the nonallergic individual, there are differences that may lead the physician and/or patient to favor one over the other. Among the differences to be considered are those in efficacy, safety, convenience, adherence, treatment of the polyallergic patient, and finally the quality of the product, not only between SCIT and SLIT, but with the latter, between tablets and liquid preparations.

Efficacy

It is difficult to compare SCIT and SLIT for efficacy because there are few instances in which the 2 approaches are included in the same study. In the systematic reviews of AIT by Dhami et al,[4,5] referenced above, the authors found 160 studies satisfying their inclusion criteria for allergic rhinitis/conjunctivitis and 98 for allergic asthma. The results of their analysis comparing each approach to placebo in their effect on symptoms and medication use are shown in Table I. Even though these studies are in different populations and with different preparations and

TABLE I. Comparison of standardized mean differences between SCIT and placebo and SLIT and placebo from meta-analyses[25]

Outcome	SCIT	SLIT
Allergic rhinoconjunctivitis		
Symptom score	−0.65 (95% CI: −0.86, −0.43)	−0.48 (95% CI: −0.61, −0.36)
Medication score	−0.52 (95% CI: −0.75, −0.29)	−0.31 (95% CI: −0.44, −0.18)
Allergic asthma		
Symptom score	−1.11 (95% CI: −1.66, −0.56)	−0.35 (95% CI: −0.82, 0.05)
Medication score	−1.21 (95% CI: −1.87, −0.54)	−0.29 (95% CI: −0.82, 0.24)

SCIT, Subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy.

TABLE II. Comparison of SLIT with timothy alone or timothy mixed with 9 other extracts to placebo[36]

Assessment	Timothy monotherapy	Timothy multiallergen
Titrated nasal challenge	$P = .02$	N.S.
Titrated skin prick test	$P < .001$	$P = .03$
Timothy-specific IgG4	$P = .005$	N.S.

N.S., Not significant; *SLIT*, sublingual immunotherapy.

TABLE III. Effective and less effective or ineffective AIT doses by subcutaneous injection[48]

Allergen extract	Major allergen	Effective doses (μg)	Less effective or ineffective doses (μg)
Short ragweed	Amb a 1	4-24	0.6 and 2.0
Timothy grass	Phl p 5	15-20	2
Dermatophagoides pteronyssinus	Der p 1	7 and 12	0.7
Dermatophagoides farinae	Der f 1	10	Not determined
Cat dander	Fel d 1	11-17	0.6 and 3.0
Dog dander	Can f 1	15	0.6 and 3.0
Birch	Bet v 1	3.28-15	Not determined
Alternaria alternate	Alt a 1	1.6 and 8.0	Not determined

AIT, Allergy immunotherapy.

doses, the finding that SCIT is more effective than SLIT is given some credence by the large number of studies included in the analysis.

Two studies directly compared the response to SCIT and SLIT with the 75,000 standard quality unit (SQ-U) timothy SLIT tablets daily and 100,000 SQ-U SCIT either monthly[26] or every 2 months.[27] Both, using a nasal allergen challenge as the clinical outcome, found SCIT significantly more effective at the time of the first assessment after attaining maintenance dosing, with nonsignificant superiority of SCIT over SLIT persisting the second year of treatment.

Safety

The online AAAAI/American College of Allergy, Asthma & Immunology (ACAAI) Subcutaneous Immunotherapy Surveillance study has been monitoring serious and fatal reactions to SCIT since 2008.[28,29] Between 2008 and 2016, a nonfatal SR occurred with 0.1% of 54.4 million injection visits.[28] Most were mild-moderate, but a near-fatal reaction (grade 4) occurred once with every 160,000 injection visits.[28] Between 2008 and 2018, 10 confirmed fatal reactions occurred for a rate of 1 for every 7.2 million injection visits.[29] For SLIT, on the other hand, there are, to my knowledge, no reports of fatal SRs in the medical literature. Nonfatal SRs do occur with SLIT. In the clinical development programs for the timothy, ragweed, and HDM SLIT tablets, 25 of 8152 subjects receiving the final approved dose and 10 of 5155 the placebo were given epinephrine injections.[30] Only 6 of the injections given to the active group were in response to SRs. Five occurred with the first dose when the full maintenance dose was administered in the physicians' office; the other SR occurred on day 6. None of the reactions fit the FDA criteria for "serious."

The multiallergic patient

Most patients presenting to allergy clinics in Europe and the United States have specific IgE to multiple, unrelated aeroallergens (polysensitized), and many have symptoms related to more than 1 of these sensitizing allergens (polyallergic).[31] Polysensitization may results from the development of IgE antibodies to multiple unrelated allergens, or alternatively, the polysensitized individual may have developed 1 or more IgE antibodies that react with structurally similar allergens from several botanically closely related plants or to panallergens occurring in several unrelated plants.[31] Distinction between multisensitization and cross-reacting antibodies can be accomplished by *in vitro* determination of IgE-mediated reactions to panallergens or major allergens. This analysis is termed component-resolved diagnosis (CRD). Studies, all in Europe, have reported that the use of CRD resulted in modification of AIT prescriptions that were based on history and skin testing alone.[31] However, there is a potential problem with the lack of sensitivity of multiallergen *in vitro* tests perhaps leading to false-negative results.[31] Therefore, the best advice is to await the results of head-to-head comparisons of the results of AIT based on CRD or skin prick tests (SPT) and patient history in a US allergic population.

Once the diagnosis is established, there is a marked difference between allergists in Europe and those in the United States in their approach to these polyallergic patients. EAACI guidelines state that in polyallergic patients, the most clinically relevant allergen(s) should be identified by history, SPT, specific IgE, and allergen provocation testing if available. The 1 or 2 most clinically relevant allergens should be used for AIT.[18] European allergists further recommend that, if there are 2 unrelated allergen extracts that are of equal importance, they be given on alternate days or during the same visit in the left and right arm with at least a 30-minute interval between injections.[32] US allergists, on the other hand, supported by the immunotherapy practice parameters third update,[19] generally treat their multiallergic patients with a mixture of allergens to which they are clinically sensitive. The US practice is supported by the small, but well-

TABLE IV. Representative major allergen contents of US standardized and nonstandardized pollen allergen extracts[48]

Allergen extract	Expressed potency	Major allergen	Mean major allergen content (μg/mL)	Range major allergen content (μg/mL)
Standardized extracts				
Timothy grass	100,000 BAU/mL	Phl p 5	620	354-1336
Bermuda grass	10,000 BAU/mL	Cyn d 1	200	125-449
Short ragweed	1:10 w/v	Amb a 1	500	
Nonstandardized extracts				
Birch pollen	1:10 w/v	Bet v 1	420	
Olive pollen	1:10 w/v	Ole e 1	>350	
Sage/mugwort pollen	1:10 w/v	Art v 1	3000	
Brome grass	1:10 w/v	Group 5	135	

Representative major allergen content of standardized and nonstandardized US pollen extracts expressed as μg/mL in the concentrated extracts obtainable from US extract manufacturers (original source: Gregg Plunket, PhD, ALK, Round Rock, Texas).
BAU, Bioequivalent allergy unit; *w/v*, weight by volume.

TABLE V. Representative major allergen contents of US standardized and nonstandardized environmental allergen extracts[48]

Allergen extract	Expressed potency	Major allergen	Mean major allergen content	Range major allergen content
Standardized extracts				
Dermatophagoides pteronyssinus	10,000 AU/mL	Der p 1 Der p 2	120 μg/mL Der p 1 + Der p 2	8-538 μg/mL Der p 1 + Der p 2
Dermatophagoides farinae	10,000 AU/mL	Der f 1 Der f 2	160 μg/mL Der f 1 + Der f 2	48-216 μg/mL Der f 1 + Der f 2
Cat hair and dander	10,000 BAU/mL	Fel d 1	40 μg/mL	26-44 μg/mL
Nonstandardized extracts				
Dog hair	1:10 w/v	Can f 1	<5 μg/mL	0.5-7.2 μg/mL
Dog (AP)	1:100 w/v	Can f 1	140 μg/mL	90-250 μg/mL

Representative major allergen content of standardized and nonstandardized US environment allergen extracts expressed as μg/mL in the concentrated extracts obtainable from US extract manufacturers (original source: Gregg Plunket, PhD, ALK, Round Rock, Texas).
AP, Acetone precipitated; *AU*, allergy unit; *BAU*, bioequivalent allergy unit; *w/v*, weight/volume.

designed and well-executed studies by Lowell and Franklin[33,34] in the 1960s that showed that the elimination or 95% reduction of ragweed in a mixture of unrelated allergen extracts caused a significant loss of protection in the subsequent ragweed pollen season.

The Lowell and Franklin[33,34] studies, alluded to above, confirmed the effectiveness of ragweed extract administered by SCIT in a mixture with multiple other unrelated allergens. With SLIT, there is an open study comparing symptoms during the respective pollen seasons of a single administration of birch and grass to those with the administration of the two together.[35] The levels of symptoms during the grass pollen and birch pollen seasons were the same whether the pollen extract had been given alone or in the 2-pollen combination. The only true multiallergen SLIT study, that I am aware of, compared SLIT with timothy pollen extract combined with 9 unrelated pollen extracts to the same dose of timothy diluted to the same degree with diluting fluid and to diluting fluid alone as a placebo[36] (Table II). Because of a very low grass pollen count that year, symptoms did not differ, but there was a marked difference in surrogate outcomes, such as titrated SPT and titrated nasal challenges, and in specific-IgG_4 levels, between monoallergen timothy and placebo that was not matched in the multiallergen timothy and placebo comparison. Until the results of this study are confirmed or refuted, the efficacy of a multiallergen mixture by SLIT remains uncertain.

Only the performance of large, well-designed studies of multiallergen SCIT and SLIT will establish, to everyone's satisfaction, whether multiallergen AIT is effective by either or both approaches for the treatment of allergic respiratory diseases. Unfortunately, commercial, government, and professional society entities have thus far not provided the funding for these studies.

Adherence

With SLIT self-administered at home once a day and SCIT requiring travel to a physician's office and a 30-minute wait after receiving the injection, it could be anticipated that adherence to SLIT would be better than to SCIT, but the opposite is regularly reported. A Netherlands community pharmacy base, with data on several thousand patients receiving SCIT or SLIT, revealed a 3-year completion rate of 23% for SCIT but only 7% for SLIT.[37] The low 3-year completion rate with SLIT was confirmed by the data from 2 Italian extract manufacturers who reported a 13% 3-year completion rate with SLIT.[38]

SLIT tablets versus SLIT liquid

The SLIT tablets that are available in the United States have all been approved based on multidose studies that determined effective and less effective doses.[39-42] There are no approved SLIT-liquid preparations in the United States, and dose-ranging studies have only been performed with liquid ragweed,[43,44] measuring responses during the ragweed pollen seasons, and HDM extract using a bronchial challenge to assess efficacy.[45] Thus, SLIT liquid is being administered by United States

TABLE VI. Range of probable effective doses of US standardized extracts

Allergen extract	Labeled potency	Range of probable effective doses
Dermatophagoides pteronyssinus	10,000 AU/mL	500-2000 AU
Dermatophagoides farina	10,000 AU/mL	500-2000 AU
Cat dander	10,000 BAU/mL	1000-4000 BAU
Northern pasture grasses	100,000 BAU/mL	1000-4000 BAU
Bermuda grass	10,000 BAU/mL	300-1500 BAU
Short ragweed	1:10, 1:20 w/v	12 Amb a 1 FDA units

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *FDA*, Food and Drug Administration; *w/v*, weight/volume.
Modified from Cox et al.[19]

allergists "off-label," using extracts approved for injection, and with few studies to guide dosing except those that have been performed with the SLIT tablets. Because there is almost no reliable information on SLIT-liquid dosing, what doses are the allergists prescribing SLIT-liquid prescribing? In response to a recent online survey, 22% of the responding US allergists reported some prescribing of SLIT using US liquid allergen extracts.[46] When the respondents were asked how their cumulative monthly dose of SLIT compared with their monthly maintenance dose of SCIT, 76.9% stated from less than 1 times up to 20 times. The ratio found to be most effective for the grass and ragweed SLIT tablets was approximately 30 times and for HDM SLIT tablets even higher. Thus, it is likely that three-quarters of the responders to the questionnaire who were prescribing liquid SLIT were using less than fully effective doses.

DOSING

The recent dose-finding studies with the SLIT tablets have demonstrated significant loss of clinical efficacy with decreases in allergen content to one-half or one-third of the effective dose.[39-42] If this steep dose-response applies also to SCIT, and there is no apparent reason why it should not, then it is possible that many US allergists are also underdosing with SCIT. Nearly a thousand US allergists responded to an online questionnaire in 2012, 1 year after the publication of the third update of the immunotherapy practice parameters.[47] The practice parameters had included a table of probable effective doses that for HDM and cat extracts had a 4-fold range in doses.[19] For HDM, 13% of responding physicians reported prescribing doses below this range and 38% and 44% reported prescribing the 2 HDM extracts in the lower half of the 4-fold range; a dose that the average major allergen content of US standardized extracts suggests is less than optimal. For cat extract, that is weaker in major allergen than HDM, 18% reported prescribing below the practice parameter recommended range and 46% prescribed in the lower half of that range, again a dose possibly less than optimal.

Why use major allergen content as a designation of extract potency? It has been long known that the conventional designations of weight by volume and protein nitrogen units used for nonstandardized extracts very poorly reflect extract potency. Units of potency for standardized extracts do reflect potency, but there is no common system employed worldwide. In the United States, the FDA designations are allergy units (AU), bioequivalent AU, or listing of major allergen content in FDA units; this system is not used elsewhere. In Europe, on the other hand, there is no common unitage; rather each extract manufacturer has internal standards that have unique and not interchangeable designations such as index of reactivity, biological units, or a complexly defined SQ-U. Thus, although there are problems with using major allergen as an expression of potency, including that the monoclonal antibodies used to measure them are not standardized, it remains the only widely interpretable method.

The effective doses for SCIT administration have been determined in randomized, double-blind, placebo-controlled studies (RDBPC) mostly performed with the US or European standardized allergen extracts of HDMs, grasses, short ragweed, and cat, but they have also been performed with nonstandardized extracts of dog, birch, and *Alternaria* for which the major allergen content of the extract used was known (Table III). In some of these studies, lower doses of the same extract were also administered, usually a reduction to 1/5th to 1/20th of the effective dose, with partial or complete loss of efficacy.

In the United States, major allergen content is not provided on the label, except for short ragweed, but many extract manufacturers have in-house capability of measuring at least some allergens. Tables IV and V contain information from 1 US extract manufacturer of the major allergen content of their own and other US manufacturers' extracts. This information is now over a decade old but still provides some indication of major allergen content of some US allergen extracts.

As mentioned above, the committee that drew up the third update of the immunotherapy practice parameters used information such as that in Tables III-V to make recommendations for allergen extract dosing in FDA-approved dosage units. These are presented in Table VI. Remembering the drop-off in efficacy in the SLIT-tablet studies with a reduction to one-half to one-third of the effective dose, the range of probably effective doses in the practice parameter may be too broad.

The authors of the practice parameters third update[19] also made recommendations for nonstandardized US extracts. For pollens that, as can be seen in Table IV, are of similar range of potency to the standardized pollen extracts, they recommend a maintenance dose of a 1:10 dilution of the stock 1:10 or 1:20 w/v extracts; for dog, they recommend a maintenance dose containing 15 μg of Can f 1, a dose reasonably attainable only with the acetone-precipitated dog extract; and, finally, for cockroach and fungal extracts, for which effective doses have not been determined (except for *Alternaria*) and where the extracts are known to be poor in major allergen content, they recommended the highest tolerated dose.[19] In a systematic review of AIT for allergic asthma, a subgroup analysis showed that the results of AIT with mold extracts were less consistent than those with HDM or pollen extracts, suggesting that different preparations may be more or less effective.[5]

Mixing a multiple-allergen treatment extract

If the US approach to SCIT is to be practiced, there are certain considerations to be honored in the selection of component allergens for inclusion in the treatment extract. Attention should be paid to the degree of cross-reactivity between proposed components to avoid overloading the mixture with related allergens. As a rule, there is rarely significant cross-

TABLE VII. Patterns of cross-reactivity[25]

Allergen	Basis for selection
Trees	
Birch, alder, hazelnut, hornbeam (strongly cross-reactive), beech, oak (moderately cross-reactive)	Use locally most important species
European olive, ash, privet, Russian olive	Use locally most important species
Cedar, cypress, juniper, arborvitae	Use locally most important species
Pecan, hickory	Use locally most important species
Poplar, aspen, cottonwood	Use locally most important species
Grasses	
Northern pasture grasses (timothy, June, orchard, redtop, meadow fescue, perennial rye, sweet vernal)	Use timothy or a mixture of locally important members
Bermuda grass	Not cross-reactive with northern pasture grasses
Bahia, Johnson grass	Use if locally important
Weeds	
Short, giant, false, and western ragweed	Use locally most important species
Southern and slender ragweed, cocklebur, burweed marsh elder	Use if locally important
Sages, mugwort	Use locally most important species
Pigweed, Palmer's amaranth, western water hemp	Use locally most important species
Russian thistle, *Kochia*, Lamb's quarters	If both Russian thistle and *Kochia* are locally important, use a mixture
Insects	
Dermatophagoides pteronyssinus and farinae	If both locally important, use a mixture
Cockroach, German, and American	Use a mixture

TABLE VIII. Representative conventional schedule for subcutaneous immunotherapy[60]

1:10,000 v/v Vial # 5* Silver cap	1:1,000 v/v Vial # 4 Blue cap	1:100 v/v Vial # 3 Green cap	1:10 v/v Vial # 2 Gold cap	1:1 v/v Maintenance Vial Red cap
0.05 mL	0.05 mL	0.05 mL	0.05 mL	0.05 mL
0.10 mL	0.10 mL	0.10 mL	0.07 mL	0.07 mL
0.20 mL	0.20 mL	0.20 mL	0.10 mL	0.10 mL
0.40 mL	0.40 mL	0.40 mL	0.15 mL	0.15 mL
			0.25 mL	0.20 mL
			0.35 mL	0.30 mL
			0.50 mL	0.40 mL
				0.50 mL

Patients with asthma or previous systemic reactions to allergy immunotherapy may require a more conservative schedule.
*Vial # 5 used for highly sensitive patients (multiple large skin test reactions). Less sensitive patients begin with vial # 4.

reactivity between members of different families; there is generally some cross-reactivity within tribes or genera of a family and generally a high degree of cross-reactivity between species of the same genus. Specific examples applicable to the United States are given in Table VII.

The other major consideration in formulating the treatment extract is to avoid combining allergen extracts with strong proteolytic activity, for example, fungi and cockroach, with other extracts whose allergens are susceptible to the proteolytic activity, including not mixing fungal and cockroach extracts.[49] Identically labeled fungal extracts show great variation in allergen content and therefore probably the type of proteolytic activity.[50] Therefore, a single or few examples of an allergen extract tolerating mixture with a fungal extract are no guarantee that this will always occur. I believe that the safest practice is to not mix fungi and cockroach extracts together and not mix either with pollen, dander, or HDM extracts.

OPTIMAL DURATION OF AIT

The rate of clinical improvement with AIT varies in different studies. Maximal improvement with SCIT has been demonstrated after 5 weeks of cluster build-up to maintenance dosing with no further improvement after a year of maintenance dosing,[51] and in a 3-year timothy SLIT-tablet study, there was no further improvement in the second and third grass pollen seasons over the first;[52] on the other hand, a study of SCIT with *Alternaria* showed additional improvement each year of a 3-year study,[53] whereas in an environmental exposure chamber study of the HDM SLIT tablets, there was a progressive further improvement at 8, 16, and 24 weeks of treatment.[42]

The duration of treatment required to induce persisting improvement on an individual basis is variable,[54] but for grass SCIT, 2 studies showed good persistence of improvement for the whole group[16] or for 70%[55] of the group for 3 years after ceasing 3–4 years of treatment. Two large grass SLIT-tablet studies showed persisting, if somewhat diminished improvement for 2 grass pollen seasons after discontinuing 3 years of treatment.[52,56] In a study designed specifically to see if less than 3 years of timothy SLIT or SCIT would suffice to produce lasting benefit, the significant improvement after 2 years of treatment with both approaches was largely lost 1 year after stopping.[26]

TABLE IX. Suggested adjustments for gaps in SCIT treatment[19]

Build-up phase	Recommended action
Up to 7 d late	Continue build-up as scheduled
8-13 d	Repeat last dose
14-21 d	Reduce dose 25%
21-28 d	Reduce dose 50%
Maintenance phase	
2-4 wk late	Reduce dose 75%
>4 weeks late	Reduce by 1 or more dilutions depending on length of time and the patient's sensitivity

SCIT, Subcutaneous immunotherapy.

TABLE X. Treatment emergent adverse events (TEAEs) with interruption in HDM SLIT-tablet treatment[74]

Interruptions and outcomes	12 SQ HDM SLIT tablet (N = 783)	Placebo (N = 782)
Treatment interruptions	476	501
Duration median (d)	7	8
Duration mean (d)	13.4	13.8
TEAEs after reinitiation (%)	29	26
SRs	0	0
Epinephrine use	0	0
Severe local swelling	0	0

HDM, House dust mite; *SLIT*, sublingual immunotherapy; *SQ*, standard quality; *SR*, systemic reaction.

Two studies in children compared 3 and 5 years of SCIT with HDM.[57,58] Although there were minimal differences favoring the 5-year treatment, both groups of authors concluded that 3 years of SCIT was probably sufficient. In a study in adults of SLIT with HDM extract, the patients were treated with medication alone or 3, 4, or 5 years of SLIT.[59] The degrees of improvement were similar, but, on discontinuation, clinical benefit persisted, on average, 7 years after 3 years of SLIT and 8 years after 4 or 5 years of SLIT. The authors suggested that, under the conditions of their study, 4 years of SLIT provided optimal results.

As a result of these and similar studies, the usual recommendation is for AIT to be administered for 3 to 5 years depending, in part, on how soon the patient appears to reach a plateau of improvement. On the other hand, AIT should be discontinued if the patient has not improved by 1 year after reaching maintenance dosing.

MEASURES TAKEN DURING THE COURSE OF AIT

Choosing the build-up schedule for SCIT

With the approved SLIT tablets, treatment is initiated with the full maintenance dose. In the only large RDBPC trial thus far conducted with an FDA-approved liquid extract, the ragweed pollen liquid SLIT was administered with a 2-dose build-up on the first day. The customary build-up schedule for SCIT begins with a 1:1000 dilution of the maintenance dose and increases with injections, usually weekly, to maintenance (Table VIII). It is recommended that for patients at increased risk for an SR, including those with multiple strongly positive SPT, persistent asthma, or prior SRs to AIT, the build-up include a greater number of increments. There are often reasons why a build-up over several months is not optimal, especially when the allergen exposure is perennial, rather than seasonal. In a rush schedule, multiple injections are administered on consecutive days, reaching maintenance in 1 to several days. Rush build-up is associated with a higher incidence of SRs than conventional build-up even with potent premedication.[61] A less aggressive accelerated approach is cluster build-up, where 2 to 3 injections are administered on nonconsecutive days. Using the schedule in Table VIII and twice weekly injection visits, maintenance can be achieved in 4 weeks. There is disagreement whether the use of cluster build-up is associated with an increased risk of SRs over what occurs with conventional build-up.[62,63]

Large local reactions

Injection site reactions occur commonly with SCIT; large local reactions may be uncomfortable and persist for 1 or more days. It was formerly common practice to reduce the dose of the next injection in the belief that large local reactions increased the likelihood of an SR with the next injection if the dose was maintained or increased. This practice was not supported by 2 large studies,[64,65] both of which reported that large local reactions (at least those no larger than the patients' palm[64]) were not predictive of an SR with the next injection even when there was no dose reduction. Two studies did report that patients who experienced a local reaction larger than their palm[66] or who had frequent local reactions >2.5 cm[67] were at increased risk for an SR sometime during the course of their SCIT. Large locals were found to be fairly poor predictors of local reactions to the next injection. All local reactions were followed by a local reaction in only 27.2% of cases,[66] and local reactions larger than the patient's palm were followed by similar sized reactions in only 6% of cases.[66]

Oral application site reactions are common with the SLIT tablets. Over half of both children and adults report, in order of occurrence, oral pruritus, throat irritation, ear pruritus, and mouth edema. Except for localized mouth edema, symptoms typically begin the first day, last less than an hour, and recur for an average of approximately 1 week.[68] Mouth edema tended to develop somewhat later and be more persistent.

Systemic reactions

The major risk factors that were identified from 1985 to 2001 for fatal SRs by the AAAAI Committee on Immunotherapy were asthma, particularly if severe or poorly controlled, first injection from a new vial of extract, and errors in dosing.[69,70] Measures to avoid SRs from these factors include querying the asthmatic patient with regard to symptoms and performing a peak expiratory flow measurement to ensure that there has not been asymptomatic deterioration in the patient's asthma control. For injections from a new vial of extract, a 30% to 50% reduction in the dose is routinely indicated to allow for increased potency of the new extract. There are no formal studies, but it is suggested that if the extracts come from a new company, as for example with a change in physician, standardized extracts should be reduced 80%, nonstandardized extracts 90%, and fungal or cockroach extracts 99%. There are no formal studies to guide future dosing after an SR. The practice parameters suggest reducing the dose to one that was previously tolerated or even lower if the reaction was severe.[19] Also, if the reaction was severe

or repeated, the risk/benefit of continuing SCIT should be assessed.

Premedication and rescue medication

A systematic review of antihistamine premedication for AIT identified 8 studies with accelerated build-up and 3 studies with conventional build-up; all employed SCIT and use was primarily during build-up.[71] Premedication was effective in both accelerated and conventional schedules in reducing local and SRs and allowed more patients to reach the targeted maintenance dose.

Many US allergists prescribe epinephrine autoinjectors for their SCIT patients. The efficacy of this practice is questioned by the observation that SCIT patients who have been prescribed epinephrine autoinjectors frequently do not use them when they do have a late SR.[29] The prescription of an epinephrine autoinjector is mandated by the FDA for patients prescribed SLIT tablets. I am aware of no data to support the utility of this practice.

Two RDBPC studies examined the efficacy of prerinsing syringes with epinephrine before drawing up allergy extract for patients with frequent large local reactions. Both studies showed that the frequency and the size of the local reactions were reduced by this procedure.[72,73]

Gaps in treatment

There are no formal studies regarding the appropriate adjustment in dose in response to interruptions of SCIT. An example of a nonvalidated schedule from the practice parameters is provided in Table IX.

The SLIT tablets are generally introduced without a build-up, but with the precaution of giving the first dose under physician observation. What if there is an interruption in the administration of the tablets at home? In 2 HDM SLIT-tablet studies, 476 interruptions of active treatment occurred, the median duration was 7 days, and the mean was 13.4 days.[74] On resumption of treatment, there were no episodes of severe oral swelling, no SRs, and no use of epinephrine (Table X).

Reduced treatment during pollen season

There is continuing disagreement among allergists whether the dose of SCIT should be reduced during pollen seasons, particularly for those allergens that are included in the patient's treatment extract. The AAAAI/ACAAI surveillance program has found that practices that did not reduce doses during the patient's pollen season had a higher rate of SRs.[6] On the other hand, 3 studies specifically examining the impact of pollen seasons on the rate of SRs failed to support the need for a seasonal reduction in dose. In a study of 5810 patients who received SCIT without seasonal adjustments, it was found that the rate of SRs did not increase during the grass and ragweed pollen seasons in patients as a whole or in those receiving those allergens in their treatment.[75] In a review of records for 8 years at the Wilford Hall Air Force allergy clinic, it was found that the rate of SRs during the Mountain Cedar (MC) pollen season, their major aeroallergen, was the same for those who were or were not allergic to that pollen, and that the rate of SRs during the MC pollen season was not increased over that of the rest of the year.[76] Finally, at Boston Children's Hospital, the practice was changed from no modification in dose during the pollen season to a 60% reduction in the targeted maintenance dose during either the spring or the fall, depending on the pollen extracts the patient was receiving.[77] When they compared the results before and during the dose adjustment, there was no significant difference in the rate or severity of SRs. These 3 studies suggest that a routine reduction in dose during a patient's pollen season may not be necessary, although it may be prudent in selected patients, particularly with unstable asthma.

Adherence

Given the poor adherence that is being reported for AIT, and especially for SLIT, various approaches to improve adherence are under study. Among the strategies suggested are better education at the beginning of AIT including discussion of time commitments, duration of therapy, and possible side effects, but also how soon improvement can be expected and the long-term benefits if the treatment is completed.[78] The patients should be involved in the decision between SCIT and SLIT.[78] One strategy that has been examined was increasing the frequency with which SLIT patients were brought back for clinic visits. Over the course of 2 years, of children brought back 4 times a year, 18.5% discontinued SLIT; of children brought back twice yearly, 32.3% discontinued; and of children seen only once a year, 70.4% discontinued.[79] Continued adherence can also be encouraged by use of digital reminders and health care apts.[78]

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