

Allergen immunotherapy: routes, safety, efficacy, and mode of action

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Abstract: Allergic rhinitis, allergic conjunctivitis, and allergic asthma have been steadily increasing in prevalence in recent years. These allergic diseases have a major impact on quality of life and are a major economic burden in the US. Although allergen avoidance and pharmacotherapy are currently the mainstays of therapy, they are not always successful in treating patients' symptoms effectively. If a patient fails allergen avoidance and medical therapy, immunotherapy may be indicated. Furthermore, immunotherapy is the only therapy that may change the course of the disease and induce long-term remission. Though subcutaneous administration has been the standard route for immunotherapy for many decades, there are several other routes of administration that have been and are currently being studied. The goal of utilizing alternative routes of immunotherapy is to improve safety without decreasing the efficacy of treatment. This paper will review the novel routes of immunotherapy, including sublingual, oral, local nasal, epicutaneous, and intralymphatic.

Keywords: immunotherapy, allergic rhinitis, allergic asthma, sublingual, intralymphatic

Introduction

Rhinitis is defined as inflammation of the nasal mucosa, which presents clinically with symptoms of nasal congestion, rhinorrhea, nasal itching, and sneezing.¹ In allergic rhinitis, airborne environmental allergens trigger nasal symptoms that are often clinically associated with ocular symptoms, such as pruritus, edema, conjunctival injection, and excessive lacrimation.

Allergic rhinitis is estimated to affect up to a quarter of the population in Westernized countries, and may be associated with multiple comorbidities, including otitis media, sinusitis, and asthma.² Seasonal allergic rhinitis is due to pollen from wind-pollinating trees, grasses, and weeds, while perennial symptoms can be triggered by indoor allergens, such as dust mites, animal dander, feathers, and mold spores. Thus, depending on sensitization, symptoms can be present throughout the year with particular seasonal exacerbations. The impact of allergic rhinitis on quality of life is often minimized, though the direct and the indirect economic costs, due to missed school and workdays, are significant.³ In 2005 alone, the estimated cost of allergic rhinitis in the US was approximately \$11.2 billion.⁴

The diagnosis of allergic rhinitis is typically simple, and can usually be made based on history and physical examination. When indicated, skin-prick testing may be performed to support a diagnosis of allergic rhinitis and to help identify the inciting allergens. Given the high negative predictive value of aeroallergen skin testing, if skin-prick testing is negative, the rhinitis is unlikely to be the result of an immunoglobulin

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(Ig)-E-mediated process. Further support for the diagnosis can also be obtained through blood testing of allergen-specific IgE concentrations.

Treatment of allergic rhinitis can be divided into three categories: allergen avoidance, pharmacotherapy, and immunotherapy. Allergen avoidance can be expensive and is not always practical or possible, especially when the allergen is an outdoor allergen, such as pollen. Pharmacotherapy most commonly includes nasal saline rinses, oral antihistamines, leukotriene inhibitors, intranasal antihistamines, and intranasal corticosteroids, with possible short-term use of oral or intranasal decongestants. Treatment failures are often secondary to poor compliance with prescribed medications and improper technique when using nasal sprays, although for many individuals, medical management fails even with appropriate technique and compliance.⁵ One of the indications for immunotherapy is severe allergic rhinitis that has been unresponsive to allergen avoidance and pharmacotherapy. Furthermore, while allergen avoidance and pharmacotherapy can treat the symptoms of allergic rhinitis, immunotherapy actually changes the course of the disease and can induce long-term remission.⁶

Allergen-specific immunotherapy is thought to work by shifting the immunological response to an allergen from a T-helper type 2 (Th2)-dominated response to a Th1-dominated response. Some studies have also demonstrated an increase in the production of regulatory T cells that secrete interleukin (IL)-10 and transforming growth factor (TGF)- β . While IL-10 inhibits T-cell proliferative responses and may reduce Th2 cytokine production associated with allergic inflammation, TGF- β downregulates the differentiation of naive T-cells into effector cells. Serologically, there is an initial increase in allergen-specific IgE, which is followed by a decrease in IgE. There is typically also a simultaneous increase in allergen-specific IgG₁ and IgG₄, though this change has not been correlated with a clinical response to immunotherapy.⁷

The most commonly used route of immunotherapy administration is subcutaneous, and while it has been proven to provide long-term success in the treatment of allergic rhinitis, there can be many barriers to its completion. Since subcutaneous immunotherapy (SCIT) requires close supervision by an appropriately trained physician, it requires many doctor visits over the 3- to 5-year treatment period.^{8,9} It can also be associated with adverse effects, ranging from local erythema and swelling to life-threatening anaphylactic reactions.¹⁰ Given the multiple obstacles to SCIT, various novel routes of administration are currently being studied. Some of the

novel routes of allergen immunotherapy to be discussed in this review include:

- sublingual – extract is placed under the tongue
- oral – extract is swallowed
- intranasal – extract is applied to the nasal mucosa
- epicutaneous – extract is applied in patch form to the skin
- intralymphatic – extract is injected directly into the lymph node.

Sublingual allergen-specific immunotherapy

Of the alternative routes for SCIT, sublingual immunotherapy (SLIT) has been studied the most and is currently approved in several countries, though not in the US. SLIT typically involves placing an extract in pill or liquid form under the tongue for 1–2 minutes.¹¹ The first dose is typically given in a physician's office followed by an observation period of at least 30 minutes. SLIT has been shown to be an effective alternative to SCIT, with a significantly decreased risk of severe adverse reactions.¹² Though SLIT has been studied extensively, a consensus statement on treatment is not available due to the large variability in dose, frequency, and duration between studies.^{11,12}

The oral mucosa is a site of many Langerhans-like dendritic cells, which are a type of antigen-presenting cell (APC). Once allergen is taken up by these APCs in the oral mucosa, they migrate to regional lymph nodes. These cells also express the high-affinity receptor for IgE (Fc ϵ RI) and signal via Toll-like receptor 4. There is production of IL-10 and TGF- β , which induce regulatory molecules and support the development of Th1 cells.¹³ Patients undergoing SLIT have been found to have an increase in serum IgG₄ and a progressive decrease in serum IgE after an initial increase. Furthermore, due to the lack of proinflammatory cells, such as mast cells, in the sublingual mucosa, it is hypothesized that the likelihood of a severe allergic reaction with sublingual immunotherapy is decreased.¹⁴

Multiple meta-analyses and systematic reviews have demonstrated that SLIT is efficacious in the treatment of allergic rhinitis in both adults and children.^{15–18} Additional studies have shown improvements in quality of life of patients treated with SLIT as well.^{19,20} Given the heterogeneity between studies, one review found that in order to find a statistically significant improvement in symptom scores, a daily dose of 15–25 μ g of major allergen was required. Lower doses were found to be ineffective, and higher doses were no more effective than 25 μ g of major allergen per day.²¹

Lin et al²² performed a systematic review that included adults and children who had received SLIT for pollen, dust-mite, or cat allergy. There was strong evidence that SLIT improves asthma symptoms, and moderate evidence that SLIT improves rhinitis and conjunctivitis symptoms, as well as medication use.

Cochrane reviews on SLIT for allergic rhinitis²³ and allergic conjunctivitis²⁴ included studies evaluating the efficacy of SLIT using pollen, dust-mite, cat, and mixed-allergen extracts. Both reviews found a significant reduction in symptoms in patients receiving SLIT compared to placebo; however, there was only a reduction in medication use for allergic rhinitis.^{23,24} When performing the meta-analysis for allergic conjunctivitis, patients in the active-treatment groups did demonstrate “an increase in the threshold dose for the conjunctival allergen provocation test.”²⁴ There were no reported cases of anaphylaxis or severe systemic reactions in response to SLIT, and there was no requirement for epinephrine in any of the systemic reactions reported²³ (Table 1).

There have been several meta-analyses examining the efficacy of SLIT in allergic asthma. Calamita et al²⁵ studied the efficacy of SLIT for allergies due to pollen, dust mite, latex, and mixed allergens. The authors found a significant improvement in forced expiratory volume in 1 second and flow between 25% and 75% of vital capacity among the respiratory function tests that were evaluated. Though there was a significant improvement in symptom scores with SLIT,

there was only a significant reduction in medication use for asthma together with rhinitis and conjunctivitis; when looking at asthma alone, there was no significant reduction in medication use.²⁵ Penagos et al²⁶ looked only at the efficacy of SLIT on allergic asthma in pediatric patients. Overall, a significant reduction in both symptoms and medication use was demonstrated following SLIT for dust mite and pollen, though the improvement was more pronounced with the dust-mite subgroup than the pollen subgroup. A more recent meta-analysis of nine studies with 452 patients (adults and children) receiving SLIT for allergic asthma and house dust-mite allergy showed a significant reduction in symptoms and medication use when compared to placebo¹⁸ (Table 1). Though a beneficial effect was seen in each of the meta-analyses, it was reported that there was considerable heterogeneity between all of the studies included in the meta-analyses.

One group performed a meta-analysis first to examine the efficacy of SLIT when compared to placebo, but then also compared meta-analyses of SLIT with SCIT. When compared to placebo, SLIT showed significant improvements in symptom scores, medication scores, quality-of-life scores, and combined symptom-medication scores; however, when a subgroup analysis was performed, medication scores were not significantly improved in pediatric patients. When SLIT was compared to SCIT, results favored SCIT with regard to symptom scores and medication scores, though there was no difference in combined

Table 1 Summary of sublingual immunotherapy meta-analyses

Study	Trials/patients	Disease	Results, SMD (95% confidence interval)
Wilson et al ¹⁵	22/979	AR	Symptoms -0.42 (-0.69 to -0.15; <i>P</i> = 0.002), medication use -0.43 (-0.63 to -0.23; <i>P</i> = 0.00003)
Penagos et al ¹⁶	10/484	AR	Symptoms -0.56 (-1.01 to -0.10; <i>P</i> = 0.02), medication use -0.76 (-1.46 to -0.06; <i>P</i> = 0.03)
Olaguibel et al ¹⁷	7/256	ARC, asthma	Symptoms AR -0.44 (-1.22 to 0.3; <i>P</i> = 0.27), symptoms AC -1.49 (-3.69 to 0.72; <i>P</i> = 0.19), symptoms asthma -1.42 (-2.51 to -0.34; <i>P</i> = 0.01), medication use -1.01 (-2.06 to 0.04; <i>P</i> = 0.06)
Compalati et al ¹⁸	8/382	AR	Symptoms -0.95 (-1.77 to -0.14; <i>P</i> = 0.02), medication use -1.88 (-3.65 to -0.12; <i>P</i> = 0.04)
	9/452	Asthma	Symptoms -0.95 (-1.74 to -0.15; <i>P</i> = 0.02), medication use -1.48 (-2.70 to -0.26; <i>P</i> = 0.02)
Radulovic et al ²³	49/4589	AR	Symptoms -0.49 (-0.64 to -0.34; <i>P</i> < 0.00001), medication use -0.32 (-0.43 to -0.21; <i>P</i> < 0.00001)
Calderon et al ²⁴	42/3958	AC	Symptoms -0.41 (-0.53 to -0.28; <i>P</i> < 0.00001), medication use -0.10 (-0.22 to 0.03; <i>P</i> = 0.13)
Penagos et al ²⁶	9/441	Asthma	Symptoms -1.14 (-2.1 to -0.18; <i>P</i> = 0.02), medication use -1.63 (-2.83 to -0.44; <i>P</i> = 0.007)
Dretzke et al ²⁷	42	AR	Symptoms -0.33 (-0.42 to -0.25; <i>P</i> < 0.00001), medication use -0.27 (-0.37 to -0.17; <i>P</i> < 0.00001)

Abbreviations: SMD, standardized mean difference; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; AC, allergic conjunctivitis.

symptom-medication scores. Quality-of-life scores trended in favor of SCIT, though the results did not reach statistical significance.²⁷

Di Bona et al²⁸ performed a meta-analysis to determine whether SCIT or SLIT was more effective in the treatment of patients with seasonal allergic rhinitis to grass pollen (Table 4). Thirty-six randomized controlled trials were included (22 for SLIT and 14 for SCIT) in the meta-analysis with 3,014 patients treated with immunotherapy and 2,768 control patients who received placebo. Sublingual drops were used in ten of the SLIT studies and tablets were used for the remaining twelve trials. While all of the SCIT trials included adults, seven of the SLIT studies only enrolled children. The final results illustrated that there was a significantly larger reduction in symptom score and medication score with SCIT than with SLIT, regardless of route of administration for SLIT (drops vs tablets).²⁸

The appeal of SLIT is largely due to the decreased frequency of severe adverse reactions rather than improved efficacy when compared to SCIT. The most common adverse events are local side effects consisting of pruritus and swelling of the lips and mouth, which occur in 60%–85% of patients. These symptoms typically occur within several minutes to hours of SLIT and are short-lived.²¹ Interestingly, a meta-analysis comparing SLIT with SCIT found that there were 0.86 adverse events per patient for SCIT, while there were 2.13 adverse events per patient for SLIT. The withdrawal rate for adverse events was also higher in the SLIT group than in the SCIT group (0.04% vs 0.019%, respectively). Though the percentage of patients who experienced adverse events was greater in the SLIT group, there were twelve reported cases of anaphylaxis in the SCIT-treated patients and only one in the SLIT-treated patients.²⁸ Despite the superior safety profile of SLIT when compared to SCIT for severe adverse events, there have been multiple case reports of anaphylaxis with SLIT, so caution must still be taken with its administration.^{29–34} The cases of anaphylaxis included both children and adults, and while some case reports detailed events occurring with the first dose, others reported events once maintenance doses were reached. Most cases of anaphylaxis involved urticaria, angioedema, and respiratory distress, and less frequently hypotension, nausea, abdominal cramping, and dizziness. The majority of patients who suffered severe systemic adverse events were treated with antihistamines, though there are two case reports of epinephrine being required, but no deaths. However, the rate of adverse events cannot fully be ascertained, and a grading system of SLIT adverse events should be developed.³⁵

The popularity of SLIT will likely continue to increase over time despite studies that have shown that SCIT is more efficacious than SLIT due to the convenience of SLIT administration, as well as the decreased rate of severe adverse events. SLIT has already become very popular in Europe, and once US Food and Drug Administration (FDA)-approved in the US, SLIT will be an attractive immunotherapy option to many patients.

Oral allergen-specific immunotherapy

Oral immunotherapy (OIT) is more commonly thought of in relation to food allergy, though it has been studied in respiratory allergies for many years as well. OIT is administered in aqueous or encapsulated form in slowly increasing doses. As opposed to SLIT, the extract is immediately swallowed so that the allergen is mainly absorbed through the gut mucosa and taken up by the APCs in the gastrointestinal tract. Oral immunotherapy is thought to decrease the Th2 response to an allergen in favor of a Th1 response, but much of the tolerogenic mechanisms are similar to the ones for the development of oral tolerance to food allergens. Patients undergoing OIT for respiratory allergies have demonstrated an increase in serum IgG₄, but the serum IgE is not altered as described in previous sections.¹⁴

Although OIT has been studied primarily in pollen-allergic individuals,^{36–46} it has also been used to treat dust mite-allergic^{47,48} and cat-allergic subjects.⁴⁹ While many of the studies have demonstrated a significant decrease in symptom-medication scores,^{36,39,41,45,47} others have only demonstrated this result when high-dose extract is used,^{37,43} and still others have not shown any significant decrease in symptom-medication scores when compared to placebo.^{44,46,49} Taudorf et al³⁸ found that in adults with birch pollen-allergic rhinitis and conjunctivitis treated with OIT, there was a significant decrease in conjunctival sensitivity, though there was no significant decrease in nasal symptom scores, nasal sensitivity, or medication use when compared to placebo. Leng et al⁴⁰ investigated the effect of pollen OIT on bronchial sensitivity, and found that after 50 days of treatment, the patients in the active-treatment group showed a significant reduction in bronchial sensitivity, which was maintained at 3 months (Table 2).

Two studies have compared the efficacy of OIT when compared to SCIT. Urbanek et al⁴² compared SCIT to OIT with grass-pollen enterosoluble capsules in 60 children with grass pollen-allergic rhinoconjunctivitis. They found that OIT was ineffective at both low and high doses in reducing symptoms when compared with SCIT. Sánchez Palacios et al⁴⁸ looked at

Table 2 Summary of oral immunotherapy trials

Study	Design	Allergen	Total pts (A/P)	Disease	Results
Björkstén et al ³⁶	PC	Birch pollen	24 (16/8)	ARC	↓ symptom scores, conjunctival sensitivity
Möller et al ³⁷	DBPC	Birch pollen	30 (14/16)	ARC	↓ symptom scores, SPT, conjunctival sensitivity
Taudorf et al ³⁸	DBPC	Birch pollen	43 (20/23)	ARC ± asthma	↓ eye symptoms score, conjunctival sensitivity ↓ nasal symptom score, nasal sensitivity, medication use (NS)
Van Niekerk and De Wet ³⁹	DBPC + CO	Grass/maize pollen	30 (14/16)	ARC	↓ symptom scores, SPT, conjunctival sensitivity
Leng et al ⁴⁰	DBPC	<i>Artemisia</i> pollen	18 (9/9)	Asthma	↓ bronchial sensitivity
Litwin et al ⁴¹	Open	Ragweed pollen	18 (9/9)	ARC	↓ symptoms
Litwin et al ⁴³	DBPC	Ragweed pollen	41 (21/20)	AR	↓ symptom-medication scores
Van Deusen et al ⁴⁴	DBPC	Ragweed pollen	23 (12/11)	AR	↓ nasal sensitivity; ↓ symptom scores (NS)
Ariano et al ⁴⁵	DBPC	<i>Parietaria</i> pollen	30 (15/15)	AR ± asthma	↓ symptom scores, medication use, nasal/bronchial sensitivity
Mosbech et al ⁴⁶	DBPC	Grass pollen	42 (20/22)	ARC	No change in medication use or symptom scores
Oppenheimer et al ⁴⁹	DBPC	Cat	48 (23/25)	ARC	No difference in symptoms or SPT
Giovane et al ⁴⁷	DBPC	<i>D. pteronyssinus</i>	18 (10/8)	Asthma ± ARC	↓ symptom scores, conjunctival sensitivity; no change in SPT

Abbreviations: pts, patients; A/P, active/placebo; PC, placebo-controlled; DBPC, double-blind placebo-controlled; CO, crossover; ARC, allergic rhinoconjunctivitis; AR, allergic rhinitis; SPT, skin-prick test; NS, not significant; ↓, decreased.

the efficacy of OIT for dust-mite allergy in allergic asthmatic children when compared with SCIT. Though both groups had a significant reduction in symptoms at 6 and 12 months of treatment, SCIT was found to be more effective than OIT (Table 4).

Though only a few studies reported systemic side effects, including urticaria and angioedema,^{36,46} several studies reported side effects affecting the gastrointestinal tract in many of the patients in the active-treatment groups.^{36,46,49} The gastrointestinal side effects ranged from nausea and indigestion to diarrhea, vomiting, abdominal cramping, pain, and distention. Furthermore, two studies reported withdrawal of subjects due to side effects, including asthma exacerbation, urticaria, shortness of breath and hypotension, and gastrointestinal symptoms.^{38,49}

Based on the studies reviewed, the efficacy of OIT is questionable, and when compared to SCIT, studies demonstrated a significantly better outcome with SCIT. Although OIT may be a more convenient method of immunotherapy administration, its side-effect profile was also unacceptable for a large number of patients. Given both of these factors, it seems unlikely that OIT will remain a viable option for immunotherapy. Furthermore, SLIT provides another option with the same benefits, more proven efficacy, and a more acceptable side-effect profile.

Local nasal allergen-specific immunotherapy

Local nasal immunotherapy (LNIT), or intranasal immunotherapy, is administered by spraying allergen extracts into the nasal cavity. LNIT was first described in the 1970s, and has since been attempted with several different allergen preparations. When clinical trials of LNIT were initially started, they were done with aqueous unmodified extract and allergoids, which are chemically modified extracts (with glutaraldehyde or formaldehyde) in soluble form. While one group studied LNIT with grass extract,⁵⁰ another used ragweed extract.⁵¹ They both demonstrated that there were decreased symptom and medication scores in both the unmodified-extract and allergoid groups when compared to placebo, though the groups treated with unmodified extract had more frequent adverse events. Another study examining efficacy of grass LNIT found symptom and medication scores were significantly decreased in the group treated with unmodified extract, while there was no difference found between the allergoid and placebo groups.⁵² The adverse events in all groups consisted of local upper respiratory symptoms, such as nasal pruritus and rhinitis, and while the allergoid groups had fewer adverse events, efficacy was also decreased, and thus the usefulness of both preparations has been limited.

Numerous trials investigating the efficacy of LNIT with allergen extract in powder form have been completed. The dry powders typically consist of granules with a diameter of 40–50 μm . Allergen extract in powder form has been shown to be effective with *Dermatophagoides*⁵³ and pollens, including grass,^{54,55} *Parietaria*,^{56–58} birch,⁵⁹ alder,⁶⁰ and ragweed.⁶¹ Each study demonstrated that treatment with allergen extract in powder form decreased symptom scores and medication use, while systemic adverse effects were rare. In one study, three patients withdrew from the active group due to bronchial symptoms, which was attributed to incorrect technique.⁵⁷ Two studies investigated the efficacy of LNIT with extract in powder form in pollen-allergic children compared to placebo. While one demonstrated a significant decrease in symptom and medication use in the active-treatment group,⁶¹ the other found that the difference dissipated by the third year of treatment.⁶² Passalacqua et al⁶³ found that LNIT is clinically effective, though only with preseasonal, prophylactic administration, and once patients discontinued therapy, they had a clinical relapse of symptoms, while another study demonstrated that if therapy is continued for 3 years, there continues to be a reduction in symptoms and medication use, along with decreased bronchial hyperresponsiveness⁶⁴ (Table 3).

One study found that poor compliance with LNIT was due to discomfort of repeated nasal reactions, with over

50% of patients withdrawing from the study because LNIT was “unpleasant.”⁶⁵ Strips coated with *Dermatophagoides pteronyssinus* have now been developed for self-administration, and Tsai et al⁶⁶ performed a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of LNIT using these strips. Thirty-five patients were recruited, with 24 patients randomized into the active-treatment group with *D. pteronyssinus*-coated strips and eleven patients randomized into the placebo-treatment group with placebo-buffered saline (NS)-coated strips. A new strip was applied to the nasal septum for 10 minutes once weekly for 4 months. After the first month, five patients withdrew from the active-treatment group and two withdrew from the placebo group due to poor response to therapy. After 4 months of treatment, all symptom scores (nasal stuffiness, sneezing, and runny nose) were significantly improved in the active-treatment group, while only nasal stuffiness was significantly improved in the placebo group. Though the improvement in the active-treatment group was greater than in the placebo group, the difference was not significant.

While there have been no trials comparing LNIT to SCIT, its ease of administration was initially appealing. The studies investigating LNIT are extremely heterogeneous, though with conflicting results, which may be due to the many different forms of allergen extract utilized or the various lengths of time that patients were studied. Regardless of the

Table 3 Summary of local nasal immunotherapy trials

Study	Design	Allergen	Total pts (A/P)	Disease	Results
Georgitis et al ⁵⁰	DBPC	Grass pollen	44 (31/13)	AR	↓ symptom scores, medication scores
Nickelsen et al ⁵¹	DBPC	Ragweed pollen	67 (45/22)	AR	↓ symptom scores
Georgitis et al ⁵²	DBPC	Grass pollen, aqueous	31 (15/16)	AR	↓ symptom-medication scores
	DBPC	Grass pollen, allergoid	30 (14/16)	AR	No change in symptom-medication scores
Andri et al ⁵³	DBPC	<i>Dermatophagoides</i>	24 (12/12)	AR	↓ symptom scores, medication scores, nasal sensitivity
Pocobelli et al ⁵⁴	DBPC	Grass pollen	43 (22/21)	ARC	↓ sneezing, rhinorrhea, congestion, eyes itching, medication use
Andri et al ⁵⁵	DBPC	Grass pollen	32 (16/16)	AR	↓ symptom scores, medication scores, nasal sensitivity
Ariano et al ⁵⁶	DBPC	<i>Parietaria</i> pollen	20 (15/5)	AR	↓ symptom scores, medication scores, nasal sensitivity
D’Amato et al ⁵⁷	DBPC	<i>Parietaria</i> pollen	36 (13/13)	AR	↓ symptom scores, medication scores, nasal sensitivity
Andri et al ⁵⁸	DBPC	<i>Parietaria</i> pollen	24 (16/8)	AR	↓ medication scores, nasal sensitivity; no change in symptoms
Andri et al ⁵⁹	DBPC	Birch pollen	30 (15/15)	AR	↓ medication scores, nasal sensitivity
Cirila et al ⁶⁰	DBPC	Birch/alder pollen	22 (11/11)	AR	↓ medication use, sneezing, rhinorrhea
Cserháti and Mezei ⁶¹	DBPC	Grass pollen	24 (12/12)	AR	↓ medication use, nasal sensitivity, symptom scores
		Ragweed pollen	24 (12/12)	AR	Less pronounced than with grass pollen
Bardare et al ⁶²	DBPC	Grass pollen	39 (19/20)	ARC	↓ nasal and eye symptoms for 2 years; no difference at 3 years
Olivieri et al ⁶⁴	Open	<i>Parietaria</i> /graminaceae	43 (24/19)	ARC ± BHR	↓ symptom scores, medication use, BHR
Tsai et al ⁶⁶	DBPC	<i>Dermatophagoides</i>	35 (24/11)	AR	↓ nasal symptoms

Abbreviations: pts, patients; A/P, active/placebo or standard; DBPC, double-blind placebo-controlled; ARC, allergic rhinoconjunctivitis; AR, allergic rhinitis; BHR, bronchial hyperresponsiveness; ↓, decreased.

Table 4 Summary of studies comparing novel routes to SCIT

Study	Type	Total pts (study route/SCIT)	Disease	Results
Di Bona et al ²⁸	SLIT	5782 (3014/2768)	ARC + asthma	SCIT, symptoms -0.92 (-1.26 to -0.58), medication use -0.58 (-0.86 to -0.30) SLIT droplets, symptoms -0.25 (-0.45 to -0.05), medication use -0.37 (-0.74 to 0.0) SLIT tablets, symptoms -0.40 (-0.54 to -0.27), medication use -0.30 (-0.44 to -0.16)
Dretzke et al ²⁷	SLIT	Unclear	AR	Favors SCIT, with greater improvement in symptom and medication scores
Urbanek et al ⁴²	OIT	45 (30/15)	ARC	No symptom improvement with OIT when compared to SCIT
Sánchez Palacios et al ⁴⁸	OIT	28 (14/14)	Asthma	SCIT is more effective
Senti et al ⁸⁵	ILIT	112 (58/54)	ARC	Comparable long-term results, but improvement seen more quickly in ILIT group

Abbreviations: pts, patients; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; OIT, oral immunotherapy; ILIT, intralymphatic immunotherapy; ARC, allergic rhinoconjunctivitis; AR, allergic rhinitis.

reason, the use of LNIT has been declining and will likely continue to decline as SLIT becomes more popular, since SLIT is easier to manage and administer. The most recent study examining LNIT used allergen-coated strips, which may become a viable option, but further research needs to be completed.

Epicutaneous allergen-specific immunotherapy

Epicutaneous, or transcutaneous, immunotherapy has been attempted as a method of allergen-specific immunotherapy since the mid-twentieth century. In 1957, Pautrizel et al⁶⁷ reported that they attempted to treat pollen and house dust-mite allergy by applying liquid drops of allergen extracts onto scarified skin, and though effective the treatment was not well tolerated. Shortly after, in 1959, Blamoutier et al⁶⁸ used the same procedure to treat pollen allergy and reported that adverse events were rare. More recently, epicutaneous immunotherapy has been conducted by applying patches containing the desired allergen to the skin after tape-stripping. The patches are left on the skin for 48 hours and applied weekly. Tape-stripping not only decreased the cornified layer of the epidermis, but also activated keratinocytes to produce proinflammatory cytokines and enhanced the penetration of the antigen into the epidermis.⁶⁹ The antigens are delivered to the many immune cells that reside in the epidermis of the skin, including epidermal dendritic cells, or Langerhans cells, which are some of the most efficient APCs in the body.^{70,71} Theoretically, these Langerhans cells then migrate to the regional lymph nodes and eventually lead to antibody responses after repeated epicutaneous exposure to protein antigens.⁷² Furthermore, since the epidermis is not

vascularized, the risk of systemic reactions and side effects should be minimized.⁷³

Senti et al⁷³ reported the results of a double-blind, placebo-controlled trial evaluating the safety and efficacy of epicutaneous allergen-specific immunotherapy with grass-pollen allergens in patients with allergic rhinitis. The authors enrolled 37 patients with grass-pollen sensitivity determined by skin-prick and nasal provocation testing. Subjects were then randomized to receive patches with petroleum jelly containing either grass allergen or placebo, and after tape-stripping each patch was applied for 48 hours once weekly for 12 weeks. Those subjects who had received grass allergen rated their overall treatment success significantly higher than the placebo-treated subjects, though there was no significant difference in nasal provocation testing and rescue-medication use between the two groups after treatment. The most common adverse event reported was eczema under the patch site, with no reports of severe adverse events.^{73–75}

In another randomized, double-blind, placebo-controlled trial, Senti et al⁷⁶ tested the effective dose range, safety, tolerability, and treatment effect of epicutaneous immunotherapy. Patients with grass pollen-induced rhinoconjunctivitis were randomly assigned to placebo or one of three different allergen-dose groups (low, medium, or high). Patches were placed on the upper arm after tape-stripping and left for 8 hours. Each subject received six weekly patches and recorded their symptoms and medications, then underwent conjunctival provocation testing and repeat skin-prick testing. A clear dose–response relationship was noted, with the high-dose group reporting the most improvement in symptoms. The high-dose group had more than 30% reduction in symptoms during the first season and 24% reduction in symptoms

the following season. There was no significant difference in the use of rescue medication, the degree of improvement in conjunctival provocation, or skin-prick testing between groups. Though the subjects in the higher-dose group had better clinical outcomes, they also experienced more adverse events. The adverse events typically included pruritus, erythema, wheal, or eczema. There were, however, eleven systemic adverse events, which prompted the cessation of treatment; only one subject with a systemic reaction was given placebo. All of the systemic allergic reactions were treated with intravenous corticosteroids and antihistamines, but none required hospitalization or epinephrine.⁷⁶

These studies suggest that epicutaneous immunotherapy can be an effective route of administration when given in appropriate doses for allergen-specific immunotherapy, although safety and tolerability of administration must be considered along with efficacy. The ease of administration will likely be attractive to many patients for the treatment of allergic rhinoconjunctivitis and allergic asthma, but further studies need to be conducted to elucidate the safety of this administration route.

Intralymphatic allergen-specific immunotherapy

Intralymphatic immunotherapy (ILIT) is administered by direct injection of an allergen into the lymph nodes. Studies were initially performed in animals, which demonstrated that direct intralymphatic injection with vaccines^{77,78} was both feasible and efficient in inducing immune responses against viruses and tumors.⁷⁹⁻⁸¹ Intralymphatic administration of allergen in mice appears to stimulate production of the Th1-dependent subclass IgG_{2a} at much lower allergen doses than subcutaneous injections. Furthermore, biodistribution studies demonstrated that intralymphatic injections delivered antigen more efficiently to lymph nodes than subcutaneous injections.⁸² Allergen-specific ILIT is now being studied in clinical trials as a possible alternative to SCIT for allergic rhinoconjunctivitis and allergic asthma.

Hylander et al⁸³ conducted a two-part study to determine if ILIT is safe and effective. The first part of the study was an open trial, which included six patients. Patients received three intralymphatic inguinal injections of either birch or grass-pollen extract separated by 4 weeks each. Each injection was performed under ultrasound guidance. In the open study, all patients tolerated the injections well, demonstrated improvement in allergic symptoms, and decreased medication use. The second part of the trial was a double-blind, placebo-controlled trial that enrolled 15 new patients. Seven

patients were randomized to receive allergen injections, and eight were randomized to the placebo group. Those patients in the active-treatment group had a significantly greater reduction in symptoms than the placebo group, and there were no severe adverse events reported.

In a randomized, double-blind, placebo-controlled trial, 20 patients were randomized to receive ILIT with either a recombinant major cat allergen (Fel d 1) vaccine or placebo. The injections were given approximately once per month under ultrasound guidance, and the vaccine was given in increasing doses with each injection for safety reasons. After three injections, the vaccine increased nasal tolerance of cat allergen 74-fold, while placebo injections only caused a three-fold increase in nasal tolerance. ILIT with the cat-allergen vaccine also stimulated T-cell responses and increased cat-specific IgG₄, whereas patients who received placebo injections did not demonstrate these changes. Reports of nasal and ocular symptoms revealed lower levels in the vaccine group when compared with the placebo group, although statistical significance was not reached, which might have been due to the low patient numbers in the study. There was no significant difference between the groups in the number of drug-related adverse events, and there were no reports of severe adverse events. The most common adverse event reported in both groups was lymph-node swelling, which resolved in all patients by the end of the trial.⁸⁴

One clinical trial compared SCIT to ILIT in 165 patients with allergic rhinoconjunctivitis due to grass pollen. Patients were randomized to receive either three intralymphatic injections over a 2-month period or conventional SCIT for 3 years. Intralymphatic injections were given directly into an inguinal lymph node under ultrasound guidance. The patients receiving the intralymphatic injections reported that the pain of the intralymphatic injection was significantly less than the pain of venous puncture done during the same visit. Fewer allergic adverse events were reported in the ILIT group when compared to the SCIT group. Furthermore, the adverse events reported by the ILIT group were all mild, while there were two severe allergic adverse events reported by the SCIT group. Allergen tolerance was induced significantly faster in the ILIT group (by 4 months) when compared with the SCIT group (by 1 year), with comparable long-term results. Additionally, there was less use of rescue medications in the ILIT group during the first pollen season, but there was no difference between the groups in medication use by the third pollen season. There was also comparable subjective-symptom amelioration and reduced skin-prick sensitivity in patients in the ILIT group when compared with patients in the SCIT group⁸⁵ (Table 4).

In the very limited number of studies to date with a limited number of treated patients, ILIT is an appealing option for allergen-specific immunotherapy because it can be completed in a few weeks as opposed to several years. While intralymphatic administration of allergen-specific immunotherapy appears to be safe, effective, and well tolerated, it also requires additional machinery and trained clinical personnel to provide the therapy. Further studies are needed to determine the appropriate treatment dose required for therapy, safety, and long-term efficacy.

Discussion

With the increasing incidence of atopy in developed countries, there is a strong desire to find safe and effective treatments for allergic diseases. Allergen immunotherapy has been demonstrated to be an effective treatment for allergic rhinitis, conjunctivitis, and asthma, leading to a reduction in symptoms and medication usage when done properly. Though SCIT is currently the only approved route of immunotherapy in the US, the FDA will likely approve SLIT in the near future, given the promising clinical trials that have been conducted. Furthermore, SLIT is used regularly in Europe, and its use is increasing in the US despite the lack of FDA approval.

Though OIT and LNIT are also viable options for immunotherapy, the convenience and breadth of data regarding SLIT will likely prevent their use from becoming widespread. If allergen-coated nasal strips are studied further for use in LNIT, it may become a more appealing option to patients and physicians. Epicutaneous immunotherapy is also a promising alternative, especially for patients who may not be able to tolerate the local side effects of sublingual, oral, or local nasal immunotherapy, though much more research needs to be completed before epicutaneous immunotherapy would be approved for general use. Lastly, ILIT may be one of the most promising routes of immunotherapy, given the small number of doses required to see results. Once again, more studies need to be done before ILIT becomes used more widely, and its administration would require substantial training of any professionals who may want to administer it for their patients.

Besides novel routes of allergen immunotherapy, there has been new research looking into allergen vaccines for potential use in immunotherapy. The goal with modified allergen vaccines is to produce allergens with reduced allergenicity to limit the adverse reactions, while they maintain their immunogenicity to provide effective treatment options for allergic respiratory diseases.⁸⁶ In conclusion, newer, more convenient, and safer routes of allergen immunotherapy are

being examined thoroughly, and one day will provide more accessible and efficacious options for the treatment of allergic respiratory diseases.

Disclosure

The authors report no potential conflicts of interest relevant to this article.

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