



Use of allergen immunotherapy for treatment of allergic conjunctivitis

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Purpose of review

The purpose of this article is to provide an overview of the literature pertaining to the use of allergen immunotherapy for treatment of allergic conjunctivitis with an emphasis on recent developments.

Recent findings

Both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy continue to show efficacy in treating allergic conjunctival disease, subcutaneous more than sublingual. Adverse effects of sublingual therapy continue to be reported since the FDA's approval of SLIT tablets in 2014. Initial SLIT studies reported high rates of adherence, while real use reports identify rates of nonadherence/discontinuation ranging between 50 and 80%. Studies in polyallergic patients evaluating the efficacy of SLIT combination therapy report encouraging results.

Summary

Both SCIT and SLIT offers improvement in allergic conjunctival symptom scores and decrease medication utilization. Although SCIT has a higher likelihood of systemic reaction, SLIT has a very high rate of mild-to-moderate adverse events – especially in the first month. Cost–benefit analyses tend to favor SCIT (greater efficacy and less impacted by discontinuation rates).

Keywords

allergic conjunctivitis, ocular allergy, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

Allergic conjunctivitis is ocular-surface inflammation that results from an IgE-mediated allergic reaction. Symptoms may be seasonal or perennial depending on the allergen. The most prevalent symptoms of allergic conjunctivitis, ranging in intensity from mild to severe, are ocular itching, redness, tearing, and conjunctival edema. These ocular symptoms are the result of both early and late phase IgE-mediated reactions, separating allergic conjunctivitis from vernal and atopic keratoconjunctivitis [1]. Allergic conjunctivitis is often associated with allergic rhinitis, affecting ~90% of patients with rhinitis at least once a week during a pollen season [2]. Although ocular symptoms were once ranked secondary to nasal symptoms, they now appear equal to, or greater than, nasal symptoms at specific seasons.

Up to 40% of the United States population is thought to be affected by allergic eye disease [3], costing Americans 2–4 billion dollars annually [4]. The exact prevalence of allergic conjunctivitis is hard to determine as conjunctival symptoms are not often spontaneously reported in medical interviews or in questionnaires designed for epidemiologic studies targeting rhinitis and/or asthma [5]. The prevalence of allergic conjunctivitis is thought to be increasing

annually, representing 25–50% of all ocular allergy [6,7]. Management of ocular allergy currently entails encouraging environmental control measures alongside one or more of the following: the use of pharmacotherapy, immunotherapy, herbal treatments, ocular lubricants, lipid conjugates, and physical barrier devices [8]. Of the aforementioned, allergen-specific immunotherapy (AIT) is the only therapy shown to modify the disease process.

MECHANISM OF ALLERGEN IMMUNOTHERAPY

Allergic eye disease involves anterior ocular surface inflammation, mediated primarily by environmental

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KEY POINTS

- Both SCIT and SLIT offer improvement in conjunctival symptom scores and decrease medication utilization.
- SCIT offers greater symptomatic control than SLIT, however SLIT has the convince factor of being able to use at home after first administration.
- Patients receiving SLIT has a very high incidence of mild-to-moderate adverse effects – especially at the initiation of therapy – but rarely develop systemic or severe reactions at the rate seen with SCIT.
- Both SLIT and SCIT are affected by high rates of nonadherence and discontinuation; however, nonadherence to SLIT may potentially be improved by either in-office or telehealth check-in visits.
- Although both are cost effective, SCIT is potentially more cost-effective as is more efficacious and less impacted by nonadherence/discontinuation rates.

aeroallergens that stimulate specific IgE-mediated mast cells to degranulate, stimulating a subsequent release of inflammatory markers [9]. The histamine H1 receptor has classically been the target of therapy for allergic conjunctivitis, but the H2 receptor is also involved in the development of vasodilation of the ocular surface [10]. The underlying mechanism by which AIT modulates the disease process, although not completely elucidated, is currently understood to be a four-stage cascade of immune responses at the cellular and molecular level [11] (Fig. 1).

BRIEF HISTORY OF ALLERGEN IMMUNOTHERAPY

The first reported use of antigen immunotherapy was in 1911, where Leonard Noon identified pollen-specific injection immunotherapy suppressed ocular symptoms by injecting patients with increasing

doses of pollen extract prior to challenging them with eye drops of antigen [12]. The concept of sublingual immunotherapy (SLIT) also was experimented with during this time but had fallen out of favor by the 1930s. In 1935, the development of a ‘protective factor’ in serum after ragweed subcutaneous immunotherapy (SCIT) was identified by Cooke *et al.* [13], which lead to the conceptualization of ‘blocking antibodies’. Anecdotal (i.e., off-label) use of SCIT continued until the 1960s, with the turning point toward more scientifically rigorous evaluation of SCIT’s efficacy being Lowell and Franklin’s [14] 1965 double-blind, placebo controlled study. In the 1980s, increasing concern regarding the safety of desensitization in the United Kingdom spurred strong international regulation of performing SCIT and heightened interest in finding a safer, alternative mode of offering specific immunotherapy [15]. A renewed focus in sublingual administration began around this time, with the first major randomized study of a sublingual protocol for house dust mite AIT published by Scadding and Brostoff in 1986 [16].

EFFICACY OF ALLERGEN-SPECIFIC IMMUNOTHERAPY IN TREATING ALLERGIC CONJUNCTIVITIS

SCIT has long been the standard for AIT, with literature traditionally focused on reduction of nasal rather than ocular symptoms. In recent years, a strong body of literature has emerged supporting the use of SCIT for symptomatic relief of conjunctival symptoms stemming from both seasonal and perineal allergies [17[■],18]. As for SLIT, Calderon *et al.* put forth the first major systematic review in 2011 evaluating the efficacy of SLIT for treating allergic conjunctivitis. They included 42 trials in their review, finding SLIT was moderately effective in reducing total and individual ocular symptom scores in participants with allergic conjunctivitis [19].

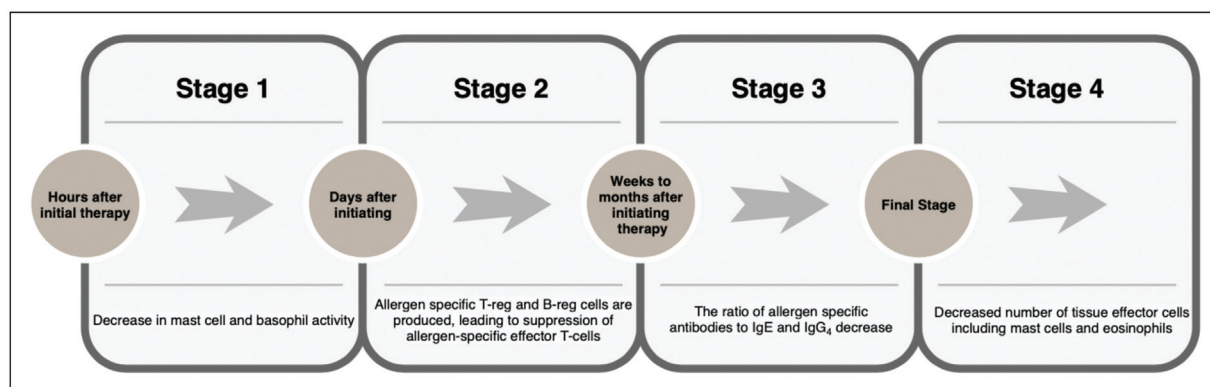


FIGURE 1. Simplified mechanism behind allergen immunotherapy.

A 2015 systematic review expanded on Calderon [20], finding SLIT offered a small benefit toward reducing symptom score and medication score in relation to a large (61%) rate of adverse effects in patients taking SLIT compared with placebo. The small benefit in symptom and medication scores, while statistically significant, was less than a one-point difference on a score scale of 0–18. Notably lower than the original studies it pulled from, authors attributed the difference to both the utilization of a different metric than original authors as they felt it offered a more accurate representation of the data and included more recent randomized control study data from the United States where efficacy had been lower than earlier European studies.

Recent publications continue to support the clinical utility of SLIT in managing allergic conjunctivitis. A Spanish cross-sectional, multicenter observational study looking at quality of life scores showed favorable levels of health-related quality of life and treatment satisfaction scores with concomitant improvements in ocular itch, tearing, and symptomatic medication use in patients treated with five-grass pollen tablets [21]. One multinational randomized, double-blind placebo-controlled phase III trial evaluating the efficacy and safety of SQ tree SLIT-tablets showed statistically significant improvement in average allergic rhinoconjunctivitis total combined score during the birch pollen season with the SQ tree SLIT-tablet compared with placebo, with a difference of 40% relative to placebo ($P < 0.0001$) exceeding clinical relevant difference of 20% compared with placebo [22]. A multinational meta-analysis inclusive of 13 pediatric randomized control studies revealed SLIT effectively reduced ocular symptom scores in children when compared with placebo [23]. They further found that SLIT effectively treated pollen-induced pediatric allergic conjunctivitis ($P < 0.0001$) but not mite-induced allergic conjunctivitis ($P = 0.34$), albeit only four studies inclusive of 318 patients pertained to mite allergen. Of note, SLIT treatment of pediatric allergic conjunctivitis or allergic rhinoconjunctivitis was effective in the study when SLIT tablets were used ($P < 0.00001$) but not drops ($P = 0.47$) [23]. In a prospective, case-control study of 120 patients being treated for mite allergy, the total symptom score for allergic conjunctivitis attributable to dust-mite decreased from 20.89 to 10.0 ($P = 0.0002$) [24]. An Egyptian prospective comparative case series of 100 patients (50 SLIT, 50 SCIT) evaluating the 1-year clinical and immunologic efficacy and safety of subcutaneous allergen immunotherapy in allergic conjunctivitis found a significant reduction in total serum IgE and wheal diameter of skin prick testing following SCIT and SLIT compared with baseline

with no significant difference between both groups and no statistically significant difference in total ocular symptom score and medication score favoring SLIT or SCIT [25].

Both SCIT and SLIT have been shown to have long-term efficacy after discontinuation of treatment. A recent Chinese study of 124 patients who received standardized extracts *Dermatophagoides pteronyssinus* for 3 years found significant control of ocular symptoms 5 years after discontinuation of treatment [26]. SLIT had similar longevity, with studies of grass SLIT demonstrate 2-year sustained clinical benefit following a 3-year course of continuous therapy [27,28]. A French prospective cohort study of 280 adults and 203 children found that five-grass-pollen extract SLIT resulted in more than 50% of patients having no recurrence of symptoms 1-year after initiating therapy, with 42.4% of children reporting signs of conjunctivitis on most days during the 2015 pollen season compared with 84.2% the year before; adults reported a similar decrease in ocular symptoms, from 90.0 to 42.1% [29]. Studies that directly compared SLIT versus SCIT in regard to difference in long-term efficacy are required.

ADVERSE EVENT REPORTING AND ALLERGEN-SPECIFIC IMMUNOTHERAPY

In 2015, the 61% adverse event rate for SLIT identified by Di Bona *et al.* was found to be predominantly localized, mild-to-moderate symptoms such as oral pruritus and throat irritation [20]. Recent studies have also found oral pruritus, ear pruritus, mouth edema, sensation of foreign body, throat irritation, pharyngolaryngeal pain, dry throat, tongue blistering, eye pruritus, and headache to be common [30]. An observational cohort looking at five grass pollen extract SLIT found 56% of patients were identified as having an adverse drug reaction in the first month; 83% of adverse drug reactions occurred within 1 week of starting treatment with more than half of reactions lasting less than 2 days, resolving spontaneously in 93% of patients [31]. The proportion of adverse event reporting did not significantly differ by age in this study (adults 26.8%, children 23.2%). A comprehensive review of 66 studies representing 4378 patients receiving SLIT (1181 000 SLIT doses) also showed oromucosal reactions occurred in up to 75% of patients but were more commonly seen in the buildup phase [32]. Although mild-to-moderate symptoms were more frequently reported, the same review showed 169 (0.056%) of 314 959 SLIT doses administered were classified as producing a systemic reaction, compared with the 0.1–0.2% rate of systemic reactions attributable to SCIT [33]. SCIT may also result in delayed systematic reactions within

Table 1. Contraindications to allergen-specific immunotherapy

Absolute contraindications	Relative contraindications
Uncontrolled or severe asthma	Partially controlled asthma
Systemic autoimmune disease unresponsive to treatment	Systemic autoimmune disease in remission
Pregnancy	Severe cardiovascular disease
	Local/systemic β -blockade
	Severe psychiatric disorder
	Poor adherence
	1° or 2° Immunodeficiency
	History of systemic reaction to immunotherapy

30 min of administration, necessitating in-office monitoring after administration [35]. Refer to Table 1 for absolute and relative contraindications to receiving AIT.

ALLERGEN-SPECIFIC IMMUNOTHERAPY FOR THE POLYALLERGIC

The prevalence of polysensitization is between 51 and 82% in patients with allergic sensitivity in both Europe and the United States [35]. This range is inclusive of both actual and potential polyallergic patients. In the United States, SCIT preparations contain eight allergens on average [36]; this compares with Europe where only one or two allergen extracts are used [36]. This discrepancy stems from a long-standing debate on whether polysensitization represents clinically significant polyallergy or allergen cross-reactivity. Although SCIT has been given in combination efficaciously for decades, there is presently no consensus pertaining to the safety or efficacy of administering multiple SLIT products in combination. Several smaller studies exist offering conflicting conclusions. Whereas favorable results were found in polyallergic patients treated with grass/olive SLIT and grass/birch SLIT [37,38], decreased specific IgG4 levels for Timothy grass were found in patients treated with timothy grass and nine other pollen allergen extracts versus timothy grass monotherapy [39]. The largest study pertaining to safety was a phase 4, multicenter, open-label North American trial that found dual administration of ragweed and grass AIT was well tolerated, with no severe local swelling or systemic reactions even when spaced 5 min apart [40]. Although study authors suggest coadministration to be safe, they noted an increase in mild-to-moderate local swelling events during the initial coadministration phase

and were unable to comment on the long-term effects of coadministration on treatment efficacy.

IMPACT OF THE PLACEBO EFFECT

With respect to efficacy versus placebo effect, a recent systematic review by Abramowicz *et al.* showed the placebo effect amounted to 39% of the overall effect of AIT, with a significantly higher share ($P < 0.01$) of 68% of the placebo effect in adult patients treated with SLIT versus 29% in adult patients treated with SCIT [41]. Although the placebo effect was higher in SLIT, it has been shown in different studies to impact clinical outcomes in a dose-dependent manner. An example of this can be seen in a recent Japanese randomized, placebo-control, double blind randomized control trial of 1042 adult and pediatric patients divided patients into four groups: experimental/experimental, experimental/placebo, placebo/experimental, and placebo/placebo and evaluated symptomatology using several different symptom scoring systems [42]. It showed superior symptom control at higher dose (5000 JAU tablet) than lower doses (2000 JAU drops), supporting dose-dependent effect in relieving allergic conjunctivitis symptoms in these patients. There was also a recent 15-year study of patients monosensitized to dust mite suggestive that SLIT may prevent future sensitizations, with the rate of new sensitizations among patients receiving SLIT was 11–21% of patients versus 100% of control group [43].

LIMITATIONS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

Although proven efficacious in many well designed studies and systematic reviews, AIT requires adherence for at least 3 years for it to be successful. As with management of any chronic disease, patient adherence to chronic disease management is the main challenge [44]. There have been many studies comparing the rates of nonadherence and discontinuation of SLIT versus SCIT, with percentages ranging between 50 and 80s (Table 2). Among reasons cited for discontinuing AIT, one study found SCIT patients report inconvenience ($P = 0.022$), whereas SLIT patients indicate efficacy concerns ($P = 0.022$) as the major basis for withdrawal [45]. There is sparse SCIT-specific and SLIT-specific literature addressing means of improving adherence to therapy. Improving adherence will likely require improved communication with patients, adequate information at the start of therapy as to the commitment required for efficacy, utilization of telehealth, and the development of a standardized follow-up protocol [44]. An

Table 2. Subcutaneous immunotherapy versus sublingual immunotherapy nonadherence/discontinuation rates

Country, citation	No of patients	SCIT discontinuation	SLIT discontinuation
Germany, [50]	2429 SLIT	46% (year 2)	59% (year 2)
	2109 SCIT	64% (year 3)	69% (year 3)
Germany, [51]	123 SLIT	39.0% (year 3)	32.4% (year 3)
	207 SCIT		
Germany, [52]	112 SLIT	41–45% (year 1)	29% (year 1)
	1297 SCIT	61–66% (year 2)	49% (year 2)
The Netherlands, [53]	3690 SLIT	77% (year 3)	93% (year 3)
	2796 SCIT		
Germany, [54]	706 SLIT	0–36% (year 1)	39–48% (year 1)
	85 241 SCIT	27–58% (year 3)	77–85% (year 3)
Italy, [55]	87 SLIT	15.6% (year 1)	33.4% (year 1)
	90 SCIT	25.6% (year 2)	44.8% (year 2)
		26.7% (year 3)	46.0% (year 3)

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

example of this can be seen in one prospective study where patients visiting the clinic every 3 months had a 8.1 and 10.4% withdrawal rate at the end of years 1 and 2, respectively; this compared with 14.7 and 17.6% rate of withdrawal with biannual visits and 29.3 and 41.1% rate of withdrawal with annual visits [46].

Regarding costs, both SCIT and SLIT are felt to be cost-effective after 6 years [47]. There is insufficient data to directly compare the effectiveness of SLIT versus SCIT. Using a Markovian model, one study found SCIT was slightly more expensive however more cost-effective than SLIT as it was less affected by discontinuation rates [48]. Although SCIT was found to systematically outperform SLIT (except when a full societal perspective was considered) in a different study evaluating cost-effectiveness of grass allergen immunotherapy also using a

nonstationary Markov model, authors were unable to conclude one or both were cost-effective for allergic rhinoconjunctivitis as a reliable threshold value for 'cost effectiveness' had not been set by national regulatory agencies for pharmaceutical products [49].

CONCLUSION

For correctly selected patients, SCIT or SLIT is recommended for allergic rhinoconjunctivitis as it is safe and well tolerated when appropriately administered [34]. AIT is the only therapy available shown to modify the disease process. Both will offer improvement in conjunctival symptom and medication utilization scores, more so with SCIT. SLIT is being increasingly used with polysensitized patients and in combination regimens with success. Adverse

Table 3. Key points: subcutaneous immunotherapy versus sublingual immunotherapy

Efficacy	Both SCIT and SLIT offer improvement in conjunctival symptom scores and decrease medication utilization; however, SCIT appears to have greater efficacy when compared with SLIT
Adverse events	Patients receiving SLIT has a very high incidence of mild-to-moderate adverse effects – especially at the initiation of therapy – but rarely develop systemic or severe reactions at the rate seen with SCIT
Adherence	Although SLIT has the convenience factor of home administration, current literature shows adherence is just as poor, if not worse, than SCIT
Polysensitization	Although SCIT is traditionally used, there is growing use of SLIT in polysensitized patients. More research is needed as to determine superiority of one treatment over the other
Cost	Although both are cost effective compared with placebo after long-term administration, SCIT is potentially superior to SLIT as has a greater impact on reducing symptom and medication scores while being less prone to discontinuation/nonadherence
Recommendation	There is insufficient evidence to recommend one over the other empirically without consideration of individual patient circumstances, thus the decision for SLIT or SCIT should remain open to patient preference based on his or her clinical situation

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

effects with SLIT are common, especially at initiation of therapy, and may contribute to the high rate of nonadherence/discontinuation. Although limited economic analyses currently favor SCIT, successful interventions to improve SLIT adherence need to be developed. The decision for either SCIT or SLIT remains a patient-directed decision, with adherence being the greatest hurdle for either method of administration (Table 3).

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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