



Advances in aeroallergen immunotherapy

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Purpose of review

Allergic rhinoconjunctivitis is the most common manifestation of allergic disease. This break in the normal natural function of the immune system to ignore harmless molecules such as pollen and pet dander to now aggressively react has lead to a substantial disease burden that is not always recognized and adequately treated.

Recent findings

Individual molecular component testing may increase the predictive value of blood sIgE and clinical symptoms. Defining the most symptoms inducing allergenic protein has led to advances in peptide-based allergen immunotherapy. There have been steady consistent reports that allergy immunotherapy for children with symptomatic allergic rhinitis prevents the onset of asthma.

Summary

Allergy immunotherapy is an effective disease-modulating treatment that alters the underlying immune dysfunction which is a currently underutilized therapy especially as it is likely effective in preventing the onset of asthma in children, at least in the short term.

Keywords

allergic rhinitis, asthma, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

Allergic diseases are common conditions that cause considerable morbidity. Symptoms of allergic rhinitis are characterized by post allergen exposure congestion, recurrent bouts of rhinorrhea, sneezing, and when combined with ocular symptoms of itchy watery swollen eyes and conjunctivitis, it is termed allergic rhinoconjunctivitis (ARC). Allergic rhinitis and ARC is a global health problem that affects 10–30% of the population [1]. Allergy to dogs and cats has long been considered a major risk factor in the development of allergic rhinitis and asthma [2,3]. Studies have estimated 33% of Americans with asthma more than 6 years old who are sensitized to dogs with exposure resulted in an additional 1 161 000 asthma attacks and 349 000 excess emergency department visits [4]. The prevalence of sensitization has increased in the United States [5], and continues to increase worldwide [6].

Despite the high prevalence, allergic rhinitis remains undertreated and underappreciated. Of 518 allergic rhinitis patients who answered a questionnaire targeting symptoms, treatments, and quality of life impairment; 26.3% of participants with self-reported symptoms did not receive pharmacologic treatment and 13.7% were undertreated [7]. Poor adherence to treatment, lack of efficacy, side-effects, duration of treatment before

symptomatic relief, and costs are all associated with the high morbidity from allergic rhinitis [8].

Traditionally, allergic rhinitis has been classified into two types: perennial or seasonally/episodic, yet there has been a shift to focus on the severity of symptoms. The World Health Organization (WHO) has been advocating the categorization of allergic rhinitis based on symptoms: intermittent, persistent, mild, or moderate-severe (Table 1) to help facilitate the discussion between treating physicians and patient on treatment strategies [9].

TESTING OPTIONS

Immediate hypersensitivity skin prick testing still remains the most popular method of detecting a person's sensitization status to allergens. Serum specific IgE (sIgE) can be obtained to aeroallergens, though no established thresholds exist that correlate with symptoms. The use of allergen-specific IgG

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KEY POINTS

- Allergic rhinitis is a very common disease with high societal burden that is underappreciated.
- Avoidance strategies in conjunction with medication can decrease symptoms.
- Allergy immunotherapy is currently the only disease-modifying treatment option though it is underutilized.
- Early intervention with allergen immunotherapy may not only improve allergic rhinitis control, but also prevent asthma.

has not been proven useful for diagnosis nor management of allergic diseases.

Although commercially available, multiplex microarray assay systems developed to simultaneously measure serum sIgE to many individual recombinant and natural component allergen proteins in a single assay is still rarely used, even in academic settings. These component resolved diagnostic (CRD) tests are gradually emerging as important tools in allergy diagnosis. In allergies to dogs, there are seven named component dog allergen [10] and CRD identified children sensitized to Can f 4 and Can f 6 were associated with nasal provocation positive tests whereas Can f 5 mono-sensitization was linked to negative challenges supporting the notion that individual allergens cause specific clinical reaction [11²²]. But, in 23 cockroach sensitized individuals with asthma, allergic rhinitis, or both, the sensitization profile to eight components were unique to each subject without immunodominance [12²³]. Allergies to different allergens will likely yield different component sensitization profiles.

Table 1. Classification of allergic rhinitis severity by duration and severity

Non allergic rhinitis
Allergic rhinitis
Intermittent
Symptoms <4 days of the week or <4 consecutive weeks
Persistent
Symptoms >4 days of the week or >4 consecutive weeks
Mild
Normal sleep without impairment of activities of daily living, sport, or leisure
Not bothersome
Moderate/severe
Abnormal sleep or impairment of activities of daily living, sports, or leisure
Bothersome symptoms

When cross-reactivity is a concern, CRD seems useful. In a study of olive and grass sensitization and cross-reactivity (both plants pollenate at the same time), when the molecular sIgE to olive specific protein Ole e 1, and grass-specific proteins Phl p 1+5 and Phl p 7+12 data was available to treating allergy specialists, the prescription of immunotherapy mixture was changed in nearly 53% of cases [13]. The component sIgE alters treatment strategies when traditional testing methods were inconclusive. Further characterization and quantification of all identified allergenic proteins in each extracts may therefore be necessary to ensure the consistency and potency of extracts used in immunotherapy and diagnostic testing.

PATHOPHYSIOLOGY OF ALLERGIC RHINITIS

The accepted paradigm underlying allergies is that allergen binding to preformed allergen sIgE bound to high affinity IgE receptors (FcεRI) on mast and basophil cell surfaces leads to cross-linking resulting in aggregation of the FcεRI thus triggering an intracellular molecular cascade that results in the immediate secretion of preformed inflammatory mediators in cytoplasmic granules that lead to vasodilation, increased vascular permeability, and contraction of smooth muscles [14]. A subsequent Th2 response ensues with the release of cytokines such as interleukin-3, interleukin-4, interleukin-5, and interleukin-13.

Interestingly, sIgE can be secreted and act locally initiating the allergic response without being detectable systemically. Studies in local allergic rhinitis (LAR) of individuals with negative immediate hypersensitivity skin prick testing and serum sIgE, but a consistent history of reproducible allergic symptoms have measurable sIgE in nasal secretions and nasal provocation challenges do elicit responses. Initially thought to be rare in children, in difficulty to treat children diagnosed with nonallergic rhinitis, nearly 29% (7/24 study participants) had confirmed LAR by nasal provocation testing [15²⁴]. A 10-year study of 176 patients with LAR suggests the natural course entails worsening symptoms with increasing incidences of asthma, but without a significantly increased rate of developing systemic markers of allergic rhinitis compared to controls [16]. Nasal provocation testing may become a necessary part of future clinical evaluations.

SYMPTOMATIC MANAGEMENT

Intranasal corticosteroids have been the mainstay treatment of choice for patient with mild persistent or moderate/severe since they are the most effective medication for controlling all rhinitis symptoms

[17,18]. Gradual alterations in formulations (to remove the alcohol) and delivery mechanisms continue such as a new exhalation-activated system for fluticasone propionate currently only used to treat nasal polyps [19]. Implantable mometasone furoate appear effective for nasal polyps [20] whereas the novel intranasal TLR7 agonist (GSK2245035) has also been shown to have beneficial effects [21] and may be future options.

Complementary and alternative medicine therapies have been gaining popularity. There remains a scarcity of well done studies for recommendations with high confidence for or against these therapies. Of these, the most data exists from small studies suggest acupuncture may be beneficial. The concurrent use of acupuncture with disease modifying sublingual allergen immunotherapy showed much better outcome results in terms of symptom relief and quality of life than immunotherapy alone [22].

ALLERGEN IMMUNOTHERAPY

In allergen immunotherapy (AIT), gradually increasing quantities of allergenic substances is administered with the goal of inducing immunologic tolerance. AIT is the only disease-modifying treatment with proven efficacy for allergic rhinitis and ARC, allergic asthma, and venom allergy. Therapeutic benefits are sustained years after therapy has stopped [23] and it may prevent the development of new allergic sensitizations [24] and even asthma. Subcutaneous immunotherapy (SCIT) injections or sublingual immunotherapy (SLIT) are the most popular forms of AIT.

SCIT therapy is unfortunately underutilized with only 2–3 million individuals in the United States compared to the over 55 million people with allergic disease [25]. SCIT AIT has long been recommended by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology [26] and the European Academy of Allergy and Clinical Immunology [27] and reiterated most recently for SLIT [28].

Although appropriate for both adults and children, SCIT in young children are often traumatized by repeated injections and the side-effects of increasing amount of allergen exposures such as the inductions and the resulting pain. Alternative AIT therapy such as SLIT may be better tolerated in younger children, unfortunately, most products are not US Food and Drug Administration (FDA) approved for them.

In the United States, allergen specific SLIT tablets are gradually becoming available. To date, these FDA-approved rapidly dissolving tablets for

Timothy grass, a 5-northern grass mix, short ragweed, and house dust mites (HDM) (Table 2) are held under the tongue until they are completely dissolved. If the report of birch tree SLIT therapy continues to show good safety and efficacy [29], this additional allergen may be available shortly. Daily home self-administered SLIT tablets have good safety and efficacy profiles.

The consensus to date is that SLIT is safer than SCIT. A 2011 review of case reports identified six episodes of anaphylaxis to even for SLIT, most were woman and individuals with asthma and two had anaphylaxis to SCIT prior [30], but there had been no fatalities [31]. In contrast, during the similar time frame, for SCIT therapy, a total of seven fatal reactions were reported in the United States from 2008 to 2017 of which three occurred between 2008 and 2016 that were associated with over 54 million injections, unfortunately, the other four fatal reactions occurred between 2016 and 2017[32]. Though manufacturers still recommend the availability of auto-injector epinephrine even for SLIT, current data suggest that SLIT has a better safety profile.

SLIT and SCIT are effective at inducing tolerance with sustained relief of symptoms after discontinuation of therapy. In 40 asthmatic patients with HDM allergy treated with SCIT for 1–8 years, those that completed 3 years or more had a relapse rate of 48% compared to 62% for those who completed less than 3 years [33]. This study among numerous others stand in stark opposition to the 1997 report that SCIT injections for over 2 years in asthmatics was of no discernible benefit [34]. Importantly, in that study, many children were on high-dose oral steroids, which are known to suppress immune function and would affect any immune modulatory effect of AIT. Similarly to SCIT studies, individuals treated with 5-grass pollen SLIT for 3 years reported sustained benefits during the subsequent 2 years off therapy [35]. AIT may even be effective for LAR. During a 2-year trial of 36 study participants with allergic symptoms to HDM, the daily combined symptom and medication scores were 42% below placebo controls ($P = 0.001$)[36].

ALLERGEN IMMUNOTHERAPY AND ASTHMA PREVENTION

Historically, AIT was reserved for those with insufficient symptom control on optimal avoidance measure and failure of pharmacotherapy. Steadily, increasing evidence suggest that AIT may be effective at primary prevention in the progression of atopy toward asthma. A meta-analysis of 32 AIT studies between 1986 and 2016 identified a reduction in the short-term (<2 years) risk of developing

Table 2. United State Federal Drug Agency (FDA)-approved sublingual immunotherapy tablets

Generic name	Brand name	Use in USA FDA approved ages	Usual dosage and duration for induction of tolerance	Common side-effects ^a
Dust mite oral extract	Odactra (2017)	Dust mite allergy. Ages 18–65 years	One tablet once a day year round –4 Years for 8 years effect	• Throat or mouth irritation, warmth, or tickle sensation • Itching of the mouth or ear sensation • Minor swelling of the back of the mouth, lip, or tongue • Stomach discomfort Changes in taste
Timothy grass pollen sublingual extract	Grastek	Treatment of allergy to timothy and similar grasses. Ages 5–65 years	One tablet once a day. First dose in doctor's office starting 12 weeks prior to grass season.	
Grass pollen sublingual extract (sweet vernal, orchard, perennial, rye, timothy, Kentucky blue)	Oralair (2014)	Allergic rhinitis with or without allergic conjunctivitis. Ages 10–65 years	One tablet once a day. First dose in doctor's office starting at least 4 months prior to the start of grass pollen season. –3 Years	
Short ragweed pollen sublingual extract	Ragwitek	Treatment of allergy to ragweed. 18–65 years	One tablet once a day. First dose in doctor's office starting 12 weeks prior to grass season. –4 years	

^aMinor and transient symptoms. These are common symptoms for all forms of SLIT. SLIT, sublingual immunotherapy.

asthma in patients with allergic rhinitis (relative risk = 0.40)[37]. The 10-year follow-up Prevention of Allergy (PAT) study that initially randomized 205 children with grass and/or birch pollen allergy for 3 years of SCIT therapy and monitored for asthma in the subsequent 7 years report significant sustained improvements in ARC and less asthma in which 24/53 developed asthma compared to 16/64 in the treated group (odds ratio of 2.5)[38]. In slightly younger children ages 5–12 years, 812 study participants on 3 years standardized Timothy grass SLIT saw a reduced risk of asthma symptoms at the end of the trial and the following 2 years afterwards [39^{***}]. Though specific for these allergens, AIT studies repeatedly show disease modifying effects not just for allergic rhinitis, but now, more consistently, for the prevention of asthma in children.

SLIT-drops using liquid allergen extracts as an off-label alternative treatment strategy in the United States is popular in Europe. A pivotal large multicenter trial with birch pollen allergy demonstrated significant ($P < .0001$) reduction of combined medication and symptom score compared to placebo after 3–6 months of therapy [40]. This encouraging data suggests a new avenue of therapy on the horizon with traditionally allergen extracts. In the course of a

year, administered SLIT allergen amounts are generally 20–200 times greater than SCIT [41[†]]. With this potentially alternative use, renewed interest into extract standardization to address the know pervasive issue of highly variable liquid extracts should occur.

MECHANISM OF ALLERGEN IMMUNOTHERAPY

Investigations into SCIT-induced tolerance have been better characterized than SLIT although both appear to involve a similar mechanism as well as increasingly complementary data from food allergy studies. During AIT, specific IgG4 increases, sIgE initial increases then a seasonal blunting occurs, CD8⁺ T-cells increases with concomitant decrease in CD4⁺ T-cells, IL-10 production and IL-12/interferon γ increases, and a decrease in tissue mast cell and eosinophils with concurrent suppression of Th2 cell occur [41[†]].

EMERGING INSIGHTS INTO IMMUNOLOGIC MODIFICATIONS BY ALLERGEN IMMUNOTHERAPY

Though used in clinical practice for over 100 years, the cellular and molecular interactions underlying

AIT remains unclear. There continues to be mounting evidence that regulatory cells are critical mediators of induced tolerance, but the specific surface markers that identify the most important regulatory cells and their subtypes are controversial. Studies in patients during 30 weeks of house dust mite AIT show a significant increase in the numbers of Der p 1 tetramer positive staining specific FOXP3⁺Helios⁺CD25⁺CD127⁻Treg cells [42]. Interestingly, Treg cells identified as CD8⁺CD25⁺CD137⁺ induced IL-10 and TGF- β and suppressed CD4⁺CD25⁻T-cell proliferation primarily by cell-cell contact inhibition [43]. Though these studies provide important data, unfortunately most evidence still remains observational for AIT or provides indirect evidence of regulation from in vitro studies. Additional insight has been provided in mice models of allergic rhinitis that suggest TGF- β 1⁺Bregs cooperated with Treg cells to modulate the immune response back towards baseline [44].

Apart from direct cell-cell contact mediated immune regulation, cytokines appear to be important. IL-35 is a newly identified inhibitory cytokine produced by CD4⁺CD25⁺Foxp3⁻Tregs, B-cells, smooth muscle cells and monocytes during SLIT therapy that inhibits the aberrant immune responses caused by group 2 innate lymphoid cells (ILC2s) and Th2 cells in grass pollen allergic patients [45] and will be a new therapeutic target.

The reasons why not all patients undergoing AIT respond are unknown. In elegant studies in which fetal laboratory C57BL/6 mice embryos were transferred into wild mice with wild mice microbiota and a different genome, they demonstrated that the microbial genome helps shape an organism's immune profile [46]. This suggests that in addition to the amount of allergen delivered during AIT desensitization, considerations of the host immune response and their microbiota maybe needed.

CHALLENGES WITH ALLERGEN IMMUNOTHERAPY

AIT requires a significant commitment of time and effort with a long treatment duration of 3–5 years of repeated SCIT injections or near daily SLIT tablets with associated safety concerns. Although effective and disease modifying, compliance to therapy is a problem with high drop-out rates thereby limiting overall effectiveness in decreasing overall disease burden. A retrospective study for persistence of prescription renewals for standardized grass pollen SLIT tabs or SCIT injections 3-year follow-up of 6954 study participants (of which >60% were for adults), showed a similarly low number of patients who

retained their prescriptions for all 3 years for SLIT-tabs and SCIT at 30% vs. 31% respectively, $P=0.51$) [47].

Managing expectations should help increase compliance. In a peanut allergic oral immunotherapy study of 50 children, when families are informed that symptoms are side-effects and potentially indicators of sensitization efficacy, they are less anxious ($P=0.03$), and less likely to skip or reduce doses 4% vs. 21% [48[■]]. As AIT is not recommended prior to establishment of asthma stability, it is not an acute therapy and symptomatic improvement usually occurs months after maintenance is reached. Effective communication of these limitations should increase compliance.

EMERGING THERAPIES

Direct injection of allergens into high concentrations of immune cells with intralymphatic immunotherapy (ILIT) have been conducted in small trials as an alternative with less side-effects and shorter duration than SCIT. In a first of kind randomised double blind placebo-controlled study of ILIT with more than 1 allergen, each injected in the inguinal lymph node (1 allergen on each side) every 4 weeks for three injections, there were reduced grass induced nasal provocation symptoms, and immune modulatory signs to grass without changes in the presence of birch allergens [49].

Recombinant peptides of allergenic proteins can be generated at known amounts and sizes that do not illicit IgE cross-linking and therefore avoid anaphylaxis events. A short 2 month SCIT protocol using overlapping Bet v 1 peptides and 5 SCIT shots multinational phase IIb trial showed benefits [50]. Conceptually similarly, a grass pollen allergen peptide mix containing seven T-cell epitope from Cyn d 1, Lol p 5, Dac g 5, Hol l 5, and Phl p 5 in a multicenter, randomized, double-blind, placebo-controlled study of 282 study participants showed an improvement in symptoms [51]. Molecular component based AIT-directed therapy will require extensive research into defining which component causes clinical symptoms and in mapping both b and t-cell epitopes.

Alterations in allergen presentation and combining it with adjuvants are being utilized to induce targeted immune responses. Single molecules of fused protein allergens to: immune activating bacteria (flagellin, MPLA, cholera, and tetanus toxin), viral (VP-1, TAT), or fungal (FIP-five) components, immune activating DNA motifs (CpG), target allergen delivery to MHC-II loading pathways, and target killing of immune cells that express allergen specific IgE by fusion allergens to diphtheria toxin [52] are

being developed. Emerging therapies like virus-like particles that act as carriers to increase an allergen's immunogenicity will also need further exploration before clinical applicability [53].

CONCLUSION

Allergic rhinitis is a very common disease that has a high impact on daily activities, but is often not treated adequately. There continues to be significant need for effective forms of therapy, not only just to treat the symptoms, but also less invasive and safer options than with current AIT. AIT is an effective but underutilized therapy that corrects the allergic immune system over the long term (years). In children, AIT may have the additional benefit of preventing the onset of asthma.

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Conflicts of interest

There are no conflicts of interest.

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