Review Article

Immunotherapy: Current indications and recommendations in the management of ocular allergy

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Allergic diseases, including allergic conjunctivitis (AC), pose a significant health burden, affecting both developed and developing nations. Despite its importance, AC is often underreported, leading to underestimated incidence and prevalence. The coexistence of AC with allergic rhinitis and its comorbidity with asthma underscore its clinical relevance. The prevalence of nasal symptoms with eye symptoms related to eye allergy varies among different age groups and regions worldwide. Climatic factors, aeroallergens, and environmental exposure play significant roles in the prevalence of ocular allergies. Allergen immunotherapy (AIT) represents the only disease-modifying treatment for IgE-mediated allergic diseases. This review provides a comprehensive overview of the history, mechanisms, and evidence of AIT for ocular allergies, with a focus on AC. The primary routes of AIT, subcutaneous immunotherapy (SCIT), and sublingual immunotherapy (SLIT) are discussed in detail. The evidence for AIT in treating AC is extensive and demonstrates its effectiveness in alleviating ocular symptoms, reducing medication usage, and improving the quality of life in patients. Both SCIT and SLIT have shown positive results, with SLIT having a more favorable safety profile. Considerations for initiating and maintaining AIT, including adherence, financial burden, and treatment duration, are highlighted. In summary, AIT is a valuable treatment option for AC, offering long-term symptom relief and potential cost-effectiveness. By understanding the history, mechanisms, and evidence of AIT, healthcare providers can better manage ocular allergies and improve patient outcomes.

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Allergic diseases are a growing concern globally, with allergic conjunctivitis (AC) being significantly underreported. This results in underestimated prevalence rates; estimates indicate that approximately 40% of North Americans suffer from AC, with similar figures in Europe and the Middle East. AC often accompanies allergic rhinitis and is a notable comorbidity of asthma.[1-3] The International Study of Asthma and Allergies in Childhood (ISAAC) found that nasal and eye symptoms in children ranged from 2.2% to 45.1%, depending on age and location, although it lacked a questionnaire specifically for AC, affecting precision in reporting. The ISAAC study, covering over 100 countries, revealed variations in allergic rhino-conjunctivitis (ARC) prevalence and a rising trend across phases. However, adult data, such as that from the US NHANES III, which showed that 40% of adults had AC symptoms yearly, is scarce. The prevalence of AC subtypes varies by region: Japan has more seasonal cases, Thailand has more perennial cases, and in Brazil, vernal keratoconjunctivitis (VKC) is common.[4,5] Climatic conditions and aeroallergens significantly influence ARC prevalence, with higher rates in areas with warm, dry climates.[6] VKC prevalence is associated with factors such as biomass fuel and dust in Ethiopia and air pollution in Japan. Pollens are linked to seasonal AC (SAC), while dust mites are more connected to perennial AC (PAC). Data scarcity from large-scale studies on AC remains a challenge for accurate assessment and understanding of this condition.[1]

AC is a condition that includes SAC and PAC. Other types of AC include VKC, atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis.

History of allergen immunotherapy

Allergen immunotherapy (AIT) constitutes the only disease-modifying treatment for IgE-mediated diseases. The

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history of AIT dates back to 1911 when Dr. John Freeman and Dr. Leonard Noon first successfully treated patients suffering from hay fever with timothy grass pollen allergen. This was followed by the publication of a report on ragweed pollen subcutaneous immunotherapy (SCIT) by Clowes.[7] This was followed by a rapid spread of this practice of injections of pollen extracts for both seasonal and perennial allergic rhinitis. During the 1950s, extensive controlled trials by Frankland and Augustin in England and simultaneously by Lowell and Franklin in the US established SCIT to be an effective form of treatment for naso-bronchial allergic diseases. Seminal works by Prausnitz and Kustner, as well as by Cooke and Loveless, helped to understand the mechanisms behind allergic diseases and AIT.[8]

Throughout the past 110 years, AIT has been practiced by the same method used by Noon. Nonetheless, relentless work by numerous researchers from all over the world has paved the way for further modification in the allergen and routes of immunotherapy to reduce the duration of treatment, decrease the side effects, and improve patient acceptance.

One of the earliest developments came in the 1930s when allergen extracts were adjuvanted with alum to improve immunogenicity and reduce the side effects of the immunotherapeutic vaccine. Thereafter in the 1960s, allergens for immunotherapy were chemically modified to reduce their IgE binding capacity while maintaining their immunogenicity, which are known as allergoids.[9] SCIT has the largest number of evidences for its practice, though other routes of immunotherapy that were studied include sublingual immunotherapy (SLIT) (which was recommended by the WHO in 1998); intra-lymphatic immunotherapy; epi-cutaneous immunotherapy; and local nasal, local bronchial, and oral immunotherapy.

Common allergens in India

In a recent study conducted in Ambala, Haryana, India, a variety of allergens were identified as major triggers for allergic reactions. Pollen was the most prevalent allergen, accounting for 51% of cases, with *Brassica campestris* (8%), *Ageratum conyzoides* (7%), and *Artemisia scoparia* (6%) being the most common types. Fungal allergens, including *Alternaria tenuis*, *Aspergillus flavus*, *Aspergillus fumigates*, *Candida albicans*, *Penicillium sp*., *Rhizopus nigricans* (3%), and *Fusarium solani* (2%), accounted for 12.6% of allergic reactions. Lastly, dust allergens were less common but still significant, with grain dust from rice (3%), straw dust, house dust, and grain dust from bajra (2%) identified.[10]

Key allergens include pollen grains, fungal spores, insect materials, and other biologically originated substances. Understanding the prevalence, seasonal, and annual variations of these aeroallergens is crucial for accurate diagnosis and effective treatment of allergies, especially in a climatically diverse country like India. Extensive atmospheric surveys across dust mites such as *D. farinae* and *D. pteronyssinus* are notable inhalant allergens, especially in coastal regions. Insects such as cockroaches, beetles, weevils, mosquitoes, and houseflies also add to the aeroallergen load.[11] To manage respiratory allergies effectively, avoiding both indoor and outdoor aeroallergens is advised.

Major allergens identified include pollen grains, fungal spores, dust mites, insect debris, and animal epithelia. To address this, the "All India Coordinated Project on Aeroallergens and Human Health" was initiated, studying aerosol prevalence across 18 centers in India. Key airborne pollen allergens, identified through clinico-immunologic evaluation, include species such as Alnus, Amaranthus, and Ricinus communis, as well as various grasses. Notably, there is significant cross-reactivity among different pollen allergens, with Ricinus communis showing reactivity with substances such as latex and seeds of the same family, despite geographical differences. Similar cross-reactivity is observed in the Arecaceae and Urticaceae families.[12]

General terms used in AIT

Sensitization refers to the process of demonstrating the presence of allergen-specific IgE antibodies in an individual's immune system. This demonstration can be achieved through various methods, including skin prick tests or in-vitro tests. These tests are essential for diagnosing allergies and identifying the specific allergens that trigger an individual's allergic reactions.

AIT, commonly known as desensitization or allergy vaccinations, involves the repeated and continuous administration of allergens at scheduled intervals. The primary goal of this treatment is to shift the immune response from the Th2 pathway to the Th1 pathway. This shift aims to reduce the severity of allergic symptoms and the need for ongoing pharmacotherapy.

Standards and practices in allergen extract procurement and preparation for effective allergy testing and immunotherapy in India

The procurement and preparation of allergens for testing and treatment are crucial aspects in managing allergic diseases. For effective allergy testing and immunotherapy, allergen extracts should be consistent and standardized. Allergen vaccines, available commercially, must be tested against an in-house reference standard. In India, significant advancements have been made in allergen standardization, with research focusing on the biological standardization of various pollens. When purified major allergens and specific antibodies are unavailable, allergen extracts are standardized based on weight/volume and protein estimation methods such as the modified Lowry's, bicinchoninic acid assay, or the micro Kjeldahl method. It has been found that freeze-drying the allergen source material enhances the quality of extracts.

The extraction process typically involves a short duration, with recent studies suggesting optimal allergenic potency achieved through 4–8 hours of extraction in buffers such as PBS or ammonium bicarbonate. Additives such as phenyl methyl sulfonyl fluoride and EDTA are essential as protease inhibitors. For stabilizing allergen solutions, glycerol is effective for skin prick test solutions, whereas alternatives such as sucrose or epsilon-amino caproic acid are used for stabilizing other allergens such as grass pollen and cockroach extracts.

Transportation of these extracts across India requires cool gel packs or a cold chain system to maintain their integrity. It is important to note that allergen extracts can vary between manufacturers; thus, for consistency in diagnosis and therapy, sourcing both diagnostic and therapeutic allergens from the same manufacturer is advised.

Regulatory oversight in India, provided by the Drug Controller of India and state units, focuses on good

manufacturing practices in allergen production. Coordination among ICAAI, Antigen Units, and Drug Regulatory Authorities is crucial for upgrading quality control following standard WHO/IUIS/EMA protocols. The creation of allergen certification centers, akin to the FDA and Center for Biologics Evaluation and Research in the USA or the Paul Ehrlich Institute in Europe, is a need in India.

In summary, the allergen extracts used for testing and treatment should be carefully procured and prepared following stringent quality control measures. This ensures the reliability and effectiveness of AIT and skin testing, thereby enhancing patient care in allergy management.

To effectively initiate AIT in India, it is essential to first ensure proper patient selection through diagnostic tests such as skin prick tests and assessment of IgE-mediated diseases. AIT should be considered only for patients with a clear history of allergic reactions and confirmed IgE sensitivity to specific allergens. The choice of allergens for AIT must be based on regional airborne pollen and the patient's exposure history. Practitioners should use standardized allergen extracts, adhering to guidelines for dosing and administration. The treatment typically involves gradually increasing doses of the allergen, starting from a highly diluted concentration. Regular monitoring and adjustment of the therapy are necessary, and it should be conducted under the supervision of physicians trained in allergy and AIT, in a facility equipped to manage anaphylaxis. The decision to continue or discontinue AIT should be individualized based on the patient's response and compliance. The AIT most widely practiced in India is subcutaneous AIT as per the Indian guidelines of AIT for aeroallergens.

Table 1 summarizes the major findings from various studies on immunotherapy in treating ocular allergy, focusing on specific allergens, the duration of studies, and their key outcomes [Table 1].

Indications and principles of AIT for AC[5]

1. Symptoms strongly suggestive of AC with/without allergic rhinitis
2. Sensitization to one or more clinically relevant allergen (positive skin prick test and/or serum-specific IgE) and corroborated with a post-test history
3. In patients having moderate to severe symptoms interfering with daily activities/sleep affecting the quality of life in spite of optimization of pharmacotherapy and allergen avoidance
4. AIT may be considered also in patients with fewer symptoms of ARC but at risk of asthma, where the AIT may have a long-term effect on the prevention of asthma.
5. Duration is for a period of 3–5 years, which is in addition to the continuation of pharmacotherapy, with a gradual reduction of pharmacological support.

Different types of AIT

Two types of AIT are available in India:

1. **Subcutaneous immunotherapy (SCIT)**
2. **Sublingual immunotherapy (SLIT)**

SCIT is a method involving the injection of purified allergens under the skin, gradually increasing the dose over time. The primary goal is to induce immune system tolerance by shifting the immune response from the Th2 pathway to the Th1 pathway. During the initial phase of SCIT, injections are typically given 1–2 times a week, with the interval between injections gradually increasing to about 4 weeks throughout the therapy duration. The initiation phase usually spans 8–12 months, and some patients may require a more extended initiation phase, depending on their tolerance, especially if they start with a lower-than-conventional dose to minimize potential adverse events. Adverse reactions to SCIT can be categorized as local or systemic. Local reactions are relatively common, with a frequency range of 26%–82%. However, their occurrence is not predictive of the severity of subsequent local or systemic reactions. Local reactions can manifest as erythema and swelling, with or without angioedema, at the injection site. These reactions can occur immediately, within a few minutes, or up to a few hours after the injection. Systemic reactions, while less common, have been reported at a rate of approximately 0.2%–0.5% in conventional schedules.[3] Factors contributing to the possibility of systemic reactions include but are not limited to poorly controlled asthma, initiation of SCIT from a fresh vial, and concurrent medication with beta-blockers. Effective control of asthma, close monitoring, reducing the SCIT dose when symptomatic during peak pollination seasons, and beginning with a new vial may help mitigate the risk of systemic reactions.[13]

Mechanisms of action of AIT

Understanding the mechanisms underpinning immunotherapy not only holds promise for advancing the treatment of AC but also provides valuable insights into the workings of this therapeutic approach. Successful immunotherapy for AC often correlates with a reduction in the population of mast cells, basophils, and eosinophils within the eye, leading to relief from symptoms. The critical actors in this process are the cytokines produced by T-cells [Fig. 1], which play a central role in orchestrating the inflammation associated with AC.

Two principal subsets of T-cells, TH1 and TH2, fulfill distinct roles in this context. TH1 cells produce IFN-γ and IL-2, while TH2 cells primarily generate IL-4, IL-13, and IL-5. Of particular significance are TH2 cells, which play a central role in allergic reactions, particularly on mucosal surfaces. The development of TH1 and TH2 responses is influenced by a variety of factors, including the antigen's route, dosage, and the type of antigen-presenting cell.[14] For example, the route and amount of allergen exposure can favor one T-cell response over the other. While earlier research on immunotherapy predominantly focused on antibody responses, recent studies have shifted their focus to T-cell responses [Figs. 2 and 3].

The attainment of immunological tolerance through AIT involves a complex interplay of cellular and molecular processes that collectively suppress both immediate and delayed immune responses upon allergen exposure.[14]

Despite the growing understanding of the mechanisms of action and the efficacy of immunotherapy, ongoing research strives to provide a deeper understanding of the long-term immune tolerance that results in changes in T-cell and B-cell responses. Recent data highlight the potential significance of IL-10-producing regulatory B (Breg) cells and "allergen-neutralizing antibodies" in contributing to long-term immune tolerance for AC. Immunotherapy for AC aims to modify the immune system's response to allergens, ultimately

Table 1: Overview of various studies on allergen immunotherapy for ocular allergy, outlining the type of immunotherapy, study design, allergens involved, and the main outcomes of each study

Study	Type of Immunotherapy	Study Design	Allergen	Key Findings
Winther *et al*. [Winther L, Malling HJ, Moseholm L, Mosbech H. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. Allergy 2000; 55:818±826.]	Subcutaneous Injection (SIT)	Double-Blind Crossover (DBCO)	Birch and Grass	Improvement in rhino-conjunctivitis symptoms, reduced need for eye drops
Moller *et al*. [Moller C, Dreborg S, Lanner A, Bjorksten B. Oral immunotherapy of children with rhino-conjunctivitis due to birch pollen allergy: a double-blind study. Allergy 1986; 41:271±279.]	Subcutaneous Injection (SIT)	Double-Blind Placebo Control (DBPC)	Birch and/or Grass	Enhanced conjunctival sensitivity in active treatment group
Walker *et al*. [Walker SM, Pajno GB, Lima MT, *et al*. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001; 107:87±93.]	Subcutaneous Injection (SIT)	Double-Blind Placebo Control (DBPC)	Grass	Reduced immediate sensitivity to conjunctival allergens
Pocobelli *et al*. [Pocobelli D, Del Bono A, Venuti L, *et al*. Nasal immunotherapy at constant dosage: a double-blinded, placebo-controlled study in grass-allergic conjunctivitis. J Investig Allergol Clin Immunol 2001; 11:79±88.]	Intranasal Immunotherapy (INIT)	Double-Blind Placebo Control (DBPC)	Grass	Decrease in eye itching, lowered medication usage in the treatment group
Nunez and Cuesta [Nunez JA, Cuesta U. Local conjunctival immunotherapy: the effect of dermatophagoides pteronyssinus local conjunctival immunotherapy on conjunctival provocation test in patients with allergic conjunctivitis. Allergol Immunopathol 2000; 28:301±306.]	Local Conjunctival Immunotherapy (LCIT)	Double-Blind Placebo Control (DBPC)	Dermatophagoides pteronyssinus (Dp)	Improved scores in conjunctival provocation test (CPT)
Purello-D'Ambrosio *et al*. [Purello-D'Ambrosio F, Gangemi S, Isola S, *et al*. Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. Allergy 1999; 54:968±973.]	Sublingual Immunotherapy (SLIT)	Double-Blind Placebo Control (DBPC)	P. judaica	Safe and effective treatment of rhino-conjunctivitis
La Rosa *et al*. [La Rosa M, Ranno C, Andre C, *et al*. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 1999; 104 (2 Pt 1):425±432.]	Sublingual Immunotherapy (SLIT)	Double-Blind Placebo Control (DBPC)	P. judaica	Increased threshold dose tolerance in CPT
Ortolani *et al*. [Ortolani C, Pastorello EA, Incorvaia C, *et al*. A double-blind, placebo controlled study of immunotherapy with an alginate-conjugated extract of Parietaria judaica in patients with Parietaria hay fever. Allergy 1994; 49:13±21.]	Subcutaneous Injection (SIT)	Double-Blind Placebo Control (DBPC)	P. judaica	Reduced conjunctival reactivity, increased specific immunoglobulins G, G1, G4
Del Prete *et al*. [Del Prete A, Loffredo C, Caqrderopoli A, *et al*. Local specific immunotherapy in allergic conjunctivitis. Acta Ophthalmol (Copenh) 1994; 72:631±634.]	Local Conjunctival Immunotherapy (LCIT)	Double-Blind Placebo Control (DBPC)	Various Allergens	Improvement in subjective/objective symptoms in seasonal allergic conjunctivitis (SAC)
Lofkvist *et al*. [Lofkvist T, Agrell B, Dreborg S, Svensson G. Effects of immunotherapy with purified standardized allergen preparation of dermatophagoides farinae in adults with perennial allergic rhinoconjunctivitis. Allergy 1994; 49:100±107.]	Subcutaneous Injection (SIT)	Open Control (OC)	House-Dust Mite	Significant changes in antibody titer, and reduced conjunctival and skin sensitivity
Vourdas *et al*. [Vourdas D, Syrigou E, Potamianou P, *et al*. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. Allergy 1998; 53:662±672.]	Sublingual Immunotherapy (SLIT)	Double-Blind Placebo Control (DBPC)	Olive	Clinical improvement, reduced dyspnea, lower conjunctivitis score in active group, no significant improvement in rhinitis

Contd...

Table 1: Contd...

Study	Type of Immunotherapy	Study Design	Allergen	Key Findings
Horak *et al*. [Horak F, Stubner P, Berger UE, *et al*. Immunotherapy with sublingual birch pollen extract: a short-term double-blind placebo study. J Investig Allergol Clin Immunol 1998; 8:165±171.]	Sublingual Immunotherapy (SLIT)	Double-Blind Placebo Control (DBPC)	Birch	Higher tolerance in CPT in actively treated group
Sabbah *et al*. [Sabbah A, Hassoun S, Le Sellin J, *et al*. A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. Allergy 1994; 49:309±313.]	Sublingual Immunotherapy (SLIT)	Double-Blind Placebo Control (DBPC)	Grass	Reduction in rhinitis and conjunctivitis symptoms, decreased medication use
Taudorf *et al*. [Taudorf E, Laursen LC, Lanner A, *et al*. Oral immunotherapy in birch pollen hay fever. J Allergy Clin Immunol 1987; 80:153±161.]	Sublingual Immunotherapy (SLIT)	Double-Blind Placebo Control (DBPC)	Birch	Lower eye symptom scores, reduced conjunctival sensitivity as per CPT
Moller *et al*. [Moller C, Dreborg S, Lanner A, Bjorksten B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy: a double blind study. Allergy 1986; 41:271±279.]	Enteric-Coated Capsules	Double-Blind Placebo Control (DBPC)	Birch	Lower conjunctival sensitivity after 3 months of treatment, not sustained after 10 months

reducing or eliminating the allergic reaction. It is a long-term treatment that typically spans several years to achieve enduring results. However, the effectiveness of immunotherapy can vary from person to person, underscoring the importance of close monitoring by an allergist or immunologist to ensure its safety and efficacy.[15] The detailed mechanism of immunotherapy underscores its capacity to modify the immune response, providing long-term relief from AC symptoms by promoting immune tolerance to specific allergens[16] [Table 2].

Evidence of immunotherapy for ocular allergy

Allergen-specific immunotherapy, recommended by the World Health Organization (WHO), has proven to be an effective strategy in managing allergic conditions such as rhino-conjunctivitis and asthma.[18] The routes of administration, whether sublingual or subcutaneous, have demonstrated the potential to induce tolerance in both short and long-term scenarios through a large range of mechanisms. When assessing the application of immunotherapy in different patient subgroups, it becomes evident that ocular symptoms are alleviated generally and significantly in specific groups, such as those experiencing pruritus, with an improvement rate exceeding 40%. Moreover, a notable reduction in medication usage, reaching a 63% decrease, is observed among patients diagnosed with rhino-conjunctivitis or SAC.

However, this reduction in medication consumption is not evident in patients suffering from PAC. These findings are corroborated by a grade-A recommendation, based on robust available evidence.[19,20] Although limited in quantity, research has explored alterations in allergen sensitivity through conjunctival challenges before and during immunotherapy. In all instances, a notable increase in the sensitivity threshold was observed (grade of recommendation A).[20] A systematic review and meta-analysis conducted by the US Agency for Healthcare Research and Quality scrutinized randomized controlled trials involving individuals, both adults and children, afflicted with rhino-conjunctivitis and/or allergic asthma who received sublingual and SCIT. While some discrepancies may arise from methodological biases, the examination of immunotherapy's effectiveness in AC (AC) indicates that SCIT effectively alleviates ocular symptoms. The available evidence strongly supports its use in adults, reflected by a grade-A recommendation [Table 2]. However, the evidence is comparatively weaker for children and adolescents [Table 2]. SLIT's available evidence is considered of intermediate strength for both adult and pediatric populations, though its ease of use and home and safety, especially in pediatric populations, is its main strength.[21] The assessment of immunotherapy's efficacy revolves around the management of symptoms and the reduction in the need for additional medications. A recent systematic review and meta-analysis confirmed the efficacy of both SCIT and SLIT in the treatment of ARC, with both modalities effectively reducing symptoms and the need for additional medication.[13]

Evidence on SCIT

SCIT represents a therapeutic approach involving the administration of allergenic substances beneath the skin. Historically, SCIT has been considered the preferred and most reliable route for AIT. It elicits a regulatory T-cell response, particularly evident in patients undergoing high-dose SCIT over a period of 3–5 years. While the early experiments on SCIT did not comprehensively document ocular symptoms, recent systematic reviews and meta-analyses of randomized controlled trials spanning the past two decades have provided compelling evidence of its effectiveness. These studies consistently report a significant reduction in conjunctival symptoms in individuals with seasonal ARC triggered by grasses and pollens, as well as perennial ARC caused by house dust mites and animal dander.[7] Notably, SCIT targeting a mixture of grasses, including timothy grass, cat allergens, Parietaria, and Alternaria, has demonstrated remarkable efficacy in alleviating conjunctivitis symptoms.[22] These trials also highlight SCIT's ability to improve overall symptoms of ARC, enhance the quality of life, and reduce the need for additional medication compared to a placebo.[23] Standardized allergen formulations are readily available for continuous

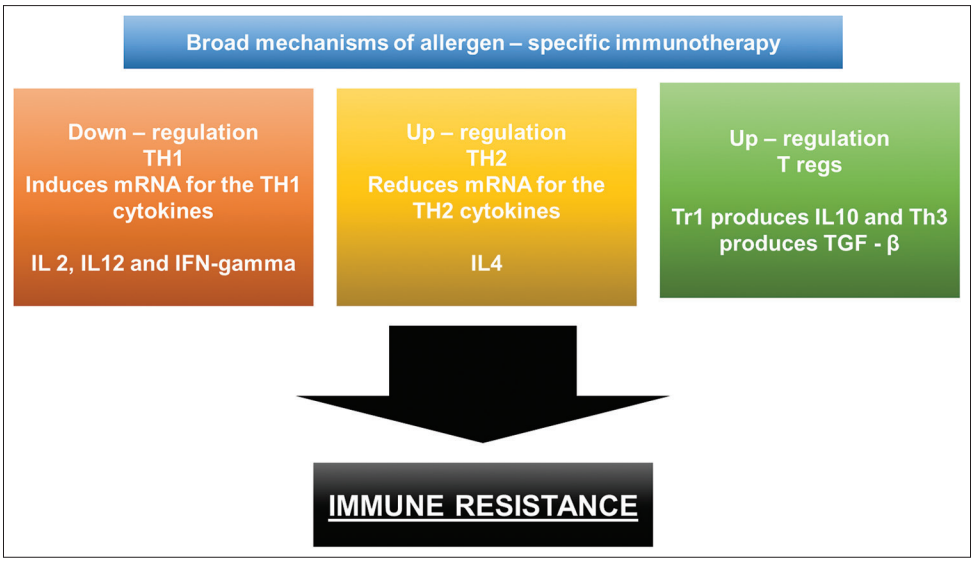

Figure 1: Broad mechanisms of allergen specific immunotherapy

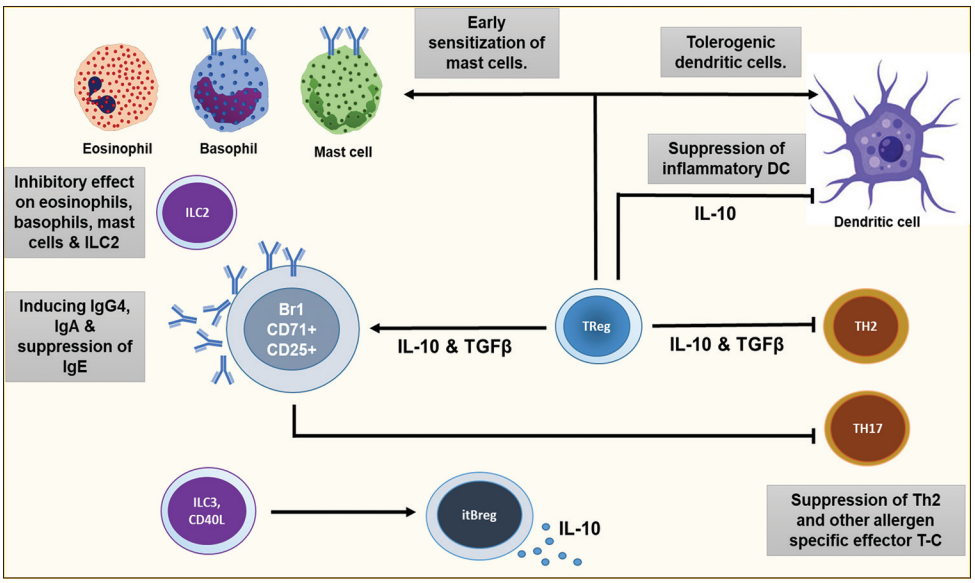

Figure 2: Cellular mechanisms of action of Immunotherapy: Immuno-therapy hinges on pivotal cellular mechanisms, encompassing elements such as sensitization of mast cells, suppression of inflammatory dendritic cells, suppression of Th2 and other allergen specific effector T-C. These mechanisms assume vital roles in the efficacy of immunotherapeutic approaches

treatment, with specific allergens for trees, ragweed, and grasses also available as pre-seasonal injections. Comparative studies between pre-seasonal SCIT and continuous SCIT have shown that both groups experience a significant reduction in ocular symptoms, with no statistically significant difference between the two arms of the study. In addition, the continuous SCIT group had lower scores for total ARC symptoms and concomitant medication usage. While conventional SCIT utilizing unaltered allergen extracts is well-established, it faces manufacturing-related constraints. These include the risk of negative systemic responses, high manufacturing costs, and challenges related to allergen accessibility, uniformity, and effectiveness.[24] Recent advancements have introduced chemically modified and depigmented polymerized extracts, known as allergoids, which address these limitations associated with SCIT. Allergoids offer enhanced safety, consistency, accessibility, and efficacy compared to native extracts, allowing for larger dosages to be administered within shorter treatment durations, thereby improving safety.[25]

Multiple double-blind, placebo-controlled trials have consistently demonstrated the efficacy of allergoid immunotherapy of SCIT in AC.[26] The treatment process typically begins with the administration of gradually escalating allergen doses, with weekly escalating doses followed by maintenance injections every 4–6 weeks for a duration of 3–5 years. Clinical improvement is often observed upon reaching the maintenance dosage.[17] However, several factors may hinder improvement, including ongoing allergen exposure, incomplete identification and treatment of relevant allergens, and non-adherence to appropriate doses.[16]

Table 2: Mechanisms of allergen immunotherapy[17]

1. Allergen Exposure: Immunotherapy involves controlled exposure to allergens and dendritic cells are the main antigen-presenting cells.
2. Dendritic Cell Modulation: Dendritic cells play a crucial role in presenting allergens to T-cells, shifting the immune response away from an allergic (Th2) response. Recently, Dendritic regulatory cells (D regs) have been in focus as an important mechanism for developing tolerance to allergens.
3. T-Cell Tolerance: Regulatory T-cells (Tregs) are activated, suppressing the activity of effector T-cells responsible for allergic reactions.
4. Immunoglobulin G (IgG) production: Immunotherapy stimulates the production of allergen-specific IgG antibodies, specifically IgG4 that can neutralize allergens.
5. Immunoglobulin A (IgA) production: Immunotherapy stimulates the production of allergen-specific IgA antibodies, specifically IgA1 that can neutralize allergens.
6. Shift from Th2 to Th1 Response: The immune response shifts from Th2 (allergic) to Th1 (tolerant), resulting in a different cytokine profile.
7. Local Immune Modulation: Immunotherapy may affect immune cells locally in the conjunctiva, reducing inflammation.
8. Long-term Immune Tolerance: The goal is to induce long-term immune tolerance, allowing the immune system to recognize the allergen as harmless.
9. Reduction in Symptoms: As the immune system becomes less reactive to the allergen, symptoms such as redness, itching, and tearing decrease.
10. Immunotherapy aims to redirect the immune response from humoral immunity to cell-mediated immunity. This results in decreased IgE antibodies and increased CD4+regulatory T-cells that secrete IL10 and TGFβ.
11. Immunotherapy also leads to a decrease in allergen-specific IgE antibodies, and a decrease in mast cells, eosinophils, and basophils, both of which play a significant role in allergic reactions. Long-term effects of immunotherapy encompass a reduction in the IgE-to-IgG4 ratio, ultimately resulting in diminished mediator release during allergic reactions.
12. SCIT and SLIT have been effective in inhibiting early and late-phase allergic reactions and in promoting long-term immune tolerance.
13. High-dose allergen administration during allergen immunotherapy induces regulatory DC markers, such as complement component 1 and stabilin-1. DCs secrete cytokines like IL-12, IL-27, and IL-10, increasing CD86 expression and leading to the proliferation of native T-cells into allergen-specific Treg cells and inducible type 1 Treg cells.
14. Treg cells release regulatory cytokines like IL10 and TGF-β, dampening TH2-driven responses.
15. Treg cells also induce IgA class-switching upon AIT, while IL-12 from macrophages in SCIT administration contributes to TH1-cell responses and the inhibition of late-phase reactions.
16. Both SCIT and SLIT induce allergen-specific IgG1, IgG4, and IgA. These blocking antibodies compete with allergens, inhibiting the formation of allergen-IgE complexes, which, in turn, inhibits degranulation and histamine release from mast cells and basophils.
17. Both SCIT and SLIT maintain inhibitory blocking antibodies even after treatment cessation, contributing to long-term immune tolerance. These therapies induce sustained immune tolerance, involving Treg cell induction, TH2 cell suppression, transition to antigen-specific TH1 cell responses, and the production of protective blocking IgG and IgA antibodies.
18. Immunotherapy stimulates the production of inducible regulatory T-cells secreting interleukin-10 specific to the allergic epitope in question. The immunological response to immunotherapy manifests as a reduced end-organ response, leading to decreased early and late allergic reactions in the skin, conjunctiva, nasal mucosa, and bronchi upon allergen exposure.

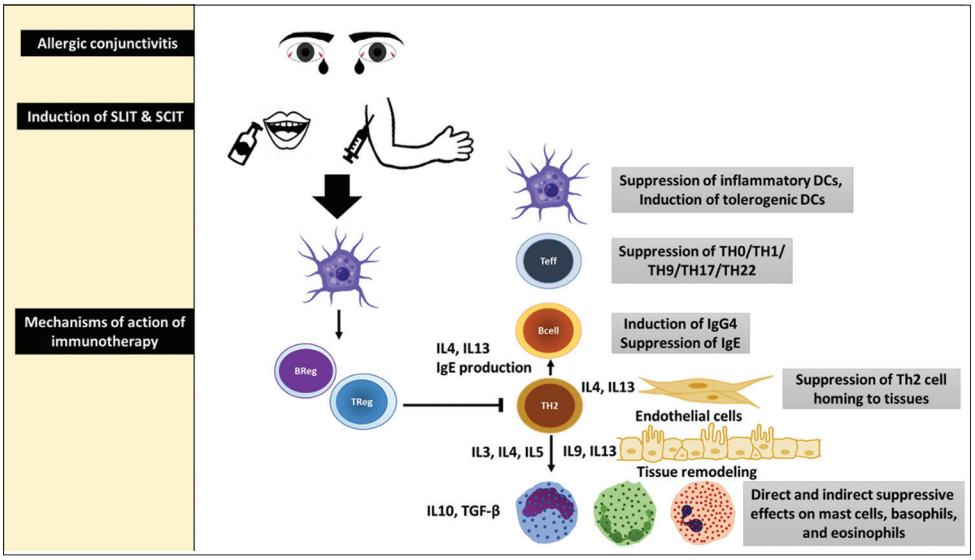

Figure 3: Humoral mechanisms of action of Immunotherapy: Immunotherapy for allergic rhinoconjunctivitis focuses on humoral mechanisms that center on antibodies. It strives to reduce allergen-specific IgE antibodies responsible for allergic reactions. By promoting the production of IgG antibodies, the therapy aims to counteract the effects of IgE. This modulation of antibody production creates immune tolerance, helping the immune system recognize allergens as harmless. The long-term goal is to establish immune memory that reduces allergic responses over time

Evidence on SLIT

SLIT is a therapeutic approach involving the administration of allergenic extracts under the tongue. It has been established as a safe and effective option for managing ARC triggered by various allergens, including grass pollen, ragweed, and house dust mites.[27,28] During SLIT, allergens are captured by dendritic cells in the oral mucosa. These dendritic cells mature and migrate to specialized lymph nodes, promoting the development of mucosal tolerance. This process results in the production of IgA1 and IgG4 antibodies and the activation of regulatory T-cells.[29] Numerous rigorous investigations conducted in the past decade have consistently demonstrated the therapeutic efficacy of SLIT. These trials have shown significant improvements in ocular symptoms, conjunctival sensitivity, the need for additional rescue medication, and quality of life among patients with ARC.[30,31] A comprehensive analysis of 63 trials involving 5131 individuals revealed that SLIT led to a significant reduction in conjunctivitis symptoms and concurrent medication usage. A systematic review by Cochrane, examining 42 studies, found that SLIT significantly reduced overall and specific ocular symptom scores in individuals with SAC when compared to a placebo. A recent meta-analysis involving 13 trials and 1592 patients revealed that SLIT significantly improved symptoms of pollen-induced AC compared to dust-mite-induced AC, including reduced total ocular symptom scores and decreased ocular redness, itchiness, and tearing. However, concomitant medication use did not show a significant reduction.[32] Another meta-analysis demonstrated a decrease in ocular symptoms and concurrent medication use.[33] However, a comprehensive meta-analysis assessing the efficacy of grass pollen SLIT in patients with SAC found only a marginal treatment advantage in terms of symptom scores and concurrent medication scores, specifically antihistamines and corticosteroids, compared to other treatments.[33] However, research is needed to investigate the efficacy and safety of multi-allergen SLIT. In the case of perennial ARC, SLIT using house dust mite tablets has proven more effective than initial pharmacotherapies, leading to a dose-dependent reduction in the need for additional medications.[34] In SAC, SLIT for grass and ragweed allergies has demonstrated effectiveness comparable to intranasal corticosteroids and superiority over other pharmacotherapies, with five-grass SLIT showing particular promise.[35]

Safety of AIT

To ensure safety, allergen extracts should undergo standardization and regulation and have documented proof of safety and efficacy. Common local effects of SCIT injections include erythema, pruritus, and edema at the injection site, which can be managed effectively with cold compresses, antihistamines, or topical corticosteroids without the need for dosage modification.[36] Premedication with antihistamines has been shown to decrease the occurrence of local reactions, enhancing patient safety.[37] SCIT carries a minimal risk of systemic allergic responses or anaphylaxis, with a reported incidence of 1.9% for systemic responses and 0.02% for anaphylaxis.[38,39] In cases of anaphylaxis, rapid initiation of proper resuscitation measures, including intramuscular adrenaline, corticosteroids, supplementary oxygen, and intravenous fluids, is crucial.[40] Delayed systemic responses, such as biphasic reactions, may also occur and warrant a longer than the usual 30-minute observation period following SCIT injection, even in the absence of initial symptoms. To reduce the likelihood of systemic responses, several measures can be employed, including pre-injection health evaluations, asthma peak flow measurements, clear documentation, dose reduction for late injections, and dosage adjustments during periods of high pollen levels. Personalized dosage titration may be necessary for individuals with heightened sensitivity during pollen seasons.[41] SLIT should begin 4 months before the pollen season, with a recommended duration of at least 3 years for grass pollen and house dust mite allergies.[42]

Safety is a key consideration in SLIT administration as it has been shown to have a more favorable safety profile compared to SCIT. It can be conveniently administered at home once the initial dose is given under the supervision of a physician at a medical facility equipped to manage anaphylaxis cases. Common local responses to SLIT include oral-mucosal pruritus and lip angioedema, which are usually temporary and tend to diminish with ongoing treatment.[43] Systemic responses may occur, and individuals who cannot tolerate SCIT have been reported to experience anaphylaxis with SLIT. However, studies have estimated the risk of anaphylaxis with SLIT to be very low, typically occurring at a rate of one per 100 million doses or one per 526,000 treatment years. No instances of anaphylaxis due to treatment have been reported in extensive randomized controlled studies utilizing SLIT. However, in certain regions, patients are required to have an adrenaline pen before starting SLIT, and the initial dose should be administered under the supervision of a physician in their office. Temporary discontinuation of SLIT may be recommended in specific circumstances, such as post-dental extraction, oral surgery, oral ulcer, or severe asthma exacerbation, for a duration of 7 days.[44]

Considerations for initiating and maintenance of AIT

Before initiating AIT, it is crucial to ensure that patients receive comprehensive information about the treatment, including its intricacies and the long-term commitment it entails. This therapy involves the regular administration of allergenic extracts, either through injections or sublingual drops, spanning a minimum duration of 3 years up to 5 years. Patients must have a clear understanding of the treatment's potential benefits, drawbacks, and financial implications. The counseling process should also cover aspects such as the expected onset of effectiveness, treatment duration, and the importance of adhering to the prescribed dosage regimen. It is important to note that immunotherapy is contraindicated in cases of uncontrolled or severe asthma and active systemic autoimmune illnesses resistant to treatment. Furthermore, it should not be initiated during pregnancy.[13] There are relative contraindications that require careful consideration, risk assessment, and close monitoring. These include partially controlled asthma, the use of beta-blockers (locally or systemically), severe cardiovascular disease, systemic autoimmune disease in remission, severe psychiatric disorders, poor treatment adherence, primary or secondary immunodeficiency, or a history of significant systemic reactions to immunotherapy. Table 3 provides a summary of risk factors associated with systemic responses during immunotherapy. Dose reductions of 25%–50% should be considered in cases of intercurrent illness or delayed SCIT injections. In contrast, SLIT should be temporarily interrupted for oral lesions, as previously described.

The initiation of immunotherapy is recommended 2–4 months before the pollen season for SAC. Similarly, it is

advisable to commence immunotherapy for PAC when allergen exposure is at its lowest. Immunotherapy should be continued for a minimum of 3 years to achieve long-term effectiveness, even after treatment withdrawal. However, symptom relief may become noticeable within the first 12 months. Importantly, there is no specific age restriction for the initiation of AIT.[13]

Table 3: Risk factors for adverse systemic reactions during allergen immunotherapy

1. Uncontrolled asthma
2. History of prior SCIT injection related systematic reactions.
3. High degree of sensitization.
4. SCIT injection peak pollen season/high allergen exposure
5. Mast cell disease.
6. Active infections
7. Dose or administration errors of therapeutic allergens, such as overdose.
8. Excess dose escalation during initiation or building up period.
9. Concomitant beta blocker use.
10. After high-intensity physical exercise.

SCIT: Subcutaneous immunotherapy, SLIT: Sublingual immunotherapy

While AIT is generally not initiated during pregnancy due to potential systemic responses' effects on both the mother and the baby, it can be safely continued throughout pregnancy if well-tolerated. Retrospective studies suggest no increased risk of adverse outcomes for pregnant women undergoing AIT.[13,44] The safety and efficacy of immunotherapy in treating ARC in pediatric patients have been demonstrated, with added benefits for asthma symptom management and reduced risk of asthma development. Asthma should be well-managed before starting SCIT, and SCIT should be avoided during episodes of severe asthma exacerbation. Uncontrolled asthma is also associated with significant systemic responses following SLIT. Adherence to immunotherapy is critical for its effectiveness. SCIT requires regular clinic visits, while SLIT can be administered at home. Adherence rates vary widely, ranging from 18% to 90%, often

Table 4: Summary of the "Grade" recommendations for allergen immunotherapy in allergic rhino-conjunctivitis[10]

Recommendation	Category	Patient Group	Benefit (Duration)
Continuous SCIT is recommended for adults	A	SAC (Seasonal Allergic Conjunctivitis)	Short-term benefit (moderate-to-severe disease)
Continuous SCIT is recommended for children	B	SAC	Short-term benefit (moderate-to-severe disease)
Pre-seasonal or co-seasonal SCIT is recommended for adults	A	SAC	Short-term benefit
Pre-seasonal or co-seasonal SCIT is recommended for children	B	SAC	Short-term benefit
Both allergoids and unmodified allergen SCIT extracts are recommended for adults	A	ARC (Allergic Rhino-conjunctivitis)	Short-term benefit
Both allergoids and unmodified allergen SCIT extracts are recommended for children	B	ARC	Short-term benefit
Continuous grass pollen SCIT is recommended for adults	A	ARC	Short-term and long-term benefit
Continuous grass pollen SCIT is recommended for children	B	ARC	Short-term and long-term benefit
Pre-seasonal or co-seasonal or continuous SLIT is recommended	A	Seasonal ARC	Short-term benefit
SLIT with tablets for pollens or house dust mites is recommended	A	ARC	Short-term benefit
SLIT aqueous solutions for pollens is recommended for children	A	ARC	Short-term benefit
SLIT aqueous solutions for house dust mites cannot be recommended	-	ARC	Short-term benefit
Continuous grass pollen SLIT tablets or SLIT solution is recommended	-	ARC	Long-term benefit
SLIT tablet for house dust mites is recommended for adults	B	ARC	Long-term benefit
Polysensitized patients who are polyallergic for taxonomically related homologous allergens can receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens	-	ARC	-
AIT can be recommended in otherwise healthy elderly patients with ARC whose symptoms are not adequately controlled by pharmacotherapy	A for SLIT, B for SCIT	Elderly patients with ARC	-
To achieve long-term efficacy, it is recommended that a minimum of three years of therapy is used	-	ARC	-
Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions. It does not eliminate the risk of other systemic adverse reactions including anaphylaxis	-	ARC	-

ARC: Allergic rhino-conjunctivitis, PAC: Perennial allergic conjunctivitis, SAC: Seasonal allergic conjunctivitis, SCIT: Subcutaneous immunotherapy, SLIT: Sublingual immunotherapy

due to adverse effects, treatment inconveniences, perceived ineffectiveness, or forgetfulness. Factors such as patient education and reminders can enhance adherence.[45] More frequent 3-monthly follow-up sessions may also improve adherence.[46] To achieve successful relief from allergic eye symptoms, evidence-based communication, patient-preferred administration methods, motivational interviewing, and collaborative decision-making are crucial elements to incorporate into AIT initiation, significantly improving the likelihood of positive outcomes.[47]

One of the primary drawbacks of AIT is its financial burden, influenced by factors such as brand choice, treatment type (SCIT or SLIT), targeted allergen, extract quantity, and kit options. Despite the initial cost, AIT offers lasting symptom relief, potentially balancing out the expense compared to long-term medication and productivity losses from uncontrolled symptoms. A meta-analysis demonstrated that both SCIT and SLIT could be cost-effective alternatives to standard medication over 6 years, with no distinct difference in cost-effectiveness between the two.[48] In general, SCIT tends to be more cost-effective than SLIT due to lower allergoid injectable extract prices compared to SLIT pills or sprays. For patients with multiple sensitivities, the approach to AIT should consider whether the sensitizations result in clinical symptoms. Patients can fall into the categories of being sensitized to multiple allergens but experiencing symptoms from only one allergen or being sensitized to multiple allergens and experiencing symptoms with multiple different allergens. Immunotherapy targeting individual extracts has shown efficacy in individuals with poly-sensitization but mono-allergy. Polysensitized patients with homologous allergens can receive mixed AIT.[49] For patients with non-homologous allergen sensitizations, distinct immunotherapy preparations for one or two of the most significant allergens should be considered.[50]

The latest guidelines, as presented in Table 4, provide evidence-based recommendations for AIT in ARC. Grade-A evidence includes level-I studies such as systematic reviews, meta-analyses, and randomized controlled trials demonstrating consistency.[51]

AIT is the only known method to alter the natural course of allergic diseases. Its mechanism of action is diverse involving both humoral and cellular immunity. There is currently good evidence for both SCIT and SLIT confirming its safety and efficacy in AC. AIT is useful for both SAC and PAC in both adults (stronger evidence) and children (weaker evidence). Evidence is stronger for short-term benefits, and more studies of longer duration are needed to confirm its long-term benefit.

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