ALLERGY RHINO

White Paper

How does allergen Immunotherapy work?

Introduction

Allergen immunotherapy (AIT) - often termed *allergy desensitization* - is a disease-modifying treatment for IgE-mediated inhalant allergies (e.g. pollen, dust mite, pet dander). Unlike pharmacotherapy which only manages symptoms, AIT aims to induce long-lasting tolerance to allergens. There are two main AIT modalities in clinical use for respiratory allergies: Subcutaneous Immunotherapy (SCIT) and Sublingual Immunotherapy (SLIT). SCIT (allergy "shots") has been used for over a century (first introduced by Noon in 1911) and involves periodic allergen extract injections, typically building up to a maintenance dose over several months and continuing for 3-5 years. SLIT (allergy drops or tablets taken under the tongue) emerged in the past few decades as a needle-free alternative, administered daily at home over 3+ years (Lawrence et al., 2016). Both routes have demonstrated efficacy in reducing allergic rhinitis and asthma symptoms and can confer prolonged clinical remission even after therapy cessation (Durham & Penagos, 2016). This whitepaper discusses the immunological mechanisms by which SCIT and SLIT achieve desensitization and reviews key clinical evidence for their efficacy. Food allergen immunotherapy is excluded from this discussion, as we focus solely on inhalant allergens.

Immunological Mechanisms of Desensitization (SCIT vs SLIT)

Overview: Allergic individuals mount exaggerated Th2-skewed immune responses to otherwise harmless inhaled proteins, leading to IgE production, mast cell activation, and allergic inflammation. AIT works by repeatedly exposing the immune system to controlled doses of allergen, driving it towards tolerance rather than hypersensitivity. SCIT and SLIT ultimately induce many overlapping immunological changes, albeit via different routes of antigen exposure (Aarestrup et al., 2024). The end result is a re-programming of the immune response away from allergy, characterized by increased regulatory and Th1 responses and reduced Th2 activity. Below we outline the key cellular and molecular changes:

Regulatory T Cell Induction

A central mechanism in successful immunotherapy is the generation of allergen-specific *regulatory T cells* (Tregs) that dampen allergic inflammation (Lawrence et al., 2016) (Aarestrup et al., 2024). Within weeks of starting SCIT, studies have detected a surge in IL-10-producing $CD4^+$ T cells that suppress allergen-specific Th2 responses (Lawrence et al., 2016). Pioneering work in bee venom immunotherapy first showed that allergen peptides could induce IL-10^+ Tregs, leading to reduced Th2 (IL-4, IL-5, IL-13) *and* Th1 (IFN-γ) cytokine production and blunted T cell proliferation. Subsequent trials in inhalant allergies (e.g. dust mite, birch pollen) confirmed that SCIT prompts peripheral Tregs (pTregs) which secrete IL-10 and TGF-β, thereby suppressing allergen-driven Th2 responses (Lawrence et al., 2016). These inducible Tregs (often $FoxP3^+$ $CD4^+$ cells) emerge early (within months) and are thought to mediate "peripheral tolerance" by releasing IL-10, IL-35 and TGF-β and by cell-contact mechanisms (CTLA-4, etc.) that broadly inhibit effector cells (Lawrence et al., 2016) (Aarestrup et al., 2024). Over time, Tregs curtail the pathogenic Th2 cell population. For example, in one study successful SCIT led to a preferential deletion of allergen-specific IL-4/IL-5-producing Th2 cells, while sparing IL-10-secreting T cells (Lawrence et al., 2016). SLIT likewise induces regulatory T cells following repeated mucosal allergen exposure. Patients on SLIT have shown increases in circulating IL-10 and TGF-β producing Tregs along with FoxP3 upregulation, paralleling the findings in SCIT (Lawrence et al., 2016). Notably, a trial of sublingual grass pollen tablets found a significant increase in $FoxP3^+$ T cells in the oral mucosa of treated patients, consistent with local induction of Tregs in tissues. Overall, both SCIT and SLIT skew the T cell response away from the Th2 phenotype and toward a regulatory (and in part Th1) profile, with sustained IL-10 production being a hallmark of successful desensitization (Lawrence et al., 2016). This T cell tolerance is durable: high-dose SCIT given for 3-4 years can induce a state of non-responsiveness that persists for years after stopping therapy (Lawrence et al., 2016).

Shift from Th2 to Th1 Cytokine Profile

In addition to Treg upregulation, allergen immunotherapy causes a broader immune deviation. The excessive Th2 activity (IL-4, IL-5, IL-13) that drives IgE production and eosinophilic inflammation is gradually diminished, and there is a relative shift toward a Th1-type response (e.g. increased interferon-γ) (Lawrence et al., 2016). After 1-2 years of therapy, peripheral T cells from immunotherapy-treated patients show significantly

lower IL-4/IL-5 and higher IFN-γ upon allergen re-stimulation compared to baseline, indicating a re-balancing of the Th1/Th2 axis (Lawrence et al., 2016). This Th2→Th1 shift has been observed with both SCIT and SLIT. For example, in a 1-year SLIT study for birch pollen allergy, patients initially exhibited non-specific T cell suppression via IL-10 (after weeks of SLIT), but by 52 weeks there was a persistent reduction in IL-4 mRNA and an increase in IFN-γ mRNA specific to the allergen (Lawrence et al., 2016). Thus, immunotherapy not only induces Tregs but also mitigates the Th2 bias of the immune system, fostering an environment less prone to allergic reactivity.

B Cell and Antibody Changes

A well-documented effect of AIT is the modulation of B cell responses and antibody production. Allergen-specific IgE levels often transiently rise during the initial months of therapy (especially with SCIT), then plateau and gradually decline over the course of years (Lawrence et al., 2016). Importantly, immunotherapy blunts the seasonal increases in IgE that allergic individuals typically experience with natural allergen exposure. Concurrently, allergen-specific IgG, particularly IgG4, increases substantially in immunotherapy-treated patients (Lawrence et al., 2016). IgG4 is considered a "blocking antibody" that can intercept allergens before they cross-link IgE on mast cells (Lawrence et al., 2016). The rise in IgG4 (as well as IgG1 and sometimes IgA) is driven by IL-10 from Tregs and IL-10-producing regulatory B cells (Bregs). IgG4 may help reduce allergen presentation to B cells and dampen low-affinity IgE-facilitated antigen presentation by dendritic cells, thereby reducing T cell activation. It can also engage inhibitory FcγRIIB receptors on mast cells and basophils, further decreasing mediator release. Notably, immunotherapy induces *regulatory B cells* as well - for instance, beekeepers with chronic venom exposure (an immunotherapy model) were found to have expanded IL-10^{+} Bregs that produced IgG4 and contributed to tolerance (Lawrence et al., 2016). Over long-term therapy, allergen-specific IgE levels tend to fall while IgG4 rises, increasing the IgG4/IgE ratio in favor of protection. However, the correlation between these antibody changes and clinical improvement is not straightforward - they are best viewed as immunologic markers of tolerance rather than direct effectors. In summary, both SCIT and SLIT lead to a remodeling of B cell responses: downregulating pathogenic IgE and upregulating non-inflammatory, blocking antibodies and regulatory B cells.

Effector Cell Modulation

By altering the immune environment, AIT also affects downstream effector cells of allergy. After immunotherapy, basophils and mast cells become less reactive to allergen stimulation. Clinically, this is seen as increased thresholds for skin test reactivity and reduced immediate-phase responses over time. Although not directly measured in routine practice, studies show that desensitized patients have reduced release of histamine and other mediators upon allergen challenge after completing therapy. This is partly due to fewer IgE molecules on effector cell surfaces and the presence of IgG4 blocking antibodies, and partly due to desensitization of these cells. Immunotherapy has also been shown to decrease tissue infiltration by inflammatory cells (like eosinophils and mast cells) during allergen exposure. For example, nasal biopsies from patients on SCIT/SLIT show reduced seasonal eosinophilia and mast cell numbers compared to untreated allergic individuals, reflecting a dampened local allergic response (Aarestrup et al., 2024). Furthermore, recent evidence indicates AIT can even downregulate *innate* immune pathways of allergy: it suppresses type 2 innate lymphoid cells (ILC2) that normally amplify allergic inflammation. Overall, by inducing Tregs and allergen-specific IgG4, immunotherapy creates an immune milieu that renders mast cells, basophils, and other effector cells less prone to activation - manifesting as higher tolerance to allergen exposure.

Route-Specific Considerations

Despite their common end-goal, SCIT and SLIT engage the immune system in distinct ways. SCIT delivers allergen into the subcutaneous tissue, where it is picked up by skin dendritic cells (especially Langerhans cells) and carried to regional lymph nodes. Adjuvants (like alum) in SCIT extracts further boost immune recognition (Lawrence et al., 2016). This often results in robust systemic IgG4 responses (30-40 fold increases are reported with SCIT). SLIT, on the other hand, introduces allergen to the oral mucosa. The sublingual mucosa is rich in dendritic cells and highly vascular (Aarestrup et al., 2024). Oral dendritic cells tend to favor a tolerogenic phenotype (partly due to constant exposure to food antigens and microbes), secreting IL-10 and promoting Treg differentiation (Aarestrup et al., 2024). The daily low-dose exposure in SLIT may preferentially activate these tolerogenic antigen-presenting cells, which could explain SLIT's excellent safety profile. One interesting difference is in antibody distribution: SLIT has been shown to induce stronger mucosal IgA responses (e.g. in nasal secretions) than SCIT (Aarestrup et al., 2024). This makes sense, as IgA is a mucosal

antibody and sublingual immunization can stimulate IgA-producing plasma cells. SCIT, by contrast, typically induces higher IgG4 levels in serum. Nonetheless, the *core* immunologic mechanisms - generation of Tregs, immune deviation to Th1, and IgG4 production - are shared between SLIT and SCIT. Both routes ultimately converge on the development of long-lasting peripheral tolerance to the allergen. This convergence is reassuring when transitioning patients from one route to another, as discussed later, because switching routes does not "reset" the immune response - the tolerance processes are complementary and ongoing (Aarestrup et al., 2024).

Summary

Through repeated low-dose allergen exposure, both SCIT and SLIT retrain the immune system. They induce regulatory T cells and B cells, dampen Th2-driven IgE responses, boost blocking IgG4/IgA antibodies, and reduce the reactivity of mast cells, basophils, and other effectors. Over a treatment course of 3-5 years, these changes can lead to sustained clinical tolerance. Immunologically, SCIT and SLIT operate via similar pathways, with differences largely in degree (e.g. systemic vs mucosal response) rather than kind. These mechanistic insights are crucial for clinicians, as they explain why AIT can alter the natural course of allergic disease - for example, reducing the risk of new sensitizations or progression to asthma - and why it remains effective long after therapy is stopped (Lawrence et al., 2016) (Aarestrup et al., 2024).

Clinical Efficacy and Evidence Base

Subcutaneous Immunotherapy (SCIT): SCIT has the longest track record of efficacy, supported by numerous randomized controlled trials and meta-analyses. For allergic rhinitis, SCIT consistently shows significant symptom improvement compared to placebo. A Cochrane review of 15 trials (1063 patients) with seasonal allergic rhinitis found a pronounced reduction in symptom scores with SCIT (standardized mean difference around -0.73 versus placebo) and reduced medication use (SMD ≈ -0.57) (Durham & Penagos, 2016). Similar effectiveness is seen in perennial (year-round) rhinitis: a meta-analysis of SCIT for dust mite allergy showed significant relief of nasal symptoms and conjunctivitis symptoms, with less rescue medication needed (Durham & Penagos, 2016). Clinically, these numbers translate to meaningful improvements in daily quality of life and less dependence on antihistamines and steroids for patients. SCIT's benefits extend to allergic asthma as well. Patients with asthma triggered by inhalant allergens (e.g. pollen-induced asthma or dust mite asthma) experience fewer

symptoms and exacerbations on immunotherapy. For instance, trials in children with both allergic rhinitis and mild asthma have demonstrated improved asthma symptom control and reduced inhaler use with SCIT compared to placebo (Penagos & Durham, 2022). Beyond symptomatic relief, SCIT can modify disease progression: the landmark Preventive Allergy Treatment (PAT) study showed that treating children with pollen SCIT reduced the development of new asthma years later. In that 3-year trial, only 25-30% of hay fever children on SCIT developed asthma after 5 years, versus 45-50% in the placebo group - a significant risk reduction (Niggemann & Jacobsen, 2006). A 10-year follow-up confirmed that the early intervention of immunotherapy had long-term preventive effects on asthma and on emergence of new allergen sensitivities (Ren & Wang, 2023) (Jacobsen & Niggemann, 2007). These findings are supported by other long-term studies: e.g. Durham et al. reported that three years of grass pollen SCIT led to sustained symptom improvement for *at least* two years post-therapy, with continued suppression of seasonal symptoms compared to untreated controls (Lawrence et al., 2016). Taken together, the evidence base for SCIT in inhalant allergies is robust - it not only provides short-term relief, but also enduring benefits and possible prevention of allergic march. Major international guidelines (e.g. WAO, EAACI, AAAAI) endorse SCIT for patients with moderate-to-severe allergic rhinitis or allergic asthma not well controlled on medications (Aarestrup et al., 2024). It's important to note that SCIT's efficacy has been demonstrated for single-allergen immunotherapy as well as multi-allergen mixtures in polysensitized patients, though optimal outcomes are generally seen when the major clinically relevant allergen is included at high dose.

Sublingual Immunotherapy (SLIT): SLIT has amassed a strong evidence base over the past two decades and is now an established treatment option for respiratory allergies. Dozens of placebo-controlled RCTs have tested SLIT (using either liquid drops or dissolvable tablets) for pollen, dust mite, mold, and animal dander allergies. The overall efficacy is confirmed by meta-analyses. A comprehensive Cochrane review of SLIT in allergic rhinitis (49 trials, ~4,500 patients) found significant improvements in symptoms (SMD ~-0.49) and reductions in medication use (SMD ~-0.32) for SLIT-treated patients compared to placebo (Durham & Penagos, 2016). Notably, benefits were seen for both seasonal allergens (e.g. grass, ragweed) and perennial allergens (dust mites), although heterogeneity was higher in perennial studies (Durham & Penagos, 2016). In pediatric patients, SLIT is likewise effective. One meta-analysis focusing on children with allergic rhinitis (10 trials, <18 years old) showed a significant reduction in symptom scores and rescue medication needs in the SLIT group - in fact,

longer courses (>18 months) of SLIT were especially efficacious in children (Penagos & Compalati, 2006). As an example, a 3-year trial of SLIT in dust mite-allergic children with asthma found that those on SLIT had fewer asthma exacerbations and better controlled rhinitis than placebo, with some effects lasting 2 years after stopping therapy (Durham & Penagos, 2016). The efficacy of SLIT-tablets (which are standardized doses approved for specific allergens like grass, ragweed, dust mite) has been demonstrated in large multicenter trials that led to their regulatory approval in Europe and the US. These trials typically show ~20-30% improvements in symptom-medication scores over placebo in seasonal allergic rhinitis, which is comparable to SCIT outcomes. For allergic asthma, SLIT has shown benefit primarily when asthma is mild and allergen-triggered; several studies (including in children) report better asthma symptom control and reduced inhaler use after SLIT, in addition to improvement of co-morbid rhinitis (Penagos & Durham, 2022). However, SLIT is generally considered an adjunct for asthma (aimed at the allergic component) rather than a standalone asthma treatment. Like SCIT, SLIT can induce sustained tolerance: a co-seasonal grass SLIT study indicated that 3 years of SLIT still conferred symptom relief 2-3 years after discontinuation (Durham & Penagos, 2016). Furthermore, there is emerging evidence that SLIT might, similar to SCIT, help prevent new sensitizations and possibly asthma onset, though data are less extensive. One long-term Italian study suggested children treated with SLIT were less likely to become sensitized to new pollens compared to untreated children over a 5-year period (Jacobsen & Niggemann, 2007). Overall, the evidence firmly supports SLIT as an effective therapy for allergic rhinitis (seasonal and perennial) and as a modifier of allergic disease in the long run.

Safety Profile: AIT's safety is a critical consideration, and it differs between SCIT and SLIT. SCIT involves injections of allergen, which carry a risk of systemic allergic reactions. In clinical trials, up to 0.1-0.2% of SCIT injections result in a systemic reaction, usually mild to moderate (e.g. generalized hives, wheezing) that is manageable with antihistamines or epinephrine (Durham & Penagos, 2016). Severe anaphylaxis on SCIT is rare but has been reported, which is why SCIT must be administered in a medical setting with a 30-minute post-injection observation period (Aarestrup et al., 2024). In fact, surveys of allergy clinics indicate approximately 1-5% of SCIT patients experience at least one systemic reaction during their treatment course, and fatalities are exceedingly rare with adherence to modern protocols (Aarestrup et al., 2024). By contrast, SLIT has a superior safety profile. The World Health Organization declared in 1998 that SLIT is a viable alternative to injections *"with proven efficacy and a superior safety profile"*. The vast majority of SLIT side effects are localized to the oral

cavity - commonly itching of the mouth or tongue, throat irritation, or mild swelling of lips - and these are usually transient and self-resolving (Aarestrup et al., 2024). Unlike SCIT, anaphylaxis from SLIT is extremely uncommon; no fatal reactions to SLIT have been reported in the literature, and only isolated cases of systemic reactions (typically after first doses) have been noted. This safety advantage allows SLIT to be administered at home (after the first dose is supervised). Patients or parents can dose daily without the need for frequent clinic visits, which partly explains the higher uptake of SLIT in some countries. For clinicians, the key safety takeaway is: SCIT requires medical supervision due to injection-related systemic risk, whereas SLIT is largely confined to local reactions. Both forms are generally well tolerated, but patient selection and education on adhering to dosing schedules (and carrying epinephrine autoinjectors in the case of SCIT patients) are important for safe therapy.

Comparative Efficacy (SCIT vs SLIT): Given that both SCIT and SLIT are effective, a natural question is whether one is superior. There have been relatively few direct head-to-head RCTs, and their results often show no significant difference in outcome between SCIT and SLIT, especially when each is optimized for dose and duration. Indirect comparisons via meta-analyses suggest that SCIT might achieve slightly larger effect sizes in symptom improvement, but the differences are small (Durham & Penagos, 2016). For example, as noted, a meta-analysis found SCIT's impact on rhinitis symptoms (SMD ~-0.7) somewhat greater than SLIT's (SMD ~-0.5), but these analyses were done in different trials and patient populations. A couple of head-to-head studies in birch and grass pollen allergy showed both routes significantly improved symptoms versus placebo, with no statistically significant efficacy difference between SCIT and SLIT groups (Khinchi & Poulsen, 2004). One trial did note that patients perceived improvement faster with SCIT (possibly due to the ability to reach high doses more quickly via injection), but by the end of treatment, both groups had comparable relief. Practical factors often guide the choice: SCIT requires regular clinic visits but may foster better adherence in a supervised setting; SLIT is needle-free and convenient for home use, but daily dosing for years can be challenging for compliance. Indeed, adherence studies indicate that by the 3-year mark, only ~50-60% of patients remain fully compliant on SLIT (many drop off due to forgetting doses), which is similar to SCIT's adherence in practice (Caruso & Brame, 2020). In terms of long-term benefits, both SCIT and SLIT have shown the ability to maintain clinical remission years after a 3-year treatment course (Durham & Penagos, 2016). Both also appear capable of altering the atopic march in children (though the strongest evidence of asthma prevention is with SCIT). Therefore, for inhalant allergies, both SCIT and SLIT are valid,

evidence-based options, and the choice can be individualized to the patient's age, preferences, comorbidities, and practical considerations.

Combination and Sequential Use of SCIT and SLIT

Clinicians have explored using SCIT and SLIT in combination or sequentially to capitalize on their respective strengths. One approach is a *sequential regimen*: initiating desensitization with SCIT (to rapidly build up tolerance under supervision) and then transitioning the patient to SLIT for long-term maintenance. This method aims to achieve the high-dose tolerance induction of injections and then sustain it with the safer oral route. A proof-of-concept for this comes from a study where patients started on cluster-build SCIT and after reaching maintenance, were switched to SLIT - the results showed no loss of efficacy or increase in reactions upon switching, and in fact improved overall adherence to therapy (Aarestrup et al., 2024). In a large 18-year observational analysis of pediatric patients (4,933 on SCIT and 4,285 on SLIT), many children at some point transitioned between SLIT and SCIT; investigators found that changing the route did not raise the risk of systemic reactions, confirming that a route switch can be done safely and smoothly. Immunologically, this makes sense: as discussed, SCIT and SLIT induce largely overlapping tolerance mechanisms, so switching routes continues stimulating the established tolerant immune cells rather than restarting the process (Aarestrup et al., 2024). In fact, some immunologists hypothesize that combining routes could even *amplify* the immunomodulation - e.g. SLIT might add stronger mucosal IgA responses while SCIT elicits robust IgG4, potentially yielding a broader protective shield. However, true *simultaneous* combination (administering SCIT and SLIT for the same allergen concurrently) is rarely practiced and not well-studied; doing so could theoretically increase side effects with little proven benefit, so it's generally not recommended.

That said, using SCIT and SLIT together in a *complementary* way is feasible in certain scenarios. For instance, a patient polysensitized to multiple pollens and dust mite might receive SCIT for the pollen mix and SLIT for dust mite, if dust mite SLIT is readily available and the clinician deems it more convenient. There is no immunologic contraindication to treating different allergens via different routes in parallel, although robust clinical trial data on this specific practice are lacking. The clinician should monitor for any additive side effects, but case reports and expert experience suggest it can be done safely in experienced hands. A more common scenario is route switching due to patient preference or life circumstances: e.g. a patient on SCIT who relocates or cannot attend injections may transition to SLIT to continue therapy, or a child on SLIT

might switch to injections once older if that seems preferable. The 2024 Brazilian immunotherapy consensus notes several such reasons and emphasizes that switching from SCIT to SLIT or vice versa can maintain effectiveness while improving patient comfort or safety as needed (Aarestrup et al., 2024). The bottom line is that SCIT and SLIT are not mutually exclusive - they can be integrated in a treatment plan. A practical combined approach is SCIT for rapid build-up followed by SLIT for maintenance, which has been reported to improve safety and convenience without compromising efficacy (Keles & Karakoc-Aydiner, 2011). As allergen immunotherapy is a long journey (3-5 years), this flexibility in route can help tailor treatment to the patient's needs over time.

Conclusion

Allergy desensitization via SCIT and SLIT is a cornerstone of modern allergy practice, offering clinicians a means to alter the natural course of allergic disease. Through mechanisms centered on inducing immunological tolerance - via regulatory T cells, blocking antibodies, and immune deviation - AIT targets the root cause of allergic hypersensitivity rather than just symptoms. High-quality clinical trials and meta-analyses have established that both SCIT and SLIT provide significant, sustained relief for inhalant allergy sufferers, with improvements in rhinitis and asthma outcomes backed by a strong evidence base (Durham & Penagos, 2016). Moreover, immunotherapy confers unique long-term benefits, such as continued remission after therapy and potential prevention of asthma and new allergies in children (Niggemann & Jacobsen, 2006) (Lawrence et al., 2016) - effects not achievable with pharmacotherapy alone. For the practicing clinician, it is important to understand the immunological pathways of AIT, as this knowledge underpins patient selection and counseling. One should explain to patients that SCIT and SLIT "re-educate" the immune system, increasing tolerance to allergens over time. Inhalant allergen immunotherapy is generally very safe; SLIT offers an excellent safety profile for home administration, whereas SCIT, administered under supervision, has a low but manageable risk of systemic reactions. Both routes are effective; the choice can be personalized, and even combined sequential strategies are possible to maximize benefit. In summary, allergen immunotherapy for respiratory allergies is a scientifically grounded, evidence-backed intervention that not only alleviates symptoms but also modifies the underlying allergic disorder. By leveraging either subcutaneous injections or sublingual doses (or both), clinicians can help patients achieve lasting desensitization - turning down the immune system's overreaction and delivering enduring relief from allergic disease (Aarestrup et al., 2024) (Lawrence et al., 2016).

References

Aarestrup, F. M., Taketomi, E., & Galvao, C. (2024). Transition between subcutaneous and sublingual allergen immunotherapy: Recommendations of the Brazilian Association of Allergy and Immunology (ASBAI). *Journal of Allergy and Clinical Immunology*, *3*(3), 100281. https://www.jaci-global.org/article/S2772-8293(24)00077-8/fulltext#:~:text=One%20of%20the%20hypotheses%20explaining,16%2C17

Caruso, C., & Brame, B. (2020). Adherence to Allergen Subcutaneous Immunotherapy is Increased by a Shortened Build-Up Phase: A Retrospective Study. *Biomed Res Int*, *18*(1), 1. https://pmc.ncbi.nlm.nih.gov/articles/PMC7049433/#:~:text=Adherence%20to%20Allergen%20Subcutaneous%20Immunotherapy,improves%20patients%27%20adherence%20to%20SCIT

Durham, S. R., & Penagos, M. (2016). Sublingual or subcutaneous immunotherapy for allergic rhinitis? *Journal of Allergy and Clinical Immunology*, *137*(2), 339-349. https://www.jacionline.org/article/S0091-6749(15)03112-7/fulltext

Jacobsen, L., & Niggemann, B. (2007). Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*, *62*(8), 943-948. https://pubmed.ncbi.nlm.nih.gov/17620073/#:~:text=Specific%20immunotherapy%20has%20long,of%20preventing%20development%20of%20asthma

Keles, S., & Karakoc-Aydiner, E. (2011). A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. *Journal of allergy and clinical immunology*, *128*(8), 808-815. https://pubmed.ncbi.nlm.nih.gov/21641635/#:~:text=PubMed%20pubmed,and%20sublingual%20maintenance%20in

Khinchi, M. S., & Poulsen, L. K. (2004). Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy*, *59*(1), 45-53. https://pubmed.ncbi.nlm.nih.gov/14674933/#:~:text=Clinical%20efficacy%20of%20sublingual%20and,between%20the%20two%20groups

Lawrence, M. G., Steinke, J. W., & Borrish, L. (2016). Basic Science for the Clinician: Mechanisms of sublingual and subcutaneous immunotherapy. *Ann Allergy Asthma Immunol*, *117*(2), 138 - 142. 10.1016/j.anai.2016.06.027

Niggemann, B., & Jacobsen, L. (2006). Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *European journal of allergy and clinical immunology*, *61*(7), 855-859. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1398-9995.2006.01068.x#:~:text=Five%E2%80%90year%20follow%E2%80%90up%20on%20the%20PAT,the%20risk%20of%20developing%20asthma

Penagos, M., & Compalati, E. (2006). Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Annals of Allergy, Asthma & Immunology*, *97*(2), 141-148. https://www.annallergy.org/article/S1081-1206(10)60004-X/abstract#:~:text=confidence%20interval%2C%201,18%20months%20and%20with%20mites

Penagos, M., & Durham, S. R. (2022). Long-term efficacy of the sublingual and subcutaneous routes in allergen immunotherapy. *Allergy Asthma Proc*, *43*(4), 292-298. https://www.ingentaconnect.com/content/ocean/aap/2022/00000043/00000004/art00009;jsessionid=1p2n1gep8l0fb.x-ic-live-01

Ren, L., & Wang, C. (2023). Long-term efficacy of HDM-SCIT in pediatric and adult patients with allergic rhinitis. *Allergy, Asthma & Clinical Immunology*, *19*(20), 1. https://aacijournal.biomedcentral.com/articles/10.1186/s13223-023-00781-8#citeas