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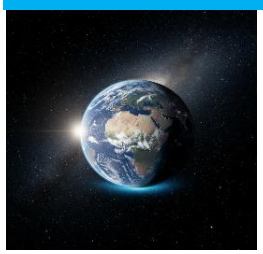

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Subcutaneous versus Sublingual Allergen Immunotherapy in Allergic Rhinitis and Asthma: A Comparative Narrative Review

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Abstract:

Allergen-specific immunotherapy (AIT) represents the only disease-modifying intervention for IgE-mediated allergic diseases, including allergic rhinitis and allergic asthma. Among the currently available administration routes, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the most extensively studied and clinically implemented. Despite their widespread use, uncertainty persists regarding their relative efficacy, safety, and real-world applicability across different patient populations and allergen types.

AIM: The aim of this study was to critically compare the clinical effectiveness, safety profile, and treatment adherence of SCIT and SLIT based on data derived from PubMed-indexed randomized controlled trials, systematic reviews, and meta-analyses.

Material and methods: A narrative synthesis of peer-reviewed literature was conducted, focusing on studies directly or indirectly comparing SCIT and SLIT in patients with allergic rhinitis, allergic asthma, or rhinoconjunctivitis. Primary endpoints included symptom score reduction and medication use, while secondary outcomes encompassed adverse events, immunological responses, and adherence rates.

Results: Both SCIT and SLIT demonstrated significant clinical efficacy compared with placebo or pharmacotherapy alone. Overall symptom reduction and medication sparing effects were largely comparable between the two modalities. SCIT showed a trend toward slightly greater efficacy in selected allergens, particularly grass pollen, whereas SLIT consistently exhibited a superior safety profile with fewer systemic adverse reactions.

Conclusion: SCIT and SLIT are both effective forms of allergen immunotherapy. While SCIT may provide marginal advantages in symptom control in specific clinical contexts, SLIT offers improved safety and convenience. Treatment choice should therefore be individualized, considering patient characteristics, allergen profile, and risk tolerance.

Keywords: Allergen immunotherapy, subcutaneous immunotherapy, sublingual immunotherapy, allergic rhinitis, allergic asthma, efficacy, safety.

Content

1. Introduction

Allergic diseases constitute one of the most prevalent chronic conditions worldwide, with allergic rhinitis and allergic asthma affecting both pediatric and adult populations across diverse geographic regions. Their prevalence has continued to rise over recent decades, particularly in industrialized countries, reflecting complex interactions between genetic susceptibility and environmental exposures. These conditions are associated with significant morbidity, impaired quality of life, and a substantial socioeconomic burden resulting from direct healthcare costs, absenteeism from school and work, and reduced overall productivity. In addition, allergic rhinitis and asthma frequently coexist, with rhinitis recognized as a major risk factor for poor asthma control and increased disease severity [1][2].

Although pharmacological therapies—including antihistamines, intranasal corticosteroids, and inhaled bronchodilators—are effective in controlling symptoms and reducing acute inflammation, they act primarily at a symptomatic level. Such treatments fail to address the underlying immunological mechanisms driving allergic inflammation and immune dysregulation. Consequently, they do not alter the natural history of allergic disease, nor do they prevent disease progression, the development of asthma in patients with allergic rhinitis, or the emergence of new allergen sensitizations over time [1][2]. These limitations underscore the need for therapeutic strategies capable of inducing sustained immune tolerance.

Allergen-specific immunotherapy (AIT) is unique among available treatments in its ability to modify the natural course of allergic disease by targeting its immunopathological basis. Through the repeated administration of gradually increasing doses of clinically relevant allergens, AIT induces long-term immunological tolerance. This process is characterized by a shift away from Th2-dominated immune responses toward regulatory and non-inflammatory pathways. Key immunological effects include the induction of allergen-specific regulatory T

cells, suppression of allergen-specific IgE responses, increased production of IgG4 “blocking” antibodies, and reduced activation of mast cells and basophils [3][4]. Collectively, these changes lead to diminished allergic inflammation upon natural allergen exposure.

Importantly, the clinical benefits of AIT extend beyond the treatment period itself. Long-term follow-up studies have demonstrated that symptom relief and reduced medication use may persist for several years after discontinuation of therapy, supporting the concept of AIT as a disease-modifying intervention rather than a purely symptomatic treatment [5]. Furthermore, evidence suggests that AIT may reduce the risk of developing asthma in patients with allergic rhinitis and limit the progression of polysensitization, reinforcing its preventive potential [3][5].

Subcutaneous immunotherapy (SCIT) represents the traditional and most extensively studied form of AIT. It has been used in clinical practice for over a century and is supported by robust evidence demonstrating efficacy across a wide spectrum of inhalant allergens, including grass and tree pollens, house dust mites, and animal dander [1][6]. SCIT has consistently been shown to reduce symptom severity, medication requirements, and allergen-specific bronchial hyperresponsiveness in both allergic rhinitis and allergic asthma.

Despite its proven efficacy, SCIT is associated with several practical and safety-related limitations. Treatment requires frequent injections administered in a medical setting, particularly during the build-up phase, which can negatively affect patient convenience and long-term adherence. Moreover, SCIT carries a non-negligible risk of systemic allergic reactions, ranging from mild generalized symptoms to severe anaphylaxis, including rare fatal events [6][7]. These risks necessitate post-injection observation periods and limit the suitability of SCIT for certain patient populations.

In response to these challenges, alternative routes of allergen administration have been developed, most notably sublingual immunotherapy (SLIT). SLIT has emerged as a viable and increasingly popular alternative, particularly in Europe, where it is widely prescribed for respiratory allergies. Administered as drops or tablets placed under the tongue, SLIT offers improved safety and greater ease of use compared with SCIT. After an initial supervised dose, treatment can be self-administered at home, enhancing patient autonomy and potentially improving adherence [8].

Numerous randomized controlled trials and meta-analyses have confirmed the efficacy of SLIT in the treatment of allergic rhinitis and, to a lesser extent, allergic asthma in both adult

and pediatric populations [8][9][10]. SLIT is associated primarily with mild local adverse effects, such as oral itching or throat irritation, while severe systemic reactions are exceedingly rare. Nevertheless, variability in dosing regimens, allergen extracts, and study designs has contributed to heterogeneity in reported outcomes, and questions remain regarding its comparative effectiveness relative to SCIT in different allergens, age groups, and disease severities [9][10].

Despite decades of research and widespread clinical use of both modalities, direct head-to-head comparisons between SCIT and SLIT remain scarce. Much of the available evidence is derived from indirect comparisons or meta-analyses, which are subject to methodological limitations and confounding factors. As a result, clinical decision-making often relies on extrapolation, physician experience, and patient preference rather than definitive comparative data. This review aims to synthesize current evidence and provide a nuanced comparison of SCIT and SLIT, with particular emphasis on efficacy, safety, treatment adherence, and clinical applicability across different patient populations.

2. Research materials and methods

A narrative synthesis of peer-reviewed literature was conducted, focusing on studies directly or indirectly comparing SCIT and SLIT in patients with allergic rhinitis, allergic asthma, or rhinoconjunctivitis. Primary endpoints included symptom score reduction and medication use, while secondary outcomes encompassed adverse events, immunological responses, and adherence rates.

3. Research results

3.1 Clinical Efficacy

Across numerous randomized controlled trials and systematic reviews, both SCIT and SLIT have consistently demonstrated clinically meaningful reductions in allergic symptom scores and medication use when compared with placebo or standard pharmacotherapy alone [1][10][11]. These improvements encompass a broad range of clinical manifestations, including nasal congestion, rhinorrhea, sneezing, ocular itching, and lower airway symptoms such as wheezing and dyspnea. The breadth of symptom control reflects the systemic immunomodulatory effects of allergen immunotherapy rather than transient or site-specific symptom suppression [3][4].

Notably, the therapeutic benefits of both SCIT and SLIT extend across different age groups, including children, adolescents, and adults, underscoring the broad applicability of these treatment modalities in routine clinical practice [10][14]. In pediatric populations, immunotherapy has been shown not only to alleviate symptoms but also to reduce medication reliance, which is of particular importance given concerns regarding long-term pharmacotherapy in children [10]. Moreover, sustained clinical efficacy following treatment discontinuation has been well documented, further supporting the disease-modifying nature of AIT [5].

Indirect comparative analyses and meta-analyses suggest that SCIT may confer a modest advantage in symptom control for certain allergens, particularly grass pollen, when assessed using combined symptom–medication scores [12][13]. These differences are most apparent in studies employing standardized allergen extracts and higher cumulative allergen doses, which may favor the parenteral route of administration. However, such findings should be interpreted with caution, as the magnitude of observed differences is generally small and frequently falls below thresholds considered clinically meaningful in everyday practice. In addition, methodological heterogeneity among studies, including variations in outcome measures and treatment duration, limits the strength of definitive conclusions [12][13].

In pediatric allergic rhinitis, several large-scale meta-analyses encompassing thousands of participants have reported no statistically significant differences in overall efficacy between SCIT and SLIT [1][10][14]. These findings reinforce the concept of therapeutic equivalence between the two approaches in children and support the use of SLIT as a less invasive alternative without compromising clinical outcomes. Similar trends have been observed in adolescents, although data remain comparatively limited in this age group.

In patients with allergic asthma, both SCIT and SLIT have demonstrated efficacy in reducing symptom burden, improving asthma control, and decreasing the need for rescue medication [15][16]. Some evidence suggests that SCIT may offer greater improvements in objective lung function parameters, such as forced expiratory volume in one second (FEV1), particularly in patients with moderate to severe disease or those sensitized to multiple allergens [15]. Nevertheless, SLIT has also shown clinically relevant benefits in asthma management, especially in studies targeting house dust mite allergy, where significant reductions in exacerbation rates and improved symptom control have been reported [16]. These findings

highlight that both modalities can play a meaningful role in asthma treatment, with selection guided by patient characteristics and risk profiles.

3.2. Safety Profile

Safety represents one of the most important distinguishing features between SCIT and SLIT and plays a central role in both clinical decision-making and patient acceptance of allergen immunotherapy. SLIT consistently exhibits a superior safety profile, with the vast majority of reported adverse events being mild, localized, and self-limiting. These reactions most commonly involve transient oral or oropharyngeal symptoms, such as itching, tingling, or mild swelling, as well as occasional gastrointestinal discomfort, particularly during the early phases of treatment [8][17]. Such events rarely require medical intervention and infrequently lead to treatment discontinuation, supporting the overall tolerability of the sublingual route.

Importantly, systemic allergic reactions associated with SLIT are uncommon, and extensive clinical trials as well as post-marketing surveillance studies have failed to document fatal events attributable to SLIT administration [8][17]. The low risk of severe systemic reactions allows for home-based administration following the initial supervised dose, which substantially enhances patient autonomy and expands access to allergen immunotherapy, especially in pediatric populations. This favorable safety profile has been a key factor driving the increasing adoption of SLIT in routine clinical practice and its endorsement in international guidelines [8].

In contrast, SCIT is associated with a higher incidence of systemic allergic reactions, ranging from generalized urticaria and angioedema to bronchospasm, hypotension, and, in rare cases, life-threatening anaphylaxis [6][18]. Although the overall frequency of such reactions is low when SCIT is administered in accordance with established dosing schedules and safety protocols, their unpredictable nature and potential severity necessitate administration in a controlled medical environment with trained personnel and immediate access to emergency treatment [6]. Identified risk factors for severe systemic reactions include uncontrolled asthma, dosing errors, and administration during periods of high allergen exposure [18].

These safety considerations are of particular importance in vulnerable patient groups, including children, elderly individuals, and patients with comorbid asthma. In such populations, the risk–benefit balance may favor SLIT due to its superior safety profile, even when marginal differences in efficacy are reported for certain allergens. Consequently, safety remains a pivotal

factor influencing treatment selection and underscores the need for individualized decision-making in allergen immunotherapy.

3.3. Adherence and Real-World Effectiveness

Adherence to allergen immunotherapy is a critical determinant of treatment success, as sustained and regular administration over several years is required to achieve durable immunological tolerance and long-term clinical benefit. Although SLIT offers greater convenience by enabling home-based administration and eliminating the need for frequent clinic visits, real-world observational studies indicate that long-term adherence to SLIT may be suboptimal [19]. Factors contributing to reduced persistence include the daily dosing schedule, the prolonged duration of therapy, and the relative lack of structured medical supervision once treatment has been initiated. Over time, these elements may diminish patient motivation and perceived treatment necessity, particularly in the absence of immediate symptomatic feedback.

Conversely, SCIT may promote better adherence through regular physician contact, scheduled injections, and ongoing clinical monitoring, which collectively reinforce patient engagement and accountability [20]. The structured nature of SCIT programs allows for frequent assessment of treatment response and adverse events, potentially strengthening the therapeutic alliance between patients and healthcare providers. However, despite these advantages, SCIT is also associated with notable logistical and time-related burdens, including travel requirements, time off work or school, and injection-related discomfort, which may negatively affect adherence in certain patient populations.

These observations highlight the complex interplay between treatment convenience, supervision, healthcare infrastructure, and patient motivation in determining adherence patterns. Importantly, real-world adherence varies considerably across healthcare systems and cultural contexts, influenced by factors such as reimbursement policies, accessibility of specialized allergy services, patient education, and societal attitudes toward long-term preventive therapies [19][20]. Consequently, local organizational factors and individual patient preferences should be carefully considered when interpreting real-world effectiveness data and when selecting the most appropriate immunotherapy modality for long-term disease management.

4. Discussion

The present review highlights that both subcutaneous and sublingual allergen immunotherapy represent effective disease-modifying interventions in allergic rhinitis and allergic asthma, with broadly comparable clinical efficacy across most patient populations and allergen types. Importantly, the apparent differences in efficacy reported in selected studies—often favoring SCIT—must be interpreted in the context of substantial methodological heterogeneity, including variability in allergen standardization, cumulative doses, treatment duration, and outcome measures [12][13][21].

A critical distinction emerging from the literature is the difference between efficacy, as demonstrated in randomized controlled trials under idealized conditions, and real-world effectiveness, which is strongly influenced by adherence, healthcare infrastructure, and patient behavior. While SCIT may achieve higher immunological exposure and, in some settings, slightly superior symptom–medication score reductions, its reliance on frequent clinic visits and supervised administration introduces practical barriers that may limit long-term effectiveness outside controlled trial environments [20][22]. Conversely, SLIT offers greater flexibility and accessibility but appears particularly vulnerable to declining adherence over prolonged treatment periods, potentially attenuating its real-world impact despite favorable safety and efficacy profiles [19][23].

From a mechanistic standpoint, accumulating evidence suggests that SCIT and SLIT induce largely overlapping immunological pathways, including regulatory T-cell expansion, immune deviation away from Th2 responses, and the generation of allergen-specific IgG4 antibodies [3][4][24]. This immunological convergence supports the concept that differences in clinical outcomes are more likely attributable to quantitative factors—such as allergen dose and duration of exposure—rather than fundamental qualitative differences between administration routes. This observation further challenges simplistic assumptions of intrinsic superiority of one modality over the other.

Safety considerations remain a decisive factor in clinical decision-making. The consistently lower risk of systemic reactions associated with SLIT supports its preferential use in children, patients with comorbid asthma, and individuals with limited access to specialized medical supervision [8][17][25]. Nevertheless, SCIT retains an important role, particularly in patients

with severe symptoms, polysensitization, or previous suboptimal response to SLIT, provided that appropriate safety protocols are rigorously followed [6][18].

An additional dimension that warrants consideration is health economics. Emerging data suggest that, despite higher upfront costs, allergen immunotherapy may be cost-effective over the long term by reducing medication use, healthcare utilization, and productivity losses [26][27]. However, comparative cost-effectiveness analyses between SCIT and SLIT remain limited and highly context-dependent, varying according to national reimbursement policies, treatment persistence, and healthcare delivery models. This represents an important gap in the current evidence base.

Finally, the relative paucity of high-quality head-to-head randomized trials directly comparing SCIT and SLIT continues to constrain evidence-based recommendations. Until such data become available, treatment selection should be guided by a nuanced integration of clinical efficacy, safety, adherence likelihood, patient preferences, and healthcare system factors, rather than by efficacy estimates derived from indirect comparisons alone.

5. Conclusion

Both subcutaneous and sublingual allergen immunotherapy are effective, evidence-based interventions capable of modifying the natural course of allergic rhinitis and allergic asthma. Current data indicate that their overall clinical efficacy is broadly comparable, with differences that are generally modest and context-specific rather than universal. While SCIT may provide incremental benefits in selected patients or allergen profiles, these advantages must be weighed against its higher risk of systemic reactions and greater logistical burden.

SLIT, by contrast, offers a superior safety profile and greater convenience, which may enhance accessibility and suitability for long-term preventive treatment, particularly in pediatric populations and patients with comorbid asthma. However, challenges related to long-term adherence underscore the need for structured follow-up and patient education to maximize therapeutic benefit.

Taken together, the available evidence supports a personalized approach to allergen immunotherapy, in which route of administration is tailored to individual patient characteristics, risk profiles, lifestyle factors, and healthcare system constraints. Future research should

prioritize large-scale, well-designed head-to-head randomized trials, standardized outcome measures, and long-term real-world data, including health economic evaluations. Such efforts are essential to refine clinical guidelines and advance precision medicine strategies in the management of allergic disease.

Disclosures

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