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SUPPLEMENT ARTICLE

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Safety of allergen-specific immunotherapy in children

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Abstract

Allergic respiratory diseases, such as asthma and allergic rhinitis, are global health issues and have had an increasing prevalence in the last decades. Allergen-specific immunotherapy (AIT) is the only curative treatment for allergic rhinitis and asthma, as it has a disease-modifying effect. AIT is generally administered by two routes: subcutaneous (SCIT) and sublingual immunotherapy (SLIT). Local side effects are common, but usually well-tolerated and self-limited. However, systemic side effects are rare, and associated with uncontrolled asthma and bronchial obstruction, or related to errors in administration. Physicians should constantly assess potential risk factors for not only reporting systemic reactions and fatalities but also implementing other therapies to improve AIT safety. This paper highlights recent evidence on local and systemic reactions related to SCIT and SLIT in children.

KEYWORDS
adverse events, allergen immunotherapy (AIT), anaphylaxis, safety, subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT)

1 | BACKGROUND

Allergen-specific immunotherapy (AIT) is the only curative treatment of allergic rhinitis and allergic asthma as it has a disease-modifying effect. AIT protocol is generally based on the administration of increasing doses of the causal allergen (building-up phase), followed by a three-year maintenance schedule. AIT induces long-lasting effects after its suspension and affects the natural course of the IgE-mediated allergy, preventing new sensitizations and the disease progression.[1] In 1911, Leonhard Noon and John Freeman, the AIT pioneers, inoculated grass pollen extracts in patients with allergic rhinitis. In the last years, several studies have been published to highlight the safety and efficacy of AIT. The concept of personalized medicine as a diagnostic and therapeutic approach is currently

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revolutionizing allergology. AIT fulfills all aspects of precision medicine: identification of molecular mechanism, diagnostic tools for the mechanism, and treatment blocking the mechanism itself. Thus, Allergic Rhinitis and its Impact on Asthma (ARIA) and Global Initiative for Asthma (GINA) guidelines recommend AIT as an add-on treatment of moderate-severe allergic rhinitis (+/- conjunctivitis) and moderate, but controlled, asthma.[2,3] Contrarily, the role of AIT in the other allergic diseases such as atopic dermatitis, in unclear and insufficient evidence, exists to suggest efficacy.[4]

The absolute contraindications to AIT are malignancies, severe immunodeficiencies, chronic and invalidating disorders, and uncontrolled asthma.[2,3] Main relative contraindications include partially controlled asthma, use of β-blocker, cardiovascular diseases, psychiatric disorders, severe adverse reactions (ARs) to AIT, and poor adherence.

AIT can be administered by different routes, but sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) are the most studied and prescribed.

This paper aims to summarize current evidence on the safety of AIT, mainly focusing on pediatric studies.

1.1 | Sublingual allergen immunotherapy

SLIT is the route prescribed in 45% of European allergic patients.[5] SLIT is available in two different formulations: drops and tablets. SLIT is usually administered at home unless the first dose is recommended to be performed in the hospital setting with medical supervision. Local sides effects are very common, such as described in 80%–90% of patients treated with SLIT, and usually mild and generally self-resolving. The most frequent are oral itching, followed by mild swelling of the tongue, and gastrointestinal complaints (vomiting, abdominal pain, and diarrhea). Oral pruritus is common in subjects suffering from pollen food syndrome (PFS). According to a grading system, local side effects are classified into mild, moderate, or severe.

Systematic reviews and meta-analysis reported low rates of severe systemic reactions SLIT-correlated (about 1%). Systemic side effects, including urticaria, angioedema, and asthma exacerbation, are dose-dependent and may occur at any time. A randomized, double-blind, placebo-controlled study, with SLIT tablets, did not report any severe AR in 278 children with grass pollen–related rhinoconjunctivitis.[6] However, anecdotal cases of severe and life-treating ARs have been described. A *post hoc* analysis of 2 trials with 201 adolescents with allergic rhinitis to house-dust mites (HDM) reported 2 cases of severe ARs, but which did not require intramuscular epinephrine.[7] Recently, an alert on the suspected anaphylactic reactions in patients undergoing SLIT HDM tablets reported 15 cases in children.[8]

Regarding the long-term safety, a recent review reported 6 cases of eosinophilic esophagitis (EoE) occurred during SLIT, suggesting a potential role of SLIT in inducing or worsening the eosinophilic esophageal inflammation in a particular subset of allergic patients.[9]

Key Messages

- Allergen-specific immunotherapy (AIT) is an effective and safe immune-modulating treatment also in the pediatric age.
- Several clinical trials, surveillance surveys, and retrospective studies have been conducted to evaluate the AIT safety.
- AIT should be prescribed by physicians able to recognize potential risk factors and manage local and systemic reactions.

Therefore, SLIT is a generally safe treatment of respiratory allergic disorders. Fatal reactions due to SLIT have not been reported, even in cases of accidental massive dosage consumption.

1.2 | Subcutaneous allergen immunotherapy

Subcutaneous allergen immunotherapy (SCIT) is an effective treatment, administered by a doctor. Injections are performed in the upper arms and usually require a monthly administration during the maintenance period (3 years). Millions of SCIT injections are administered annually. The risk of fatal or near-fatal reaction is minimal but is not absent. Local ARs are common, involving 26%–82% of the patients and 0.7%–4% of injections.[10] Local ARs are characterized by hyperemia and swelling at the site of the injection. Large lesion size (>10 cm) or local granuloma formation due to aluminum hydroxide suggests the need for dose reducing or shifting to therapy with another adjuvant. Normally, local ARs are not related to a significant risk of developing systemic reactions.[11] In children, the prevalence of severe systemic reactions is fortunately low, <0.1% of injections. A US survey conducted among allergists showed that non-fatal systemic reactions occurred in 0.15% of injections and 0.7% of patients treated with SCIT.[12] Moreover, between 2008 and 2017 seven fatalities were observed in 54.4 million injection visits.[12] In contrast, an Italian survey reported an overall rate of systemic reactions of about 5% and 4 patients required epinephrine injection, but no fatalities were reported.[13]

In the last decades, several authors tried to identify the risk factors for severe and fatal systemic reactions due to SCIT, ensuring a significant safety profile. Uncontrolled asthma is the most crucial risk factor for developing severe systemic reactions. Acute asthma attacks occurred in 50% of severe reactions. Other relevant risk factors are the administration of SCIT during the pollen season pick, a history of a prior severe reaction, use of accelerated buildup regimens, and administration errors.[12] From 2008 to 2017, a US study reported that 15% of all systemic reactions occur after 31–60 min and only 0.5% after 60 min, suggesting the importance of an adequate post-administration observation in adults and children.[12] Although the guidelines do not recommend

TABLE 1 Feature and safety of allergy immunotherapy

	SLIT	SCIT
Setting administration	At home, except for the first dose	Hospital setting
Duration of observation	30 min after the first dose	30 min or more each time
Local side effects	+++	++
Systemic side effects	+*	++
Use in pediatric	+++	+

*HDM tablet–related anaphylaxis remains an uncommon event, but more studies are needed.

TABLE 2 Allergen immunotherapy: recommendations (modified from Cardinale et al.)

Continue therapy in:	Interrupt therapy in:
• Healthy children with a negative test. • Children with an adverse history of recent exposure to SARS-CoV-2 infection.	• Children with a positive history of recent contact. • Children with suggestive symptoms of COVID-19. • Asymptomatic patients with a positive test. • Children with an accentuation of respiratory symptoms related to possible infection, even if only an allergic component is suspected.

the epinephrine auto-injector prescription in patients receiving SCIT, some authors highlighted that this practice might increase SCIT safety.

The add-on use of the monoclonal anti-IgE antibody (omalizumab) has been associated with a reduction in systemic AR in adults and children with severe asthma. In a retrospective study in children with moderate-severe allergic asthma, Har et al. compared SCIT alone with SCIT +omalizumab and omalizumab alone. The authors reported a significantly low rate of ARs in patients treated with omalizumab.[14] Thus, combined therapy, such as omalizumab +AIT, might represent a promising approach to potentially avoid ARs in patients with severe asthma.

2 | CONCLUSION

SCIT and SLIT are the cornerstones of treating IgE-mediated allergic diseases but continue to be underutilized for fear of potential ARs. However, current evidence suggests that both formulations are reasonably safe when correctly administered (Table 1); namely, also during the coronavirus disease pandemic, AIT should be continued (Table 2).

CONFLICT OF INTERESTS

The authors declared they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Maria De Filippo: Conceptualization (equal); writing—review and editing (equal); validation (equal). **Martina Votto**: Writing—review and editing (equal); validation (equal). **Lucia Caminiti**: Visualization (equal). **Francesco Carelli:** Visualization (equal). **Giovanna De Castro:** Supervision (lead); writing—review and editing (equal). **Massimo Landi:** Supervision (lead); writing—review and editing (equal). **Roberta Olcese:** Visualization (equal). **Mario Vernich:** Visualization (equal). **Gian Luigi Marseglia**: Supervision (lead); writing—review and editing (equal). **Giorgio Ciprandi:** Conceptualization (equal); supervision (lead); writing—review and editing (equal). **Salvatore Barberi**: Supervision (lead); writing—review and editing (equal).

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REFERENCES

1. Licari A, Castagnoli R, Brambilla I, et al. Biomarkers of immunotherapy response in patients with allergic rhinitis. *Expert Rev Clin Immunol*. 2018;14:657-663.
2. Bousquet J, Pfaar O, Togias A, et al. 2019 ARIA Care pathways for allergen immunotherapy. *Allergy*. 2019;74:2087-2102
3. Global initiative for asthma. https://ginasthma.org/wp-content/uploads/2020/04/Main-pocket-guide_2020_04_03-final-wms.pdf. (Accessed July 21, 2020).
4. Caminiti L, Panasiti I, Landi M, et al. Allergen immunotherapy in atopic dermatitis: Light and shadow in children. *Pediatr Allergy Immunol*. 2020;31(26):46-48
5. Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for treating allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013;309:1278-1288
6. Wahn U, Tabar A, Kuna P, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2009;123:160-166
7. Matsuoka T, Bernstein DI, Masuyama K, et al. Pooled efficacy and safety data for house dust mite sublingual immunotherapy tablets in adolescents. *Pediatr Allergy Immunol*. 2017;28:661-667
8. Mösges R, Passali D, Di Gioacchino M. Worldwide surveys on anaphylaxis to sublingual immunotherapy with house dust mite tablets are urgently needed. *Clin Transl Allergy*. 2021;11:e12012
9. Votto M, De Filippo M, Caminiti L, et al. Eosinophilic gastrointestinal disorders and allergen immunotherapy: Lights and shadows. *Pediatr Allergy Immunol*. 2021;32(5):814-823
10. Giannetti A, Ricci G, Procaccianti M, et al. Safety, Efficacy, and Preventive Role of Subcutaneous and Sublingual Allergen Immunotherapy for the Treatment of Pediatric Asthma. *J Asthma Allergy*. 2020;13:575-587

11. Tophof MA, Hermanns A, Adelt T, et al. Side effects during subcutaneous immunotherapy in children with allergic diseases. *Pediatr Allergy Immunol*. 2018;29:267-274.
12. Bernstein DI, Epstein TEG. Safety of allergen immunotherapy in North America from 2008–2017: Lessons learned from the ACAAI/AAAAI National Surveillance Study of adverse reactions to allergen immunotherapy. *Allergy Asthma Proc*. 2020;41:108-111
13. Schiappoli M, Ridolo E, Senna G, et al. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. *Clin Exp Allergy*. 2009;39:1569-1574
14. Har D, Lee MJ. Systemic reaction rates with omalizumab, subcutaneous immunotherapy, and combination therapy in children with allergic asthma. *Allergy Asthma Proc*. 2019;40:35-40

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