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Review

Safety and adverse reactions in subcutaneous allergen immunotherapy: a review

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Abstract. *Background and aim:* Allergen immunotherapy (AIT) is the only treatment which acts on the causes of allergic diseases by modifying their natural history. In the eighties subcutaneous immunotherapy (SCIT) with high bio-logical power allergen extracts caused a number of severe systemic reactions and also fatalities in the UK and the US, resulting in its limitation and in the introduction of other routes of administration. The aim of this review is to make a reflection about still unclear and unidentified factors favoring severe reactions during SCIT. *Methods:* Approaches to prevent fatal or life-threatening reactions to AIT and the current consensus on how to prevent life-threatening reactions to AIT have been taken into account. *Results:* A decisive advance for SCIT safety was understanding that the major cause of mortality was injecting the allergen extract to patients with uncontrolled asthma. This awareness resulted in a significant decrease in fatalities, but not in their abolition, except for Hymenoptera venom immunotherapy. Among the factors favoring severe reactions there are the administration of a wrong extract or of allergen doses higher than listed, unintentional intravenous administration, and missed dose reduction after protracted interruption. Moreover, in the context of the improving of the safety, the role played in tolerance-promoting by adjuvants such as CpG oligodeoxynucleotides has to be taken into account, as well as the potential preventive effect performed by the monoclonal anti-IgE antibody omalizumab against the exacerbation of severe reactions during SCIT. *Conclusions:* The safety of SCIT is good, but the research to improve it further must continue. In particular, the pathophysiological mechanisms related to AIT for inhalants and for Hymenoptera venom should be studied, based on the evident diversity demonstrated by the complete absence of fatal reactions to Hymenoptera venom immunotherapy from its introduction in comparison with the history of serious and fatal offenses examined in this review. (www.actabiomedica.it)

Key words: Allergen immunotherapy, safety, systemic reactions, fatalities, uncontrolled asthma, Hymenoptera venom immunotherapy, pathophysiological mechanisms

Background

Allergic diseases can be treated with a series of symptomatic drugs, but only allergen immunotherapy (AIT) acts on the causes of allergy by modifying its natural history and thus ensuring a prolonged duration over time, which can be indefinite. From the earliest empirical studies conducted more than one hundred years ago, it was reported that the subcutaneous injection of the causative allergen could provoke adverse reactions, some of which even serious (1). For what concerns local reactions they include more frequently

redness, swelling and itching at the injection site and can be easily treated through the use of topical steroids, cooling and systemic antihistamines. In the context of systemic reactions to SCIT mild to severe reactions of the skin, gastrointestinal tract, airways or cardiovascular system may be experienced (2). When in the eighties, the progressive qualitative improvement of allergenic extracts made products of high biological power available, serious adverse reactions, and in particular fatal events reported in the UK and the US (3, 4), which resulted in limitations, and in some countries in leaving, of AIT (5). Since then, various interventions have been proposed to prevent severe and especially fatal reactions. A retrospective study performed on more than two thousands patients with a total number of 192.505 injections showed that 5.2% of patients (0.06% of injections) experienced systemic reactions (0 fatalities), mostly occurring within the 30 minutes after the injection (6). In 1978, a placebo-controlled trial paved the way for a new type of immunotherapy, venom immunotherapy (VIT), which aims to prevent serious, potentially fatal reactions to stings in patients allergic to Hymenoptera venom (7). Concerning safety, despite the fact that systemic reactions in both build-up and maintenance therapy may occur, no fatal reactions have ever been described (8).

Approaches to prevent fatal or life-threatening reactions to AIT

The first tactic to prevent serious adverse reactions consisted of identifying for each allergen to be administered the dosage capable of ensuring the effectiveness of AIT without causing systemic reactions (9]). The use of allergoids, based on the chemical modification of allergen extracts resulting both in the reduction of allergenicity and in the maintaining of immunogenicity, has evidence of higher safety (10). The problem of life-threatening reactions was a stimulus to the search for alternative routes of administration instead of injection: in this context, life-threatening reactions described in patients treated with dust mite allergens aside (11), the sublingual route having been shown to be safer and in particular since no fatal reactions have been reported (12). Significant progress for subcutaneous immunotherapy has come with the understanding that the leading cause of mortality was injecting the allergen extract to patients with uncontrolled asthma at the time of injection (13), whose avoidance resulted in a substantial decrease in the number of fatal reactions. Still, a slight increase has been observed in recent years, suggesting that physicians and healthcare professionals need to maintain a high level of attention (14).

The current consensus on how to prevent life-threatening reactions to AIT

In 2019, a survey promoted by the American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology found that despite the mean annual reported fatalities per year had declined, an unexplained slight increase in SCIT-related fatalities from 2015 to 2017 was detected (15). This implies that research on factors still unidentified favoring severe reactions should continue, but at the same time, the importance of factors long known and still present must not be overlooked. They include errors, sometimes serious, such as the administration of a wrong extract, the administration of allergen doses higher than scheduled, and the inadvertent intravenous administration; others are less dangerous, such as the failure to reduce the dose after prolonged interruption and the insufficient duration of the waiting period after injection (16). Actually, although the risk of fatal reactions has been greatly reduced, near-fatal reactions may occur, this requiring that doctors who practice AIT receive specialized training and are aware of the risk factors for anaphylaxis and current measures to draw any type of reaction (17). In a recent review, Dhamija et al. highlighted that together with the high efficacy, the potential risks of systemic reactions in each patient must be considered, the latest estimate corresponding to 1 systemic reaction per 1000 injection visits (0.1%) and 1/160,000 life-threatening anaphylactic reactions (18). The most recent ruling was made by a group of opinion leaders on AIT, who have reconsidered the entire history of the sublingual route and the advances that have led to its current role as the chief treatment

for allergic patients. Regarding safety, in addition to the known risk factors already described (13-15), the authors highlighted the role of adjuvants in enhancing immunogenicity when associated to improved safety. The clinical outcome has also been demonstrated with passive immunotherapy with monoclonal blocking IgG4 antibodies in a phase 2 study on cat allergy, and it can likely be used in trials on other allergens. Recently, immune tolerance-promoting properties of CpG oligodeoxynucleotides (CpG-ODN) placed this adjuvant in a prominent position as immune modulator in the treatment of allergic diseases. CpG-ODN dose at low concentrations, in fact, was found to be crucial in endorsing immune regulation and IL-10 producing B regulatory cells, while low doses of plasmacytoid dendritic cells induce an inflammatory response. These properties suggest a role for CpG-ODN as an adjuvant or immune modulator in AIT and deserve additional attention (19). Lastly, treatment with nucleic acid-based is in the initial evaluation phase by controlled trials, but no positive effects have yet been reported thus far (20).

Despite the significant reduction in fatalities caused by AIT, systemic and even life-threatening reactions still may occur. In 1995, in a group of 1056 children undergoing SCIT, a percentage of 3.7% had systemic reactions and house dust mites were the extracts most commonly responsible for systemic reactions, with a prevalence significantly higher than in those treated with pollen extracts (21). However, this observation was not confirmed by further studies. Recent studies did not find consistent differences among diverse allergens. In the first, 28 of 380 patients had a systemic reaction necessitating epinephrine administration, with a frequency of one per 1,047 injections. Twenty-six of the 28 reactions happened in the 30-minute observation period post AIT administration. Of patients with systemic reactions, 11 had asthma, and five had a history of likely food allergy (22). The other study included 37 patients, 78.7% being females, with a mean age of 29.8 years; 76.6% of them had allergic rhinitis, and 23.4% of them had both asthma and allergic rhinitis. The global rate of local adverse reactions and systemic adverse reactions were 19% and 2.1%, respectively (23). Other factors suspected of favoring systemic reactions are pediatric age (24) and female sex (25), but the literature is not yet sufficient to demonstrate their real importance.

The obstacle to reaching the effective dose of AIT caused by repeated reactions has been shown to be effectively overcome with biologics. In particular for the monoclonal anti-IgE antibody omalizumab, evidence of effectiveness in oral immunotherapy for food allergies have been reported (26, 27). Some studies on patients undergoing subcutaneous immunotherapy are available. Comparing patients of pediatric age receiving SCIT to those receiving a combination of SCIT and omalizumab, 19 severe reactions (1.2% of injections) occurred in 10 patients of the SCIT group, compared to the 3 severe reactions (0.4% of injections) of the omalizumab group, this difference being significant. The authors concluded that such a combination was safe and may serve as a bridge to administer SCIT safely (28). Further studies confirmed the success of such treatment in preventing systemic reactions to allergen immunotherapy in both children and adults (29, 30).

A particular problem is the COVID-19 pandemic, which has been shown to adversely affect many diseases. Pfaar et al. evaluated the effect of COVID-19 on allergen immunotherapy in Germany through a web□based retrospective survey by using an online platform including 26 standardized questions. The results showed that adherence to national and international position papers of allergen immunotherapy (31, 32) was maintained during the COVID□19 pandemic and, as confirmed by ther surveys, a good treatment tolerability has been observed (33).

Conclusion

The worldwide prevalence of respiratory allergy, in particular allergic rhinitis, is constantly increasing (34). The natural history of allergy includes its regression over time as well as relative stability or worsening, but it is not possible to predict which one will occur (35). The allergic symptoms may be treated, according to their kind or severity, with drugs including antihistamines, chromones, beta-2 adrenergic agonists, antileukotrienes, and corticosteroids. The efficacy of drug treatment on allergic rhinitis is acknowledged in consensus documents (36) but it is limited

to symptom control. Actually, the only treatment able to modify the natural history of allergy is AIT. Once the risk factors for severe systemic reactions to SCIT and, in particular, the triggers of fatal reactions were understood, the frequency of both underwent a significant reduction, particularly of fatalities, while systemic reactions remain not uncommon: this suggests that the search for risk factors still unidentified must go on. Examples include the discovery of the responsibility for undiagnosed mastocytosis in patients with history of anaphylaxis caused by insect venom who experienced severe reactions during SCIT (37) and the effective prevention obtained by regularly measuring the levels of tryptase, which is the marker of mast cell disorders (38). Due to its high frequency, especially in pediatric age (39), food allergy was also treated with immunotherapy. As for respiratory allergy, the subcutaneous routes were associated with systemic reactions, even severe ones, while the oral route reduced the rate of severe reactions, though they may still occur (40).

Regarding possible factors influencing the severity of the reactions to AIT, the striking difference between AIT in general, whose history has shown a risk of severe life-threatening reactions now reduced but not abolished, and the specific venom immunotherapy (VIT), that since its introduction has never caused fatal reactions (41), should be considered carefully. This could lead to the speculation that receiving VIT through the same cutaneous route that caused the allergic reaction to the insect sting could be partially tolerogenic. Only in-depth studies aimed at investigating the different types of allergen specific immunotherapies through their respective pathophysiological mechanisms could suggest the credibility of this hypothesis.

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References

1. Frati F, Incorvaia C, Lombardi C, et al. Allergen immunotherapy: 100 years, but it does not look like. Eur Ann Allergy Clin Immunol. 2012 Jun;44(3):99-106.
2. Pfaar O, Bachert C, Bufe A, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014;23(8):282-319. doi: 10.1007/s40629-014-0032-2
3. Bem JL, Breckenridge AM, Mann RD, et al. Review of yellow cards (1986): report to the Committee on the Safety of Medicines. Br J Clin Pharmacol. 1988 Dec;26(6):679-89. doi: 10.1111/j.1365-2125.1988.tb05305.x
4. Lockey RF, Benedict LM, Turkeltaub PC, et al. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol. 1987 Apr;79(4):660-77. doi: 10.1016/s0091-6749(87)80164-1
5. Frew AJ. Injection immunotherapy. British Society for Allergy and Clinical Immunology Working Party. BMJ. 1993 Oct 9;307(6909):919-23. doi: 10.1136/bmj.307.6909.919.
6. Malling HJ. Minimising the risks of allergen-specific injection immunotherapy. Drug Saf. 2000 Oct;23(4):323-32. doi: 10.2165/00002018-200023040-00005
7. Hunt KJ, Valentine MD, Sobotka AK, et al. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med. 1978 Jul 27;299(4):157-61. doi: 10.1056/NEJM197807272990401
8. Kosnik M, Korosec P. Venom immunotherapy: clinical efficacy, safety and contraindications. Expert Rev Clin Immunol. 2015;11(8):877-84. doi:10.1586/1744666X.2015.1052409
9. Incorvaia C, Frati F, Puccinelli P, et al. Dose dependence of efficacy and safety of subcutaneous immunotherapy. Monaldi Arch Chest Dis. 2006 Mar;65(1):41-3. doi: 10.4081/monaldi.2006.585

10. Carnes J, Gallego MT, Moya R, et al. Allergoids for Allergy Treatment. Recent Pat Inflamm Allergy Drug Discov. 2018;12(2):110-119. doi: 10.2174/1872213X12666180221155908
11. 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 Mar;11(1):e12012. doi: 10.1002/clt2.12012
12. Passalacqua G, Canonica GW. Allergen-specific sublingual immunotherapy for respiratory allergy. BioDrugs. 2001; 15(8):509-19. doi: 10.2165/00063030-200115080-00003
13. Epstein TG, Liss GM, Murphy-Berendts K, et al. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008-2013). Ann Allergy Asthma Immunol. 2016 Apr;116(4):354-359.e2. doi: 10.1016/j.anai.2016.02.001
14. Epstein TG, Murphy-Berendts K, Liss GM, et al. Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): postinjection monitoring and severe asthma. Ann Allergy Asthma Immunol. 2021 Jul;127(1):64-69.e1. doi: 10.1016/j.anai.2021.03.011
15. Epstein TG, Liss GM, Berendts KM, et al. AAAAI/ACAAI Subcutaneous Immunotherapy Surveillance Study (2013-2017): Fatalities, Infections, Delayed Reactions, and Use of Epinephrine Autoinjectors. J Allergy Clin Immunol Pract. 2019 Jul-Aug;7(6):1996-2003.e1. doi: 10.1016/j.jaip.2019.01.058
16. Borchers AT, Keen CL, Gershwin ME. Fatalities following allergen immunotherapy. Clin Rev Allergy Immunol. 2004 Oct;27(2):147-58. doi: 10.1385/CRIAI:27:2:147
17. Sánchez-Borges M, Bernstein DI, Calabria C. Subcutaneous Immunotherapy Safety: Incidence per Surveys and Risk Factors. Immunol Allergy Clin North Am. 2020 Feb;40(1): 25-39. doi: 10.1016/j.iac.2019.09.001
18. Dhamija Y, Epstein TEG, Bernstein DI. Systemic Allergic Reactions and Anaphylaxis Associated with Allergen Immunotherapy. Immunol Allergy Clin North Am. 2022 Feb;42(1):105-119. doi: 10.1016/j.iac.2021.09.012
19. Montamat G, Leonard C, Poli A, et al. CpG Adjuvant in Allergen-Specific Immunotherapy: Finding the Sweet Spot for the Induction of Immune Tolerance. Front Immunol. 2021 Feb 23;12:590054. doi: 10.3389/fimmu.2021.590054
20. Pfaar O, Bousquet J, Durham SR, et al. One hundred and ten years of Allergen Immunotherapy: A journey from empiric observation to evidence. Allergy. 2022 Feb;77(2): 454-468. doi: 10.1111/all.15023
21. Businco L, Zannino L, Cantani A, et al. Systemic reactions to specific immunotherapy in children with respiratory allergy: a prospective study. Pediatr Allergy Immunol. 1995 Feb;6(1):44-7. doi: 10.1111/j.1399-3038.1995.tb00257.x
22. Robertson K, Montazeri N, Shelke U, et al. A single centre retrospective study of systemic reactions to subcutaneous immunotherapy. Allergy Asthma Clin Immunol. 2020 Nov 2;16(1):93. doi: 10.1186/s13223-020-00491-5
23. Sánchez-VillalobosJY,Caballero-LópezC,López-GarcíaAI, et al. Eficacia y seguridad de la inmunoterapia subcutánea para alérgenos inhalables en pacientes con alergia respiratoria a un año de tratamiento [The effectiveness and safety of subcutaneous immunotherapy for inhalable allergens in patients with respiratory allergies after one year of treatment]. Rev Alerg Mex. 2020 Oct-Dec;67(4):309-315. Spanish. doi: 10.29262/ram.v67i4.758
24. Lim CE, Sison CP, Ponda P. Comparison of Pediatric and Adult Systemic Reactions to Subcutaneous Immunotherapy. J Allergy Clin Immunol Pract. 2017 Sep-Oct;5(5):1241-1247.e2. doi: 10.1016/j.jaip.2017.01.014
25. Sani S, Gupta R, Fonacier L, et al. Risk stratification of systemic reactions to subcutaneous immunotherapy: A retrospective study. Allergy Asthma Proc. 2019 Sep 1;40(5): 338-342. doi: 10.2500/aap.2019.40.4238
26. Ayats-Vidal R, Riera-Rubió S, Valdesoiro-Navarrete L, et al. Long-term outcome of omalizumab-assisted desensitisation to cow's milk and eggs in patients refractory to conventional oral immunotherapy: real-life study. Allergol Immunopathol (Madr). 2022 May 1;50(3):1-7. doi: 10.15586/aei.v50i3.537
27. Har D, Lee MJ. Systemic reaction rates with omalizumab, subcutaneous immunotherapy, and combination therapy in children with allergic asthma. Allergy Asthma Proc. 2019 Jan 1;40(1):35-40. doi: 10.2500/aap.2019.40.4173
28. Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol. 2010 Feb;125(2):383-9. doi: 10.1016/j.jaci.2009.11.022
29. Bernaola M, Hamadi SA, Lynch DM, et al. Successful administration of omalizumab by desensitization protocol following systemic reactions in 12 patients. J Allergy Clin Immunol Pract. 2021 Jun;9(6):2505-2508.e1. doi: 10.1016/j.jaip.2020.11.066
30. Valdesoiro-Navarrete L, León ME, Rodríguez M, et al. Combination therapy of specific aeroallergens immunotherapy and omalizumab, in children with severe asthma. Allergol Immunopathol (Madr). 2022 Mar 1;50(2):1-6. doi: 10.15586/aei.v50i2.469
31. Klimek L, Jutel M, Akdis C, et al; ARIA-MASK Study Group. Handling of allergen immunotherapy in the COVID-19 pandemic: An ARIA-EAACI statement. Allergy. 2020 Jul;75(7):1546-1554. doi: 10.1111/all.14336
32. Pfaar O, Hamelmann E, Klimek Let al. Allergen immunotherapy during the COVID-19 pandemic-A survey of the German Society for Allergy and Clinical Immunology. Clin Transl Allergy. 2022 Mar;12(3):e12134. doi: 10.1002/clt2.12134
33. Masieri S, Bachert C, Ojeda P, et al. Study Group on AIT & Vaccinations. Allergen Immunotherapy management during vaccinations: An international survey. World Allergy Organ J. 2021 Nov;14(11):100601. doi: 10.1016/j.waojou.2021.100601
34. Savouré M, Bousquet J, Jaakkola JJK, et al. Worldwide prevalence of rhinitis in adults: A review of

definitions and temporal evolution. Clin Transl Allergy. 2022 Mar;12(3):e12130. doi: 10.1002/clt2.12130
35. Lombardi C, Passalacqua G, Gargioni S, et al. The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years. Respir Med. 2001 Jan;95(1):9-12. doi: 10.1053/rmed.2000.0945
36. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. Int Forum Allergy Rhinol. 2018 Feb;8(2):108-352. doi: 10.1002/alr.22073
37. González-de-Olano D, Alvarez-Twose I, Vega A, et al. Venom immunotherapy in patients with mastocytosis and hymenoptera venom anaphylaxis. Immunotherapy. 2011 May;3(5):637-51. doi: 10.2217/imt.11.44
38. Bonadonna P, Zanotti R, Müller U. Mastocytosis and insect venom allergy. Curr Opin Allergy Clin Immunol. 2010 Aug;10(4):347-53. doi: 10.1097/ACI.0b013e32833b280c
39. Sampath V, Abrams EM, Adlou B, et al. Food allergy across the globe. J Allergy Clin Immunol. 2021 Dec;148(6):1347-1364. doi: 10.1016/j.jaci.2021.10.018
40. Costa C, Coimbra A, Vítor A, et al. Food allergy-From food avoidance to active treatment. Scand J Immunol. 2020 Jan;91(1):e12824. doi: 10.1111/sji.12824
41. Incorvaia C, Ridolo E, Mauro M, et al. Venom Immunotherapy and Aeroallergen Immunotherapy: How Do Their Outcomes Differ? Front Allergy. 2022 Feb 16;3:854080. doi: 10.3389/falgy.2022.854080.

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