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REVIEW

Allergen immunotherapy for respiratory allergy: to what extent can the risk of systemic reactions be reduced?

Cristoforo Incorvaia[a], Francesco Pucciarini[b], Eleni Makri[a], Bruna L Gritti[c] and Erminia Ridolo[b]

[a]Cardiac/Pulmonary Rehabilitation, ASST Pini-CTO, Milan, Italy; [b]Allergy and Clinical Immunology, Medicine and Surgery Department, University of Parma, Parma, Italy; [c]School of Human Sciences, Gaetana Agnesi, Milan, Italy

ABSTRACT

Introduction: Allergen immunotherapy is an effective treatment for respiratory allergy, but the administration to patients of extracts of the causative allergen may elicit systemic reactions, which include, particularly with subcutaneous immunotherapy (SCIT), anaphylaxis. In the past, the occurrence (tough rare) of fatal reactions has represented a serious problem that has limited the prescription of SCIT.

Areas covered: The authors analyzed in this review the safety data of SCIT, especially concerning the years following the identification of uncontrolled asthma at the moment of allergen injection as the major risk of life-threatening reactions and fatalities. The safety of SLIT, which is far better than SCIT, was analyzed and its specific risk factors for systemic reactions were highlighted.

Expert opinion: Presently, the safety profile of SCIT and SLIT is satisfactory, provided the treatment is administered by physicians experienced in this treatment, who are aware of the known risk factors for severe reactions and who implement all measures to avoid them. For SLIT, which is self-administered by the patient, receiving the first dose under medical control is recommended.

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1. Introduction

Already at the time of the invention of allergen immunotherapy (AIT), then called desensitization, researcher noted that the injection of allergenic extracts reduced allergic symptoms but exposed patients to acute hypersensitivity reactions. Even Dunbar, one of the inventors, was directly affected by such reaction, developing severe anaphylaxis after grass pollen injection [1]. The most alarming data for AIT safety were reported in the 1980 s, when the introduction of AIT products with high biological potency was associated with a series of fatal reactions in the UK, inducing to enact restrictive safety rules which resulted in a significant decline of AIT prescription [2]. In US, where traditional non-standardized allergen extracts titrated in protein nitrogen units (PNU), to be diluted by the physician before the injection, were used, the possible causes of fatalities were suspected to be errors of administration, injection of newly prepared extracts, and presence of symptoms at the time of the injection [3]. A web-based surveillance program started in North America in 2008 among members of the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) showed that uncontrolled asthma was the major risk factor for fatal and near-fatal systemic reactions (SRs) and that avoiding subcutaneous immunotherapy (SCIT) in patients with uncontrolled asthma resulted in a significantly lower rate of SRs [4]. There are no studies that have identified the mechanisms underlying the higher risk of SRs in patients with asthma or possible risk predictive tests, the only one proposed in consensus documents being the peak expiratory flow (PEF) [5]. In the most recent survey by the same authors, which analyzed the data from 54.4 million injection visits, an unexplained slight increase in SCIT-related fatalities (5 in total) in the 2015–2017 period was observed [6]. On the other hand, it cannot be excluded that a not negligible number of systemic reactions and even fatalities, that happen after the patient has left the medical clinic, is not reported. This highlights the importance of keeping the utmost attention on the risk for SRs to SCIT. On the other hand, severe reactions to SCIT were a major driver for the development of sublingual immunotherapy (SLIT) in 1986 [7].In fact, after 20 years of SLIT use, a systematic review of its safety found no fatalities and a low incidence of SRs, while local reactions in the site of contact with the administered allergen, especially the oral cavity and, less frequently, the gastrointestinal mucosa, were quite common [8]. The present review is aimed at assessing the current knowledge on safety profile of AIT for respiratory allergy with the two different routes.

2. Analysis of current data on SCIT safety

In the last of their three meta-analyses on SCIT in allergic asthma in 2010, which included 85 trials, Abramson et al. estimated that every 16 SCIT treated patients, one would be expected to develop a local adverse reaction, and every 9 SCIT treated patients, one would be expected to develop SRs of any severity, concluding that with this treatment the possibility of systemic adverse effects – also consisting of anaphylaxis – has to be considered [9]. Since then, several studies analyzed such issue. In order to focus the current data on safety, we have

CONTACT Cristoforo Incorvaia cristoforo.incorvaia@gmail.com Cardiac/Pulmonary Rehabilitation, ASST Pini-CTO, Via Bignami 1, Milan, Italy

Article highlights

- Allergen immunotherapy is the only treatment acting on the causes of allergy, but the administration of the culprit allergen may elicit systemic reactions, which include, particularly if the subcutaneous route is used, anaphylaxis.
- The most worrying safety aspect of SCIT has been the fatalities associated with severe anaphylaxis, which mostly concerned patients with uncontrolled asthma, the frequency of which significantly declined by avoiding the allergen administration in patient with such condition.
- Other risk factors are errors in administering SCIT, a history of prior systemic reactions to SCIT, and receiving the injection during the exposure to the specific allergen, as occurs for the pollen peak period.
- Sublingual immunotherapy is much safer, being mostly concerned by local reactions in the site of administration, while anaphylaxis is very rare. However, the guidelines recommend that the first dose of the allergen extract is administered under medical control.
- Based on the available data, the safety profile of allergen immunotherapy is suitable, provided the patient is monitored by expert physicians, who know the risk factors for severe reactions and are able to apply all procedures to avoid them.

This box summarizes key points contained in the article.

reviewed the articles published in the past 3 years which included a sufficiently large number of patients. Their results according to the allergens and the different products used, the treatment schedules, and the suggested risk factors for SRs are shown in Table 1. The rate of SRs ranged from 0.364% [10] to 15.62% [11], mostly mild to moderate. No fatalities were reported. Recent systematic reviews and meta-analyses of controlled trials and observational studies are available. Rice et al. analyzed 17 trials addressing pediatric asthma. Various SRs, such as cough, dyspnea, asthma, hives, rhinoconjunctivitis, eczema, and unspecified reactions, concerned 6% to 17% of patients (0.7 to 1.1 events per patient in the treatment arms vs. 0% to 3% or 0.5 to 0.8 events per patient in the control arms). Anaphylaxis was reported in 2% of patients, with no such event in controls. One fatal reaction occurred in a 17-year -old girl with moderate persistent asthma who had interrupted a previous SCIT course because of a skin reaction; 12 hours after the first dose of a new regimen she presented abdominal pain, vomiting, and diarrhea, and 2 days later developed acute respiratory failure with hypoxic coma, which required intubation and mechanical ventilation, followed by shock and multiorgan failure causing death [12]. A meta-analysis assessed the risk of SRs comparing the conventional and cluster schedules (shorter but based on higher allergen doses than those administered with conventional programs). No differences between cluster and conventional schedules were found when analyzing SRs by the number of patients, delayed SRs, and grade 2 SRs [13].

An approach to reduce the risk of SRs known since the 1980s is based on the use of allergoids, instead of native allergens. Allergoids are obtained by chemically modifying allergens to lessen allergenicity while maintaining immunogenicity. To this aim, several agents may be used, such as glutaraldehyde or formaldehyde (which modifies allergens in high molecular weight molecules by allergen polymerization), L-tyrosine, monophosphoryl lipid A, aluminum hydroxide, and depigmentation (which reduces enzymatic activity) [19]. The most recent meta-analysis had as primary endpoint to compare the efficacy of SCIT with depigmented-polymerized allergen extracts resulting from 8 controlled trials (6 with grass pollen and 2 with dust mites). The safety data showed no significant difference between actively and placebo-treated patients concerning the numbers of patients developing adverse events, but as to the number of SRs developed after the administration of active treatment, the odds ratio attained significance ($p < 0.05$) [20]. A very recent narrative review discussed the importance of the different risk factors for SRs to SCIT in addition to the well-known presence of uncontrolled asthma. A history of prior SRs to SCIT seems to enhance the risk of anaphylactic reactions, as indicated by the data from US that 36% of severe anaphylactic events were preceded by previous SRs [21]. Also in the large European survey on systemic reactions to AIT in real life, which included 4216 patients of any age, a previous episode of anaphylaxis significantly increased the risk for anaphylaxis to SCIT ($P = 0.01$) [22]. In regards to SCIT with pollen extracts, administration during the peak pollen season was reported to be related to anaphylactic reactions; the reduction of allergen's doses in such period in patients with strong responses to skin tests resulted in a decrease of all grade SRs [21]. However, this finding was not confirmed for SCIT with mountain cedar extracts [23]. Other risk factors with conflicting observations are accelerated schedules [22,24,25], specified allergens [10,26,27], female gender [26,27], and concomitant food allergy or drug allergy [27]. Indeed, an obvious risk of SRs is linked to physician's error in administering SCIT, including mistaken patients identification (it is recommended that two different health workers identify the patient and verify the allergenic extract to be administered) [21]. As far as the prevention of SRs to AIT is concerned, the use of antihistamines before allergen injection is acknowledged for venom immunotherapy in the EAACI guidelines [28], while for respiratory allergy only an old study reported the ability of cetirizine to prevent SRs to SCIT with inhalant allergens, but there have been no confirmations of such effect from other studies [29]. Otherwise, solid data are available on the ability to decrease the incidence of systemic reactions to AIT with the anti-IgE antibody omalizumab, as demonstrated by four randomized, placebo-controlled trials in patients with allergic rhinitis or asthma [30].

3. Analysis of current data on SLIT safety

As stated above, SLIT until now was not been concerned by the serious problem of fatal reactions. A systematic review of 25 studies performed in 2005 demonstrated that local reactions in the site of contact with the allergen extracts are quite common, while systemic reactions are usually rare, and mostly of mild-to-moderate grade. However, three years later a case of anaphylactic shock was reported as a consequence of the intake of a very high dose of the allergen SLIT product. In fact, the patient, at that time in his third year of SLIT treatment, interrupted the therapy for 3 weeks and on the resumption of SLIT resolved to take all the previously missed doses [31]. Indeed, such a huge mistake does not appear to have been repeated every again. However, a relationship between the higher doses administered with latest

Table 1. Studies on safety of SCIT in the past three years.

Authors, year (ref)	Population	Type of allergen	Results
Morais-Almeda et al, [14]	100 pediatric patients	Dust mites, pollens	Two SRs to an ultrarush schedules with modified allergens, both immediate and mild.
Nacaroglu et al., [15]	319 pediatric patients	Mixed	SRs in 4.7% of patients. Increased risk with mites or multiple allergens
Molina-Saenz et al., [11]	733 adult patients	Dust mites	45 SRs to tyrosine-absorbed allergens: 12 were grade 1 (30%), 27 grade 2 (67.5 %) and 1 grade 3 (2.5%
Liu et al., [16]	265 children and 134 adolescents with asthma	Mixed	SRs in 15.62% of patients (18.49% children and 10.98% adolescents). There were 54.57% SRs of grade 1; 42.37% SRs of grade 2; 3.05% SRs of grade 3.
Rodriguez Del Rio et al., [17]	1563 pediatric patients	Mixed	SRs in 1.53% of patients. Respiratory symptoms in 55.7%) and skin symptoms in 37.9%. Anaphylaxis in 10.3%, adrenaline administered in 2 cases.
Calderon et al., [22]	4216 patients (adults and children)	Mixed	109 SRs, 90 patients had at least 1 SR. The most frequently reported symptoms were urticaria, rhinitis, dyspnea and cough. Independent risk factors for SRs were: the use of natural extracts, the absence of symptomatic allergy, asthma diagnosis sensitization to animal dander or pollen and cluster regimens (vs rush).
Albuhairi et al., [10]	246 pediatric patients, in 118 of whom (group 2) the updosing was adjusted according to pollen season	Grass pollen and weed pollen	SRs in 0.429% in group 1 and 0.364% in group 2. No severe SRs
Di Bona et al., [26]	2200 adult patients	Mixed	SRs in 29 patients with 42 anaphylaxis, two severe. Adrenalin administered in one case; 1.8% pf patients discontinued SCIT because of SRs. Parietaria pollen was allergen most frequently associated to SRs. Female gender, number of allergen extracts administered (2 vs. 1) and year of SCIT inception (1996–2018 vs. 1988–1995) were independently associated to SRs.
Kopp et al., [24]	87 adult patients	Grass pollen allergoid	Two schedule based on 3 (group 1) and 7 (group 2) injections, respectively, were used. SRs in 5.8% of patients, more being reported in group 1. All SRs reactions were classified as grade 1 or grade 2.
Alba et. Al, [18]	130 adult and children	Multiallergen	SRs (all mild) in 3.1% of patients

generation SLIT tablets and the risk of systemic reactions was reported in 2009: two cases of anaphylaxis were reported, concerning patients undergoing SLIT with one-grass pollen tablets because of previous severe reactions to SCIT. This specific tablet product starts directly with the maintenance dose, with no buildup, and actually anaphylaxis occurred after the first dose administration [32]. This observation resulted in the current recommendation to avoid shifting patients with severe reactions to SCIT to SLIT with no buildup and, in any patient, to administer the first dose under medical control in hospital [33]. In the large trial performed to achieve the registration of the one-grass pollen tablets by regulatory agencies (EMA in Europe and FDA in US), in which patients with previous reactions to AIT were not admitted and any procedure was strictly controlled, no safety concerns were raised [34]. Similarly, in the large trials on efficacy and safety of the 5-grass pollen SLIT tablets no serious side effects were reported in adults [35] and children [36]. Further large trials involved dust mite tablets. In the first product to be studied the allergen content was measured in standardized quality (SQ) and administered with no buildup to 604 patients. They were randomized to receive three dosages (1, 3, and 6 SQ) or placebo, and adverse events were more frequent in patients receiving 3 and 6 SQ-HDM. Globally, 33 reactions were classified as severe, the higher rate concerning the 3 SQ-HDM dosage. Fifteen patients (2%) withdrew the trial because of a reaction, with highest rates concerning 3 and 6 SQ-HDM [37]. The same product was investigated in a trial on 1482 patients, using the International Council on Harmonization definition to define a serious adverse event. No serious reaction was reported, while 1 nonserious allergic reaction occurred at first administration and was treated with epinephrine [38]. The other dust tablet product was standardized in index of reactivity (IR), 509 patients being randomized to receive 300 or 500 IR, or placebo. Adverse reactions were generally mild to moderate, but patients treated with 500IR and 300IR stopped the treatment because of reactions in 11.8% and 10% of cases, respectively. The reactions consisted mainly of pharyngeal and mouth edema, dyspepsia, and nausea [39]. In the trial conducted in Japan on 968 patients randomized to receive 300 or 500 IR, or placebo, active treatment was associated with more frequent local allergic reactions than in placebo treatment, withdrawal being higher in the 500 IR group. Serious reactions were reported in 16 patients, but none of them were treatment related [40]. Nolte et al. analyzed the safety data from 29 trials (13 on one-grass pollen, 5 of ragweed pollen, and 11 on dust mite tablets). Tough no systemic reaction was classified as severe, epinephrine was used 10 times with one-grass, 7 times with ragweed, and 8 times with dust mite SLIT tablets. Epinephrine was also administered in 9 placebo-treated patients. The authors concluded that epinephrine use for adverse events to SLIT tablets, mostly occurring within the first week of treatment and not being severe, is uncommon [41]. Elliot et al. performed an 'umbrella review' including 23 systematic reviews on the efficacy and safety of SCIT and SLIT [42]. Focusing on the latter, only 6 of 15 trials reported severe reactions, as shown in Table 2. Globally, 18 reactions were classified as severe, but in 8 of them the classification criterion was based only on the use of adrenaline, which (as seen above) is not necessarily related to severity. As for SCIT, allergoids are available, obtained by carbamylation, resulting in monomeric molecules. A recent pharmacovigilance study on grass pollen and

Table 2. Meta-analyses on SLIT reporting severe adverse reactions.

Authors, year (ref)	No. of trials included	Type of allergen	Results
Calderon et al, [44]	31	Dust mites	One SR with severe asthma.
Meadows et al., [45]	17	Various pollens	Anaphylactic reactions in 4 patients
Manzotti et al. [46]	4	Grass pollen	Anaphylactic reactions in 2 patients
Tao et al., [47]	16	Various	Three SRs with severe asthma
Canadian agency for drugs and technologies in health [48]	8	Grass pollen	One SR requiring epinephrine after the first administration
Di Bona et al., [49]	13	Grass pollen	7 reactions requiring epinephrine

dust mites monomeric allergoids found that, out of about 15,000,000 tablets globally administered, there were 25 spontaneous reports of ADRs, corresponding to 0.0004% of all doses [43].

4. Conclusion

The fatal reactions reported in the 1980s characterized the most difficult challenge for AIT with inhalant allergens, which led to a rethinking of the risk-benefit ratio of this treatment and, particularly in the UK, a decline in its prescription. The identification of not controlled asthma at the time of the injection of the allergen as a major risk for severe, life-threatening reactions was a milestone; postponing the injection only after asthma under control resulted in a significant decrease in severe reactions and fatalities. Another consequence of the safety issue was the search for routes of administration other than the injection route. The sublingual route was found to be more effective than other tested routes such as the oral and nasal immunotherapy. A number of trials comparing the injective and sublingual route made apparent that SLIT was safer than SCIT, being characterized by frequent local reactions in the site of contact with the administered allergen but no anaphylactic reactions. The introduction of standardized high allergen dose tablets in 2006 [50] changed the scenario because these products were concerned by the first reports of anaphylaxis, but the rate of such reactions is globally very low. If we summarize the current basic concepts to prevent serious reactions to SCIT and SLIT, the most important remains to avoid the administration of the allergen extract to patients with uncontrolled asthma and, for SLIT taking the first dose under medical supervision, especially if the product schedule does not include a buildup [51].

5. Expert opinion

Adverse drug events cause substantial morbidity and mortality, with different modalities depending on the mechanism of action of the various drugs, the administered dose being often a factor that increases the risk of reaction [52]. This is clearly apparent for AIT, which is based on the administration to patients of extracts of the causative allergen. Actually, the AIT safety issue came into view when high biological potency allergen extracts were introduced in the 1980 s [2]. The dose dependence of systemic reactions was clearly shown in a controlled dose-response study on 75 patients with dust mite-induced asthma, who received 0.7, 7, or 21 micrograms (mcg) of the major mite allergen Der p 1 during 2 years of SCIT. Out of a global number of 2104 injections, the rate systemic reactions were 0.56% for 0.7, 3.30% for 7, and 7.10% for 21mcg, this difference being highly significant ($p < 0.0001$) [53]. The SCIT safety issue has been greatly improved, in particular for fatal reactions, when the high risk associated with allergen injections in patients with uncontrolled asthma has been recognized and therefore avoided [4,6]. However, the contraindication to SCIT in patients with severe asthma prevents a disease-modifying therapy in patients who would most deserve it. The introduction of biologics, which act by blocking crucial targets, including IgE synthesis or type 2 cytokines production, has been a great advance in personalized medicine for patients with asthma [54]. In particular, achieving control of allergic asthma by treatment with the anti-IgE monoclonal antibody omalizumab could allow to recuperate patients otherwise excluded from SCIT [55]. The sublingual route, as shown by several trials systematically reviewed in 2005 [7], was only marginally concerned by anaphylactic reactions, which however were subsequently reported in case of intake of very high allergen doses [31] or as an effect of the first dose of products with schedule without buildup in patients with previous systemic reactions to SCIT [32]. Today there is general agreement on the substantial safety of AIT in its two routes of administration, with a risk of anaphylactic reactions quite low for SCIT and very low for SLIT, provided the treatment is administered by highly qualified physicians able to avoid the errors we have reported above [21,27] and experienced in managing treatment-related reactions [56].

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Cohen S, Frankland AW, Dworetzky M. Noon and Freeman on prophylactic inoculation against hay fever. J Allergy Clin Immunol. 2003;111(5):1142–1150.
2. Committee on safety in medicine. CSM update: desensitizing vaccines. BMJ. 1986;293:948.
3. Lockey RF, Benedict LM, Turkeltaub PC, et al. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol. 1987;79:660–677.
4. 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;116(4):354–359.
5. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1–55.
6. 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;7(6):1996–2003.
7. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy. 1986;16 (5):483–491.
8. Gidaro GB, Marcucci F, Sensi L, et al. The safety of sublingual-swallow immunotherapy: an analysis of published studies. Clin Exp Allergy. 2005;35(5):565–571.
9. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev. 2010 Aug 4;(8): CD001186.
10. Albuhairi S, Sare T, Lakin P, et al. Systemic reactions in pediatric patients receiving standardized allergen subcutaneous immunotherapy with and without seasonal dose adjustment. J Allergy Clin Immunol Pract. 2018;6(5):1711–1716.
11. Molina-Sáenz MM, Villa-Arango AM, Cardona-Villa R. Safety of subcutaneous immunotherapy with tyrosine-adsorbed house dust mite extracts in patients with allergic disease. Rev Alerg Mex. 2017;64(1):52–65.
12. Rice JL, Diette GB, Suarez-Cuervo C, et al. Allergen-specific immunotherapy in the treatment of pediatric asthma: a systematic review. Pediatrics. 2018;141:5.
13. Jiang Z, Xiao H, Zhang H, et al. Comparison of adverse events between cluster and conventional immunotherapy for allergic rhinitis patients with or without asthma: A systematic review and meta-analysis. Am J Otolaryngol. 2019;40(6):102269.
14. Morais-Almeida M, Arêde C, Sampaio G, et al. Ultrarush schedule of subcutaneous immunotherapy with modified allergen extracts is safe in paediatric age. Asia Pac Allergy. 2016;6(1):35–42.
15. Nacaroglu HT, Erdem SB, Sumer O, et al. Local and systemic reactions to subcutaneous allergen immunotherapy: ten years' experience in a pediatric clinic. Ann Allergy Asthma Immunol. 2016;116 (4):349–353.
16. Liu JL, Ning WX, Li SX, et al. The safety profile of subcutaneous allergen immunotherapy in children with asthma in Hangzhou, East China. Allergol Immunopathol (Madr). 2017;45(6):541–548.
17. Rodríguez Del Río P, Vidal C, Just J, et al. The European survey on adverse systemic reactions in allergen immunotherapy (EASSI): A paediatric assessment. Pediatr Allergy Immunol. 2017;28(1):60–70.
18. Alba P, Moreno V, Arias-Irigoyen J, et al. Safety evaluation of a multiallergen immunotherapy treatment in polyallergic patients. APOLO observational study. Immunotherapy. 2020 Epub ahead of print
19. Bonertz A, Roberts G, Slate JE, et al. Allergen manufacturing and quality aspects for allergen immunotherapy in Europe and the United States: an analysis from the EAACI AIT guidelines project. Allergy. 2018;73(4):816–826.
20. Mösges R, Valero Santiago A, Allekotte S, et al. Subcutaneous immunotherapy with depigmented-polymerized allergen extracts: a systematic review and meta-analysis. Clin Transl Allergy. 2019;9:29.
21. Sánchez-Borges M, Bernstein DI, Calabria C. Subcutaneous immunotherapy safety: incidence per surveys and risk factors. Immunol Allergy Clin North Am. 2020;40(1):25–39.
22. Calderón MA, Vidal C, Rodríguez Del Río P, et al. EASSI Doctors' group. European survey on adverse systemic reactions in allergen immunotherapy (EASSI): a real-life clinical assessment. Allergy. 2017;72(3):462–472.
23. Wong PH, Quinn JM, Gomez RA, et al. Systemic reactions to immunotherapy during mountain cedar season: implications for seasonal dose adjustment. J Allergy Clin Immunol Pract. 2017;5(5):1438–1439.
24. Kopp MV, Bovermann X, Klimek L. Accelerated dose escalation with three Injections of an Aluminum Hydroxide-adsorbed allergoid preparation of six Grasses is safe for patients with moderate to severe allergic rhinitis. Int Arch Allergy Immunol. 2019;20:1–9.
25. Winslow AW, Turbyville JC, Sublett JW, et al. Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy. Ann Allergy Asthma Immunol. 2016;117:542–545.
26. Di Bona D, Magistà S, Masciopinto L, et al. AIT Study Group. Safety and treatment compliance of subcutaneous immunotherapy: A 30-year retrospective study. Respir Med. 2019;161:105843.
27. Sani S, Gupta R, Fonacier L, et al. Risk stratification of systemic reactions to subcutaneous immunotherapy: A retrospective study. Allergy Asthma Proc. 2019;40(5):338–342.
28. Sturm GJ, Varga EM, Roberts G, et al. EAACI guidelines on allergen immunotherapy: hymenoptera venom allergy. Allergy. 2018;73 (4):744–764.
29. Kruszewski J, Zaraś E. Effect of cetirizine therapy on the rate of adverse reactions to specific desensitization. Pol Tyg Lek. 1994;49 (14–15):337–340.
30. Shankar T, Petrov AA. Omalizumab and hypersensitivity reactions. Curr Opin Allergy Clin Immunol. 2013;13(1):19–24.
31. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. Allergy. 2008;63(3):374.
32. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. Allergy. 2009;64(6):963–964.
33. Roberts G, Pfaar O, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy. 2018;73(4):765–798.
34. Durham SR, Yang WH, Pedersen, et al. sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;117:802–809.
35. Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol. 2007;120:1338–1345.
36. 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.
37. Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2014;134(3):568–575.
38. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2016;138(6):1631–1638.
39. Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual immunotherapy of house dust mite allergen extract in adults with allergic rhinitis. J Allergy Clin Immunol. 2014;133:1608–1614.
40. Okamoto Y, Fujieda S, Okano M, et al. House dust mite sublingual tablet is effective and safe in patients with allergic rhinitis. Allergy. 2017;72(3):435–443.
41. Nolte H, Casale TB, Lockey RF, et al. Epinephrine use in clinical trials of sublingual immunotherapy tablets. J Allergy Clin Immunol Pract. 2017;5:84–89.

42. Elliott J, Kelly SE, Johnston A, et al. Allergen immunotherapy for the treatment of allergic rhinitis and/or asthma: an umbrella review. CMAJ Open. 2017 10;5(2):E373–E385.
43. Compalati E, Incorvaia C, Urbano S, et al. The Safety of Carbamylated monomeric allergoids for sublingual immunotherapy. Data from a pharmacovigilance study. Immunotherapy. 2020;12(3):195–202.
44. Calderón MA, Casale TB, Nelson HS, et al. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. J Allergy Clin Immunol. 2013;132:1322–1336.
45. Meadows A, Kaambwa B, Novielli N, et al. A Systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess. 2013;17(vi, ix–xiv):1–322.
46. Manzotti G, Lombardi C. Allergen immunotherapy as a drug: the new deal of grass allergen tablets from clinical trials to current practice. Eur Ann Allergy Clin Immunol. 2013;45:34–42.
47. Tao L, Shi B, Shi G, et al. Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials. Clin Respir J. 2014;8:192–205.
48. Timothy grass standardized allergenic extract (Grastek — merck Canada Inc.) indication: allergic rhinitis (grass pollen). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2014.
49. Di Bona D, Plaia A, Leto-Barone MS, et al. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. JAMA Intern Med. 2015;175:1301–1309.
50. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy. 2006;61:185–190.
51. Agache I, Lau S, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: house dust mite-driven allergic asthma. Allergy. 2019;74(5):855–887.
52. Nebeker JR, Barach P, Samore MH. Clarifying Adverse Drug Events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004;140(10):795–801.
53. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. J Allergy Clin Immunol. 1993;91(3):709–722.
54. Godar M, Blanchetot C, de Haard H, et al. Personalized medicine with biologics for severe type 2 Asthma: current status and future prospects. MAbs. 2018;10(1):34–45.
55. Incorvaia C, Riario-Sforza GG, Ridolo E. The many abilities of Omalizumab and the unbeaten path. J Allergy Clin Immunol. 2019;143(6):2335–2336.
56. James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. Curr Opin Allergy Clin Immunol. 2017;17(1):55–59.