



POINT OF VIEW

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Tablet allergen immunotherapy: the anaphylaxis issue

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Received 6 September 2023; Accepted 21 November 2023

Available online 1 May 2024

KEYWORDS

adults;
allergen
immunotherapy;
anaphylactic
reaction;
children;
safety;
tablets

Abstract

For the first time 15 years ago, tablet allergen immunotherapy (T-AIT) formulations were approved by regulatory agencies for treating allergic rhinitis caused by grass pollen in adults and children aged >5 years. Extensive evidences existed about effectiveness and safety of AIT. However, the safety profile is particularly compelling in children. Generally, T-AIT causes local reactions, mostly in the oral cavity, that are usually mild-to-moderate and often self-resolving. However, systemic allergic reactions are also observed with T-AIT, anaphylaxis representing the most fearsome adverse event, considering that it occurs in subjects treated for allergic rhinitis. Therefore, we conducted a literature search of patients reporting anaphylaxis because of T-AIT. Nine cases of anaphylactic reactions were reported in literature. Notably, no death was reported using T-AIT. This outcome was very important as it underscored the substantial safety of T-AIT. However, T-AIT deserves careful attention, mainly in the pediatric population. In this regard, after the first report of anaphylactic reaction at the first administration of T-AIT, manufacturers recommended that the first dose should be administered in a medical facility in the presence of staff with experience in managing anaphylaxis and the patient should be observed for at least 30 min. Interestingly, reported anaphylactic reactions were due to grass pollen extracts, with no report concerning other allergen extracts. However, it is relevant to note that anaphylactic reactions because of T-AIT are not reported in recent years.

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<https://doi.org/10.15586/aei.v52i3.990>

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Allergic rhinitis and asthma are prevalent diseases that share a type-2 inflammation caused by specific and functional defects in regulatory T cells. Allergen immunotherapy (AIT) is a unique causal therapy, specifically dampening type-2 immunity and restoring physiologic regulatory mechanisms.¹

For the first time, 15 years ago, tablet AIT (T-AIT) formulations were approved by regulatory agencies for treating allergic rhinitis because of grass pollen allergy in adults and children aged >5 years.² Consequently, presently, T-AIT is a drug, so safety constitutes a compelling issue.

Extensive evidences, provided by pivotal trials, exist that T-AIT is effective and usually safe.³ However, the safety profile is particularly relevant, mainly in children. Generally, T-AIT may cause local reactions, mostly in the oral cavity (similar to sublingual drops), that are usually mild to moderate and often self-resolving.⁴ However, systemic allergic reactions are also possible with T-AIT. Concerning this issue, anaphylaxis represents the most fearsome adverse event.

The term “anaphylaxis” is derived from the old Greek words *ανά* (over) and *φύλαξις* (defense); therefore, it means a reaction of excessive response toward allergens. Namely, anaphylaxis is a relevant clinical event that may evolve toward a life-threatening condition requiring immediate identification and treatment, as stated by the updated European Academy of Allergy and Clinical Immunology (EAACI) guidelines.⁵ However, there are different definitions and criteria for diagnosing anaphylaxis.⁶ Nevertheless, an immediate and severe multi-organ involvement represents a shared definition of anaphylaxis. In other words, at least two systems must be affected to define anaphylaxis.

Allergen immunotherapy through sublingual route may induce an anaphylactic reaction in susceptible individuals who are usually very sensitive to a causal allergen. It is well-known fact that allergic patients, depending on different immunological and clinical characteristics, significantly differ from one another.⁷ In particular, there are allergy patients who may tolerate very low doses of an allergen, while others can tolerate very high doses of the same allergen. In addition, some subjects are only sensitized but not allergic.⁸ Thus, the spectrum of the degree of allergy and immunization varies. Several factors influence these different phenotypes, such as subject's age, duration of allergic disease, organs involved (e.g., rhinitis only or rhinitis with asthma), comorbidities, intercurrent illnesses, medications used, physical exertion, and hormonal factors, such as menstrual cycle.⁹ Therefore, in allergic patients, anaphylactic reaction could be triggered even with a low dose of an allergen. Paradigmatic examples are food, drug, and hymenoptera venom allergies.¹⁰ In fact, once the ingested allergen is exposed to immunoglobulin E (IgE) expressed on the surface of mast cells, it causes a massive and rapid release of preformed mediators (especially histamines) that, once released into the circulation, cause clinical manifestations typical of anaphylaxis.¹¹ It must be noted that anaphylactic reactions are usually unpredictable and not necessarily dose-dependent.

Anaphylaxis represents an exceptionally high risk during AIT, mainly considering that it could occur in a patient, primarily a child, treated for allergic rhinitis, such as a common and trivial disease. For this reason, it is essential to

know the number of anaphylaxis patients reported during T-AIT in literature. Therefore, we conducted a literature search, consulting PubMed and Scopus, for pediatric (aged <18 years) and adult (aged ≥18 years) patients reporting anaphylaxis because of T-AIT.

Some patients of anaphylactic reactions are reported in the literature (Table 1). In particular, T-AIT with pollen extracts caused anaphylaxis in 11 children and 13 adults. However, T-AIT with house dust mite extracts caused anaphylaxis in four adults, not in children.

Considering the frequency of anaphylaxis, we stratified the reported cases by the type of allergen extracts and the age. The proportion of anaphylaxis caused by five-grass-pollen products ranged from 0.01% to 0.32% in the pediatric population. The proportion of anaphylaxis caused by Timothy grass (*Phleum pratense* of the Pooideae family) extract ranged from 0.6% to 3.03% in children. In the adult population, the five-grass-pollen product had an anaphylaxis proportion of 0.01%-0.36%. The *Phleum pratense* extract caused a rate ranging from 0.17% to 1.23% in adults. T-AIT with dust mite showed a proportion of 0.26% in the adult population. These data emphasized the relevance of allergen extract used for AIT, that is, pollens were more frequently a cause of anaphylaxis than mites. It depends on the biological and immunological characteristics of different allergens. In this regard, a previous study showed that response to allergen nasal challenge significantly differed depending on single allergen.¹² In particular, each single allergen caused different immunological, inflammatory, functional, and clinical responses.

In addition, comparing the pediatric and adult population data, the prevalence was slightly more in children as reported in Table 2. However, the calculation of proportions deserves particular caution in interpretation, as the frequencies are obviously a function of the number of cases studied as well as the type of studies. Indeed, the studies conducted for regulatory purposes resulted in a higher frequency of anaphylaxis cases than the real-life studies.

This discrepancy was derived due to intentness to adverse events in the registration studies and the selected case series regarding the severity of allergic diseases. Furthermore, this literature review could not exclude the cases of anaphylaxis that were not published in literature.

Remarkably, no death has been reported with T-AIT up to now. This outcome is essential as it underscores the safety of T-AIT. However, T-AIT deserves careful attention, mainly in the pediatric population. In this regard, after the first reported instance of anaphylactic reaction following the first administration of T-AIT, manufacturers recommended that the first dose must be administered in a medical facility with the staff experienced in managing anaphylaxis, and the patient should be observed for at least 30 min.

Interestingly, anaphylactic reactions in children were due to grass pollen extracts only; no reaction has been reported regarding other allergen extracts at present. Moreover, it is relevant to note that in recent past, no anaphylactic reactions are reported because of T-AIT. This confirmed the substantial safety of T-AIT in children.

Table 1 Studies reporting cases of anaphylaxis because of tablet-allergen immunotherapy.

Author, year, reference No.	Design	Allergen	Manufacturer	Duration	Pediatric study	Number of patients	Frequency of anaphylaxis	Rate of anaphylaxis	Adult study	Number of patients	Frequency of anaphylaxis	Rate of anaphylaxis
Grass												
Hsiao and Smart, 2014 ¹³	Case-report	Grass pollen	Stallergènes	N/A	Yes	1	1	N/A	No	N/A	N/A	N/A
Eberle et al., 2014 ¹⁴	O-OL	Grass pollen	Stallergènes	2 years	Yes	829	2	0.24%	No	N/A	N/A	N/A
Didier and Bons, 2015 ¹⁵	Review on 5 years of experience	Grass pollen	Stallergènes	6 years	Yes	55,056	4	0.01%	Yes	115,729	8	0.01%
Blin et al., 2015 ¹⁶	O	Grass pollen	Stallergènes	1 year	Yes	203	0	N/A	Yes	280	1	0.36%
Gerstlauer et al., 2019 ¹⁷	O	Grass pollen	Stallergènes	1 month	Yes	307	1	0.32%	No	N/A	N/A	N/A
De groot and Bijl, 2009 ¹⁸	Case-report	Phleum pratense	ALK-Abello'	N/A	No	N/A	N/A	N/A	Yes	1	1	N/A
European Union Clinical Trials Register, 2009 ¹⁹ ; Halcken et al., 2020 ²⁰	RCDB	Phleum pratense	ALK-Abello'	N/R	Yes	33	1	3.03%	No	N/A	N/A	N/A
Bufe et al., 2009 ²¹	RCDB	Phleum pratense	ALK-Abello'	10 months	Yes	126	1 (two episodes on different days in the same patient)	0.79%	No	N/A	N/A	N/A
Blais et al., 2011 ²²	RCDB	Phleum pratense	ALK-Abello'	6 months	Yes	175	1	0.57%	No	N/A	N/A	N/A
Murphy et al., 2013 ²³	RCDB	Phleum pratense	ALK-Abello'	4-6 months	No	N/A	N/A	N/A	Yes	163	2	1.23%
Schwab et al., 2013 ²⁴	NI, OL	Phleum pratense	ALK-Abello'	3 months	Yes	75	0	N/A	Yes	587	1	0.17%
House dust mites												
Reiber et al., 2021 ²⁵	OL, NI	HDM	ALK-Abello'	1 year	Yes	6	0	N/A	Yes	1519	4	0.26%

RCDB: randomized controlled double-blind; OL: open label; O: observational; N/A: not applicable; N/R: not reported; HDM: house dust mites.

Table 2 Comparison between pediatric and adult cases of anaphylaxis because of tablet allergen immunotherapy.

Allergen	Allergen extracts	Frequency of anaphylaxis reported in pediatric studies (n)	Rate of anaphylaxis in pediatric patients (mean [range])	Frequency of anaphylaxis reported in adult studies (n)	Rate of anaphylaxis in adult patients (mean [range])
Grass		11	0.83% (0.01-3.03%)	13	0.44% (0.01-1.23%)
	Grass pollen	8	0.19% (0.01-0.32%)	9	0.19% (0.01-0.36%)
	Phleum pratense	3	1.46% (0.6-3.03%)	4	0.7% (0.17-1.23%)
HDM	D. farinae and D. pteronyssinus	0	N/A	4	0.26%

HDM: house dust mites; N/A: not applicable.

5 grass pollen allergy pediatric studies (0.24%, 0.01%, and 0.32%).

5 grass pollen allergy adult studies (0.36% and 0.01%).

Phleum pratense pediatric studies (3.03%, 0.79%, and 0.57%).

Phleum pratense adult studies (1.23% and 0.17%).

Conclusion

T-AIT very rarely determined an anaphylactic reaction and never caused a death. However, care is always required for T-AIT management, and the first dose of T-AIT must be administered in a medical setting. It would be even more prudent, at least in the pediatric population, to administer the second and third dose in a protected environment. In addition, a close contact must be ensured with the referral center through telemedicine, considering that T-AIT management is managed typically at home. Finally, as a good procedural principle, the patient should always be in good/optimal health, with a forced expiratory volume in 1 s (FEV₁) being within the normal range (spirometry must be conducted, especially in case of asthmatic patients) at the beginning of the treatment as well as in general, thus avoiding administration of the product in a condition of poor symptomatology in spite of controlling intercurrent facts.

Funding

This work was supported by the Italian Ministry of Health, RICERCA CORRENTE 2023 - RRC-2023-23683432.

Conflict of interest

The authors stated no conflict of interest.

Author contributions

Giorgio Ciprandi designed the study, Matteo Naso collected the literature data, and Maria Angela Tosca discussed the results. Giorgio Ciprandi wrote the manuscript, Matteo Naso and Maria Angela Tosca discussed the final text.

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