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RESEARCH ARTICLE

Safety and tolerability of allergen-specific immunotherapy in pediatric patients with respiratory allergy: a single-center study

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ABSTRACT

Allergen-specific immunotherapy (AIT) is the only disease-modifying therapy for allergic diseases, but its safety is still being questioned. This study aimed to 1) characterize the demographics and clinical profiles of children with allergic asthma (AA) and/or allergic rhinitis (AR) who underwent AIT, 2) assess the frequency and nature of adverse reactions associated with AIT, and 3) investigate potential correlations between these reactions and risk factors such as age, comorbidities, diagnosis, allergen composition, and AIT administration schedule.

We retrospectively analyzed data from children who received AIT at the Pediatric Clinic in Pavia, Italy, between 2010 and 2022. AIT was administered subcutaneously (SCIT) or sublingually (SLIT) using various schedules. Standardized allergen extracts for grass pollen, house dust mites (HDM), mold, and ragweed were employed.

Three hundred patients were enrolled in the study. A total of 35 (11.5%) patients experienced adverse events related to AIT. Common reactions in the SCIT group (14%) included local swelling, skin redness, and pain at the injection site. In the SLIT group, 12 patients (4%) reported oral itching. Additionally, three patients receiving SLIT experienced systemic reactions including hives, angioedema, and asthma exacerbation. Furthermore, three SLIT patients developed eosinophilic gastrointestinal disorders 3-6 months after treatment initiation.

Our study supports the safety and tolerability of AIT for respiratory allergy. AIT has a favorable safety profile with minimal adverse events in the pediatric population.

HIGHLIGHTS BOX

What is already known about this topic? AIT is the only disease-modifying therapy for allergic diseases. **What does this article add to our knowledge?** While AIT is a well-established and effective method for treating allergies, some concern about its safety have been raised. Our research confirms that AIT is both effective and safe, with minimal and manageable side effects. **How does this study impact current management guidelines?** Our study emphasizes the safety of prescribing AIT for asthmatic children with or without rhinitis by current management guidelines.

KEY WORDS

Local adverse events; systemic adverse events; allergen-specific immunotherapy; eosinophilic gastrointestinal disorders.

INTRODUCTION

Allergen-specific immunotherapy (AIT) is the only disease-modifying therapy for IgE-mediated allergic respiratory diseases (1). AIT is a widely used therapy for over 100 years. However, it still represents a modern strategy in precision medicine for treating allergic rhinitis and asthma. Identifying the patient phenotype and endotype through the newly available laboratory diagnostic test, the Component-Resolved Diagnostics (CRD), allows the clinician to provide a patient's targeted therapy, favoring AIT success (2). Recent evidence supports the use of AIT as an adjuvant therapy in children with severe atopic dermatitis, sensitization to house dust mites, and skin inflammation exacerbated by allergen exposure (3). AIT can be administrated by both subcutaneous (SCIT) and sublingual (SLIT) routes. In consensus reports and metanalyses, SCIT and SLIT are being reported to be effective in providing short- and long-term benefits in allergic patients reducing allergic symptoms and drug consumption (4, 5). While several studies widely demonstrate tolerance and effectiveness, there is still some concern regarding its safety (6-8). However, few observational studies and RCTs have described AEs due to AIT; recent data from the Allergen Immunotherapy Adverse Reactions Registry supported by the European Academy of Allergy and Clinical Immunology have been published. The Authors confirm that AIT is safe and well tolerated in children and adolescents with respiratory allergies in real-life clinical practice and severe AEs are rare and mostly related with SCIT (9). This report aims to describe the safety of immunotherapy by assessing local and systemic AEs in children and adolescents with AR and/or AA who underwent AIT for allergic respiratory disease due to grass pollen, house dust mites (HDM), ragweed, and molds (*Alternaria alternata*). This study also investigates the relationship between allergic comorbidities and AEs during AIT administration to identify potential risk factors. Our secondary outcome is to highlight AIT efficacy in a pediatric population, showing how it can improve Quality of Life (QoL) and reduce the use of antiallergic drugs such as antihistaminic and topical steroids.

METHODS

This single-center, retrospective study included 300 patients with a diagnosis of moderate-to-severe AR with or without conjunctivitis and/or allergic asthma referred to the Pediatric Allergy Department of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) between January 2010 and January 2022 underwent AIT (SCIT or SLIT). Diagnosis of rhinitis and asthma was based on the international guidelines Allergic Rhinitis and its Impact on Asthma (ARIA) (10) and the Global Initiative for Asthma (GINA) document, respectively (11). Data on medical records, including sex, age, sensitization, past medical history and allergy history, current treatments, and characteristics of the AIT schedule, were collected from the patient's clinical files. Every patient identifier (name and surname) was replaced with a specific numeric code. Data were collected and managed in compliance with the European Union General Data Protection Regulation (GDPR). All patients provided written informed consent. The Ethical Committee approved this study (22253/2017).

Patients were divided into different groups according to the allergen chosen for desensitization (HDM, grass pollen, *Alternaria alternata*, ragweed) and to the method of AIT administration (SCIT or SLIT).

To assess AIT safety, we described AIT-related AEs occurred during SCIT and SLIT administration. The severity of AEs was categorized according to the WAO grade classification system as mild, moderate, or severe for local AEs occurring during SLIT therapy and as grade 1 to 5 for systemic AEs occurring during SCIT therapy (12, 13). We reported the onset time of the AEs, focusing on the possible need for topic or systemic treatment. Furthermore, allergic comorbidities in patients presenting AEs were evaluated and compared to allergic comorbidities in patients without AEs.

Moreover, we collected data on the timing of AE occurrence after AIT administration and the need for topical or systemic therapy. To describe AIT efficacy, we collected data on the antiallergic medications used before and after the AIT course and the time needed to reduce and discontinue antihistaminic therapy. Our study adheres to national and European ethical and regulatory requirements, including patients' health information privacy.

Means and standard deviations were used to evaluate normally distributed continuous data and frequencies and percentages. Fisher's Exact test was used to assess correlations between categorical variables. The statistical significance for all analyses was defined as a

p-value <0.05. The statistical analyses were performed through GraphPad Prism version 9.3.0 (San Diego, CA, USA).

RESULTS

Population description

We enrolled 300 children and adolescents aged 6 to 18 years old at the beginning of AIT with AR and/or AA who underwent SCIT or SLIT for grass pollen, HDM, ragweed and/or molds *(Alternaria alternata*) for a total of approximately 180.000 SLIT doses (135.000 tablets and 45.000 drops) and 365 SCIT doses.

The average age at the AIT beginning was 14.5 ± 3.23 years old. Adolescents aged ≥12 years represented 79% (n = 236) of patients, while children aged between 6 and 11 years old were 21% (n = 64). Patients who underwent SCIT were older than those who received SLIT (18 ± 0.5 years *vs.* 13 ± 3.2 years). In our population, a male sex predominance emerged (71%). The patients were diagnosed as having only AR (73%, n = 219), AR + AA (21%, n = 62), and AA in the presence of an IgE-mediated aeroallergen sensitization (6%, n = 19). According to ARIA guidelines, patients with AR were classified into intermittent AR (90%, n = 270), persistent AR (10%, n = 30), moderate AR (95%, n = 285), and severe AR (5%, n = 15) (**Table 1**).

***Table 1**. Classification of allergic rhinitis among AIT study participants.*

Intermittent n = 270 (89.67%)	**Persistent** n = 30 (10.33%)
Moderate AR n = 285 (94.67%)	**Severe AR** n = 15 (5.33%).

AR: Allergic Rhinitis.

The most frequently reported comorbidity was atopic dermatitis (AD) in 56 patients, followed by food allergy (n = 39) and chronic rhinosinusitis with or without nasal polyposis in 7 cases. To ensure safety, only participants with mild-to-moderate, well-controlled asthma, as defined by the European Academy of Allergy & Clinical Immunology (EAACI), were eligible. Excluding those with poorly controlled or partially controlled asthma was crucial due to the potential risks associated with AIT (14).

House dust mite (HDM) was the most common allergen targeted in AIT courses (55%), followed by grass pollen (38%), mold (6%), and ragweed (1%). **Figure 1** details the distribution of allergens. All patients undergoing SCIT therapy were treated for grass pollen, while the most common allergen in SLIT patients was HDM (59%). Most patients received SLIT (n = 283) administered as tablets (n = 153) or drops (n = 130) (**Table 2**). Five patients underwent SLIT therapy both for HDM and grass pollen consequentially. SCIT for grass pollen was limited to participants above 12 years old (n = 22). We performed only single-allergen AITs. The types of allergenic extracts were used, and the posology patterns followed are summarized in **Table 3**. The average duration of SLIT was 3.15 years *vs.* 4.2 years in SCIT therapy. Fifteen patients discontinued the follow-up from our Center, 14 in the SLIT and one in the SCIT group. Demographic and clinical characteristics of patients receiving AIT are reported in **Tables 4** and **5**.

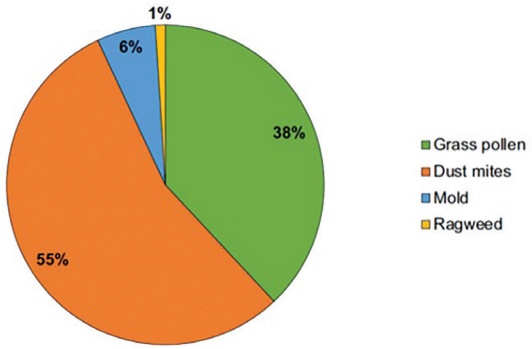

***Figure 1.** Distribution of allergen types administered to the participants.*

***Table 2**. AIT: routes of administration and type of allergens in patients with an adverse event compared with those without.*

	All patients	Without AEs	With AEs
SLIT formulation			
Tablets	153 (51%)	131 (86%)	21 (14%)
Drops	130 (43%)	119 (92%)	10 (8%)
SLIT allergens			
HDM	166 (59%)	154 (93%)	12 (7%)
Grass pollen	97 (34%)	80 (83%)	17 (17%)
Molds	17 (6%)	16 (94%)	1 (6%)
Ragweed	3 (1%)	2 (67%)	1 (33%)
SCIT allergens			
Grass pollen	22 (8%)	18 (82%)	4 (18%)

AEs: Adverse Events; AIT: Allergen Immunotherapy; HDM: House Dust Mites; SCIT: Subcutaneous Immunotherapy; SLIT: Sublingual Immunotherapy.

Table 3. *Summary of types of allergenic extracts used and dosage.*

Manufacturer and brand name	Type of allergenic extract	Dose
	Grass pollen SCIT	
Allergy Therapeutics Pollinex Quattro ®	12-grass/rye cereal pollen extract that is adsorbed by co-precipitation to L-tyrosine and then to MPL® adjuvant.	Four preseasonal * injections Build-up: 1 ml (300 SU/ml) injection at week 1 1 ml (800 SU/ml) injection at week 2 1 ml (2000 SU/ml) injection at weeks 3 1 ml (2000 SU/ml) injection at weeks 4
	Grass pollen slit	
Stallergènes Oralair ®	5-grass extract (cocksfoot, rye grass, sweet vernal grass, timothy grass, and meadow grass).	Grass Pollen Pre-Co-Seasonal ** Tablets Build-up: 1st day: 1 tablet (100 IR) 2nd day: 2 tablets (200 IR) Maintenance: From the 3rd day: 1 tablet (300 IR) every day
ALK-Abelló GRAZAX ®	Standardized allergen extract of grass pollen from timothy grass	Grass Pollen Tablets Continuously *** 1 tablet (75.000 SQ-T) every day
	HDM SLIT	
Allergy Therapeutics Oralvac Compact ®	*Dermatophagoides Farinae* and *Dermatophagoides Pteronyssinus*	HDM drops Ultra-rush schedule: 2 Pumps on the 1st day 3 Pumps from the 2nd day (daily)
Stallergènes Staloral BM/300 IR ®	*Dermatophagoides Farinae* and *Dermatophagoides Pteronyssinus*	HDM drops Ultra-rush schedule: 1 Pump on the 1st day 2 Pump from the 2nd day (daily)
Lofarma LAIS ®	Monomeric Allergoid *Dermatophagoides Farinae* and *Dermatophagoides Pteronyssinus*	HDM tablets 2 tablets (1.000 UA/tab) per week
	Molds SLIT	
Allergy Therapeutics Oralvac Compact ®	*Alternaria alternata*	Molds drops Ultra-rush schedule: 2 Pumps on the 1st day 3 Pumps from the 2nd day (daily)
ALK-Abelló SLIToneULTRA®	*Alternaria alternata, Cladosporium*	Molds drops Build-up schedule drops: 50 SRU/day for five consecutive days followed by 150 SRU/day for five additional consecutive days. Maintenance: 300 SRU/day

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	Ragweed SLIT	
Allergy Therapeutics Oralvac Compact ®	Not available data	Weed pollen drops Ultra-rush schedule: 2 Pumps on the 1st day 3 Pumps from the 2nd day (daily)

Our choice of different allergen immunotherapy manufacturer and brand over the years depended according to intrahospital regulation.
SU: Standardized Unit; IR: Reactivity Index; SQ-T: Standardized Quality Units Tablets; UA: Allergenic Unit; SRU: Standardized Reactivity Units.
* Beginning about 4 months before the expected start of the grass pollen season.
** Beginning about 4 months before the expected start of the grass pollen season and is continued throughout the grass pollen season (about 7 months).
*** Beginning about 4 months before the expected start of the grass pollen season and continued daily.
**** Beginning about 4 months before the expected start of the ragweed season and is continued throughout the ragweed pollen season (about 5 months).

***Table 4**. Demographic and clinical characteristics of patients receiving SLIT in patients with an adverse event compared with those without.*

	All patients	Without AEs	With AEs
	283 (100%)	282 (89%)	31 (11%)
Sex			
Male	199 (71%)	174 (87%)	25 (13%)
Age			
6-11 years	64 (23%)	59 (92%)	5 (8%)
≥12 years	219 (77%)	192 (88%)	26 (12%)
Indication for AIT			
AR	206 (73%)	187 (91%)	19 (9%)
AR + AA	58 (21%)	50 (86%)	8 (14%)
AA only	18 (6%)	14 (78%)	4 (22%)
Allergic comorbidities			
AD	53 (19%)	48 (91%)	5 (9%)
Food allergy	36 (13%)	31 (86%)	5 (14%)
Chronic Rhinosinusitis with and without nasal polyposis	7 (2%)	7 (100%)	0 (0%)

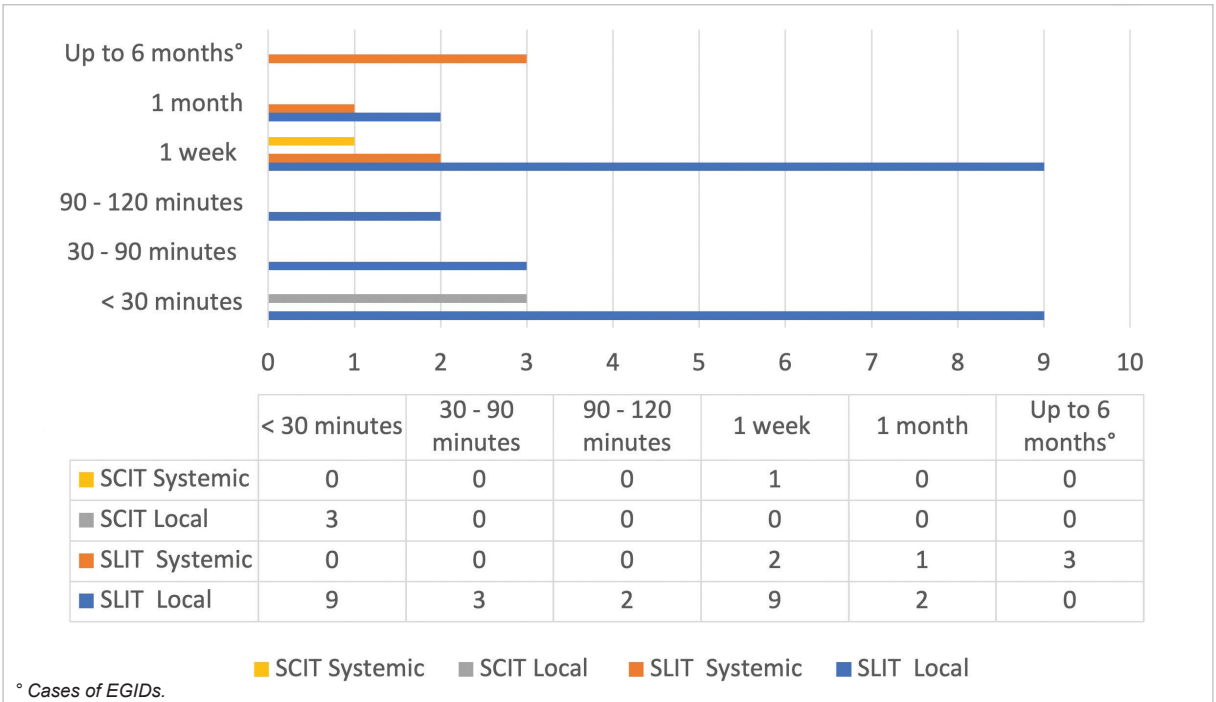
AA: Allergic Asthma; AD: Atopic Dermatitis; AEs: Adverse Events; AIT: Allergen Immunotherapy; AR: Allergic Rhinitis; SLIT: Sublingual Immunotherapy.

AEs evaluation

AEs were reported in 35 patients (12%), 31 receiving SLIT (11%), and 4 receiving SCIT (18%). The timing and type of AEs of patients receiving AIT are described in **Figure 2**. Three patients developed eosinophilic gastrointestinal diseases (EGIDs) symptoms during SLIT. Two were subsequently diagnosed with eosinophilic esophagitis (EoE), and one with eosinophilic duodenitis (EoD). None of our patients needed therapy discontinuation due to severe AEs, and no anaphylaxis was observed. However, one patient interrupted AIT due to laboratory findings of IgA and IgM deficiency from an analysis carried out for recurrent bronchitis.

The rate of AEs was higher in patients treated with AIT for grass pollens than for HDM (p = 0.014). No significant difference in the overall rate of adverse events was found between SCIT and SLIT groups.

According to our data, the probability of developing AEs was higher in patients >12 years old (p = < 0.0001) and in those who underwent AIT with tablets (p = 0.01). No statistical differences were observed according to sex, type of allergen, and presence of allergic comorbidities.



	< 30 minutes	30 - 90 minutes	90 - 120 minutes	1 week	1 month	Up to 6 months°
SCIT Systemic	0	0	0	1	0	0
SCIT Local	3	0	0	0	0	0
SLIT Systemic	0	0	0	2	1	3
SLIT Local	9	3	2	9	2	0

° *Cases of EGIDs.*

Figure 2. *Timing and type of adverse reactions in AIT patients.*

SLIT

Local AEs

According to the WAO grade classification system, 25 local AEs occurred during SLIT administration. Most were mild (n = 17), while eight reactions required medication or were troublesome and classified as moderate. None of our patients had severe AEs requiring therapy discontinuation.

Most local AEs occurred within the first 120 minutes (56%), of which nine were within the first 30 minutes after administration. 36% (n = 9) of patients developed symptoms in the first week and 8% (n = 2) in the first 30 days.

Among local AEs occurred during SLIT, the most frequently reported was oral itching in 48% of patients (n = 12). In comparison, gastrointestinal symptoms were described in 16% (n = 4), oral angioedema in 24% (n = 6), ear edema and itching in 8% (n = 2), and pharyngitis in one patient (4%).

In 20 patients (80%), AEs resolved spontaneously, while five patients (20%) required oral non sedative antihistamine therapy.

Systemic AEs

Three patients developed systemic reactions; in particular, one presented an asthma exacerbation requiring oral corticosteroids (OCs) and short-acting beta-agonists (SABA), one patient showed systemic urticaria treated with oral antihistamine and OCs, and one patient had eyes and lips angioedema needing oral antihistamine and OCs. None of them required therapy discontinuation. No anaphylaxis case was registered.

During the first 3-6 months of follow-up, late onset EGIDs were reported in three patient requiring therapy discontinuation.

SCIT

AEs occurred in four (18%) of the twenty-two patients receiving SCIT. Three developed local AEs in the first 30 minutes after administration. All of them were mild (itching, erythema, and pain in the injection site), and none required any therapy. One patient reported general itching within the first week of treatment. This AE is classified as grade 1 according to the WAO grade classification system and was treated with oral antihistamine therapy. None of them had severe AEs requiring therapy discontinuation. No anaphylaxis case was registered. **Table 5** summarizes the clinical features of patients experiencing adverse reactions during SCIT.

***Table 5**. Demographic and clinical characteristics of patients receiving SCIT in patients with an adverse event compared with those without.*

	All patients	Without AEs	With AEs
	22 (100%)	18 (82%)	4 (18%)
Sex			
Male	14 (64%)	11 (79%)	3 (21%)
Indication for AIT			
AR	16 (73%)	14 (87%)	2 (13%)
AR + AA	5 (23%)	3 (60%)	2 (40%)
AA only	1 (4%)	1 (100%)	0 (0%)
Comorbidities			
AD	3 (14%)	2 (67%)	1 (33%)
Food allergy	5 (23%)	3 (60%)	2 (40%)
Chronic rhinosinusitis	1 (5%)	1 (100%)	0 (0%)

AA: Allergic Asthma; AD: Atopic Dermatitis; AEs: Adverse Events; AIT: Allergen Immunotherapy; AR: Allergic Rhinitis; SCIT: Subcutaneous Immunotherapy.

Efficacy evaluation

SLIT

The average time needed to discontinue daily antiallergic therapy was 1.5 years for SLIT patients. Furthermore, 127 patients (45%) could discontinue daily antiallergic therapy during the allergen period after the first year of AIT. This allowed patients to assume on-demand antiallergic treatment only in case of symptoms. Twenty-four patients (8%) did not complete the follow-up period due to poor compliance or could not discontinue antiallergic therapy.

SCIT

The average time needed to discontinue daily antiallergic allergic therapy was 1.1 years for SCIT patients, and 81% of patients could discontinue daily antiallergic allergic therapy during the allergen period after the first AIT cycle. This allowed patients to assume on-demand antiallergic treatment only in case of symptoms. One patient was lost during the follow-up period due to poor compliance. The time to achieve medication-free allergy control with AIT is reported in **Table 6**.

***Table 6**. Time to achieve medication-free allergy control with AIT.*

	SCIT	SLIT
1 year	127 (45%)	18 (81%)
2 years	67 (24%)	3 (14%)
3 years	62 (22%)	0 (0%)
5 years	2 (1%)	0 (0%)
Other (lost during follow-up or not able to discontinue anti-allergic therapy)	24 (8%)	1 (5%)

AIT: Allergen Immunotherapy; SCIT: Subcutaneous Immunotherapy; SLIT: Sublingual Immunotherapy.

DISCUSSION

In our study both SCIT and SLIT were found to be safe with a manageable side effect profile in children and adolescents.

Most of our patients received SLIT (93% *vs*. 7%), and this data is consistent with the literature. In fact, since the use of SCIT in pediatric age, especially in younger children, is limited by needle fear and puncture pain, SLIT is more often used, also due to the possibility of home administration, better safety profile, and a better overall acceptance of therapy (15, 16).

AEs were reported in 35 of our patients (11.5%), and this is consistent with the Allergen Immunotherapy Adverse Registry (ADER) study, a multinational registry of AIT established with the support of the EAACI focused on AIT safety (17); in this study, AEs rate occurred in about 10% of patients.

In our study, we reported AEs in 16% of patients who underwent SLIT for pollen grass *versus* 7% of those receiving AIT for HDM from different products, schedules, and routes of administration. In our population, all children undergoing AIT with grass pollen received tablets and children undergoing AIT with HDM received both tables and drops. Our findings differ from other studies that reported no significant difference between the two allergens. We suppose this difference depends on the retrospective nature of this study. In the past, the dosage in HDM drops was mostly unknown and possibly ineffective, and on the other hand, there was easily the possibility of error administrations. Instead, in the European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI), Rodriguez Del Rio *et al*. reported a greater incidence of systemic AEs in patients using SCIT grass pollen extracts due to an overexposure to the disease-inducing allergen during the pollen season (18). A significant AE frequency in asthmatic patients was also reported in the European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI),

where patients with asthma had a twofold more significant risk of AEs (19).

During the SARS-CoV-2 pandemic, we continued administering AIT without detecting an increase in AEs. This is consistent with the EAACI survey concerning the COVID-19 pandemic (20).

According to literature data, AEs were more frequently registered in the SCIT group (respectively, 11% of AEs in SLIT patients and 18% of AEs in SCIT patients). Most of the reactions were mild during the first week of AIT. This result is consistent with the literature (21). In particular, the most frequently reported AEs SLIT-related were local reactions such as oral itching and angioedema, occurring primarily within the first two hours after the first therapy administration. Similar data are reported in a Colombian study (22). Nine patients presented local AEs during the first 30 minutes after administration. This underlines the importance of performing the first sublingual administration in a hospital setting under medical surveillance to observe the patient for at least 30 minutes before discharge, as per international recommendations. In our center, we perform a 120-minute clinical observation period after the first administration of AIT as a standard precautionary measure to monitor patients for potential AEs. However, some AEs happened in the home setting, thus was not possible to assess with absolute certainty the possibility of errors in the dosage or mode of immunotherapy administration. Anyway, no patient reported errors in AIT home administration, but this data was not assessed with a proper questionnaire. In the last years, we have been providing patients with personalized schedules to better evaluate and report AEs, and to evaluate mistakes in AIT administration and possible co-factors in case of reaction. Also, these questionnaires will help us in the future to assess and monitor the appropriate adherence to therapy, as this is still one of the major problems of SLIT immunotherapy home administration.

An important observation from our data is the infrequent occurrence of AE during the maintenance phase of over six weeks. This event may correspond to a time window for key immunological changes. Further studies, including molecular and biochemical features, need to be performed.

Three patients developed EoE three to six months after starting SLIT. As a result, the treatment was stopped. How often EoE happen during AIT has yet to be discovered. It is still debated whether eosinophilic disorders were present before the treatment or if they developed as a long-term effect of the immunotherapy (23).

By investigating allergic comorbidities of patients with AEs undergoing SLIT, 13% had food allergies, and 19% suffered from AD, suggesting a potential connection between the allergic burden and the development of AEs. Further studies are needed to assess the possibility of a correlation between allergic comorbidities and AEs occurring during AIT.

Analyzing AIT efficacy, 45% of patients undergoing SLIT and 81% of patients undergoing SCIT were able to discontinue daily antiallergic therapy during the seasonal allergen period after the first AIT cycle, underlining the efficacy of AIT. This allowed patients to assume on-demand antiallergic treatment only in case of symptoms. This data confirms that AIT can modify the natural course of patient's allergy. AIT therapy had a significant impact on quality of life both from an economic and a psychological point of view.

The main limitations of our study were the exclusion of preschoolers, the retrospective study structure, and the need for long-term follow-up to assess the long-lasting beneficial effects of AIT. Given our study's retrospective nature, it was impossible to gain data regarding the prevention of asthma development in patients with AR undergoing AIT. Also, QoL was not assessed.

CONCLUSIONS

Although AIT has been a widely used therapeutic strategy for over 100 years, it still represents a modern personalized medicine for treating allergic respiratory diseases. Proper family compliance is essential for AIT efficacy, especially in SLIT therapy. Therefore, good allergy counseling is mandatory. Our data corroborate the AIT safety and tolerability, confirming that it is the only disease-modifying therapy capable of alleviating symptoms and reducing the number of medications required, with few and manageable side effects.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors declare that they have no financial or personal conflicts of interest that might have influenced the work reported in this article.

Financial support

The Authors declare that the mention of pharmaceutical products in this article is purely for informational and scientific purposes, with no intent to promote or advertise. The Authors have not received compensation or sponsorship from the manufacturers.

Author contributions

Conceptualization: MDF, MV, AL; methodology: MDF, MV; investigation: MDF, MV, AL; data curation: GAM, MPB; writing-original draft preparation: MDF, MLV, GM; writing- review and editing: MDF, MV, GLM, AL. All Authors have reviewed and agree to the content of the published manuscript.

Ethical approval

Human studies and subjects

This study was approved by the Ethical Committee of Pavia (protocol number 22253/2017).

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this study are available from the Corresponding Author upon reasonable request.

Publication ethics

Plagiarism

The Authors confirm that the content of this article is original and that any overlapping text from other sources is properly cited. All figures and tables are original.

Data falsification and fabrication

The data is based on real-world observations.

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