Journal of Asthma and Allergy

Dovepress
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Open Access Full Text Article

ORIGINAL RESEARCH

Safety and Effectiveness of Allergen Immunotherapy in Patients with Severe Allergic Asthma

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Objective: Allergen immunotherapy (AIT) is an established treatment for mild to moderate allergic asthma. However, limited data are available regarding its safety and efficacy in patients with severe asthma. This study aimed to gather real-world evidence (RWE) on the safety and effectiveness of AIT in individuals with severe asthma caused by sensitization to at least 1 allergen, who were either currently undergoing AIT or had received it within the past five years.

Methods: A retrospective study was conducted in Spain, including patients aged ≥6 years with severe asthma (Spanish Guideline for Asthma Management [GEMA] steps 5–6 and Global Initiative for Asthma [GINA] step 5) sensitized to at least 1 allergen who had received AIT within the previous 5 years, to evaluate safety and effectiveness.

Results: The study included 93 patients (54.8% female) with a median age of 40.3 years, including 5 under 14. A total of 16 systemic reactions (SRs) were reported in 8 patients (8.6%), mostly immediate (13/16) and occurring during the initiation phase (12/16), all in patients receiving subcutaneous immunotherapy. Most SRs were mild to moderate, except for 2 severe reactions in 1 patient. Only 3 patients discontinued treatment. Significant improvements in both FeNO and FEV_1 (%) were observed after 6 and 12 months of AIT, respectively. Quality of Life (through mini-AQLQ) scores improved at 1, 2 and 3 years after initiation of AIT compared to baseline. The number of patients who did not require rescue medication for asthma was significantly higher after starting AIT than before treatment. AIT was also associated with a 75.8% reduction in the number of emergency visits.

Conclusion: This study confirms the safety and effectiveness of AIT in patients with well-controlled severe asthma in routine clinical practice. Additional prospective real-world studies are needed to better understand the efficacy of AIT in severe asthma.

Keywords: allergen immunotherapy, allergic asthma, severe asthma, real-world evidence, safety

Introduction

Asthma is a chronic respiratory disease characterized by persistent airway inflammation, which leads to bronchial hyperresponsiveness and variable airflow obstruction.[1] Common clinical symptoms include wheezing, shortness of breath, coughing, and tightness in the chest.[2] As of 2019, it was estimated to affect nearly 300 million people worldwide and was responsible for more than 450,000 deaths.[3–5]

This heterogeneous condition encompasses multiple endotypes and is broadly classified into two main phenotypes: T2 (allergic and eosinophilic) and non-T2 asthma.[6] T2 asthma accounts for up to 70% of severe cases —which are characterized by high treatment needs (Spanish Guideline for Asthma Management [GEMA] steps 5–6 and Global Initiative for Asthma [GINA] step 5)—, about half of whom have allergic asthma.[2,7] Despite intensive treatment, more than 60% of individuals within this subgroup remain uncontrolled.[8] Identifying preventable factors is crucial to guiding research, policy, and clinical care priorities.[9]

Received: 21 June 2025
Accepted: 5 August 2025
Published: 19 September 2025

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Although conventional pharmacotherapy remains central to asthma management, some patients with uncontrolled disease, particularly T2 asthma, may benefit from novel add-on biologic therapies. These treatments have been shown to reduce exacerbation rates and oral corticosteroid use, while improving disease control, lung function, and asthma-related quality of life.[10,11] Nonetheless, some patients remain inadequately controlled even with the available biologic therapies for T2 diseases.[12] This underscores the ongoing need for alternative, disease-modifying strategies to improve outcomes in this population.

Allergen immunotherapy (AIT) is the only treatment known to target the underlying cause of IgE-mediated allergy and provide long-term clinical benefits— even after discontinuation— particularly in patients with mild to moderate allergic asthma.[13–19] Both sublingual (SLIT) and subcutaneous (SCIT) immunotherapy have been shown to be safe for patients with respiratory diseases, with adverse reactions typically being mild and the incidence of severe reactions relatively low.[20] SLIT is generally associated with a more favorable safety profile than SCIT.[21,22] However, most historical safety data were based on AIT using native allergen extracts, which retain intrinsic properties —such as high IgE-binding capacity— that are linked to an increased risk of adverse events. In contrast, chemically modified allergen extracts, which exhibit reduced IgE-binding capacity, have been associated with improved tolerability while maintaining clinical efficacy.[23,24] Emerging evidence suggests that, depending on the allergenic source, SCIT with modified extracts may achieve a safety profile comparable to that of SLIT.[25]

According to current guidelines, severe asthma is a major risk factor for serious or fatal reactions to AIT and is considered an absolute contraindication.[2,14,26,27] However, further research is needed to determine whether the benefits of AIT may outweigh the risks in patients with well-controlled severe asthma.[28] Additionally, combining AIT with biologics may enhance disease management, even in patients who are not considered a priori candidates for immunotherapy.[15]

In this context, we conducted the SAGITAL study —a real-world, multicenter, observational, retrospective study with a prospective character— across 16 centers in Spain to assess the safety and effectiveness of AIT in patients aged ≥6 years with severe allergic asthma.

Material and Methods

Study Design

SAGITAL (Severe Asthma: a Gap for Inmuno Therapy with ALlergens) was a real-world, multicenter, observational, retrospective study with prospective elements, designed to collect real-life data from 16 centers in Spain on the safety and effectiveness of AIT administered over the past five years to patients with severe asthma in a clinical setting (Supplementary Table S1). Data were collected retrospectively from the patients' medical records in the 6 months following the effective start of the study. All data were reviewed by the responsible physician and pseudo-anonymized before inclusion in the study database. Given the cross-sectional nature of the study, treatment duration varied across participants. Some patients were still undergoing AIT at the time of data collection, while others had already completed their treatment. The specific duration of AIT for each individual was not systematically documented as part of the study protocol. However, all included patients had received or were receiving AIT during the defined study period. Exemption from informed consent was requested for the data of those patients who could not be contacted.

Study Population

The study included patients with a diagnosis of severe allergic asthma due to sensitization to aeroallergens who had received or were receiving AIT in routine clinical practice in the previous 5 years. Detailed inclusion criteria were: (i) patients ≥6 years of age; (ii) signed informed consent; (iii) asthma due to sensitization to one or more allergens belonging to one of the following groups (confirmed by skin prick test [SPT]/IgE): a) mites, b) epithelia, c) pollen, d) mold, e) occupational; (iv) diagnosis of severe asthma according to GEMA (step 5–6) or GINA (step 5) criteria, controlled; (v) patients had to be receiving AIT (subcutaneous, sublingual tablets or sublingual drops) or have received it within the last 5 years. Due to the retrospective, observational, real-world nature of the study, the exclusion criteria were aligned with standard clinical practice. They were based on the absence of inclusion criteria and the presence of conditions that are considered to be relative or absolute contraindications to

AIT, according to international guidelines. Specifically, patients with active malignancies, uncontrolled autoimmune diseases or other contraindications to AIT were excluded. The treating physicians made these clinical decisions based on established recommendations (eg EAACI guidelines) and the summary of product characteristics for each AIT extract. Regarding pregnancy status, although systematic pregnancy screening was not part of the data collection process, it is standard practice to avoid initiating AIT during pregnancy. Any pregnancies occurring during treatment would also have been reported through the corresponding manufacturers' pharmacovigilance systems, as they actively monitor such events.

Skin Prick Testing and Specific Serum IgE Levels to Complete Aeroallergen Extracts

SPT reactivity and specific serum IgE levels (kU/L) to common aeroallergens were determined for mites, molds, pollen, and mammals. The results for the most relevant species are summarized in Supplementary Table S2.

Study Endpoints

The primary outcome of the study was the number of subjects (%) who experienced adverse reactions (ARs) during the administration of AIT overall and classified by severity (local/systemic and other). An AR was defined as any undesirable event that occurred in a patient during the use of a medication and was suspected to be caused by the medication. ARs were classified as local reactions (LRs), systemic reactions (SRs), and other types of reactions. For SCIT, LRs were classified according to the time of onset of the reaction as immediate or delayed if occurring <30 minutes or ≥30 minutes after AIT administration, respectively, and according to the size of the wheal as mild (<5 cm for immediate LRs and <10 cm for late LRs), moderate (5–10 cm for immediate LRs and 10–15 cm for delayed LRs), and severe (>10 cm for immediate LRs and >15 cm for delayed LRs).[18,29,30] For SLIT, LRs were classified according to the grading system for local side effects proposed by Passalacqua et al in 2013, namely grade 1 (mild), grade 2 (moderate), grade 3 (severe) and unknown.[31] SRs were classified according to the WAO 2010 criteria ranging from grade 1 to grade 5, and it was also noted whether it was an immediate or delayed reaction.[32] In addition, this study aimed to explore several secondary outcomes related to the safety, effectiveness, and clinical impact of AIT in patients with severe asthma. A detailed analysis of ARs to AIT was conducted, considering factors such as the degree of asthma control at the time of AIT initiation, baseline and rescue treatments, prior or concomitant use of biologics, sensitization profiles, type and route of AIT, initiation protocol, treatment phase, seasonality, comorbidities, and history of previous AIT reactions.

The study also evaluated changes in AIT protocols following adverse events and other key clinical outcomes in the year before and after AIT initiation, including asthma exacerbations, emergency department visits, hospital admissions, oral corticosteroid use, and spirometric and FeNO levels. Impact on quality of life was measured using the miniAQLQ, and asthma control was assessed using the ACT or CAN (for children) questionnaires. Medication use, both for asthma control and symptom relief, was also recorded over time. Other objectives included analysis of the time between asthma diagnosis and AIT initiation, the type of AIT administered according to sensitization profiles and routes, and the treatments used during adverse reactions. The role of biologics in the management of severe allergic asthma in AIT recipients was also examined.

Statistical Analyses

Sample size

It has been estimated that approximately 1.5% of asthmatic patients who visit the clinic have severe asthma. In children, severe asthma is more common from school age, with a prevalence of 2–5%, with the allergic phenotype being the most common. On the other hand, allergic asthma accounts for about 40–50% of patients with severe asthma (GEMA Guide 5.1).[7,33] On this basis, it was estimated that at least 90 patients would need to be included. With 90 patients and an expected adverse event rate of 80%,[18,29,30,34] the amplitude of the 95% confidence interval would be 16.4 percentage units. The percentage of expected adverse events in this type of population is unknown, so the data obtained from the general asthmatic population were extrapolated.

Data Analysis

Descriptive analyses were conducted for all collected variables. Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using measures of central tendency and dispersion (ie, mean, standard deviation, median, 25th (Q1) and 75th (Q3) percentiles, and extreme [minimum and maximum] values). When statistical analysis of differences between groups were of interest: (i) for subgroup analysis of categorical variables, Chi-square tests or Fisher's exact tests were conducted; for paired data, McNemar's test was used for dichotomous variables or marginal homogeneity test for polytomous variables; (ii) for subgroup analysis of numerical variables, independent samples *T*-test, one-way ANOVA, or non-parametric tests like Wilcoxon-Mann–Whitney or Kruskal–Wallis tests were performed; for paired data, paired T-tests or Wilcoxon non-parametric tests were used. When analyzing the relationship between variables: (i) for dichotomous outcome variables, logistic regression was performed with the outcome variable as the dependent variable and sociodemographic and clinically relevant variables as independent variables. The odds ratio and its 95% confidence interval were reported; (ii) for continuous outcome variables, linear regression was performed with the outcome variable as the dependent variable and sociodemographic and clinically relevant variables as independent variables. The regression coefficient was reported with its 95% confidence interval. All analyses included the corresponding *p*-value from the statistical test. Statistical analyses were performed using SAS Enterprise Guide v8.3 or higher. A threshold of $p < 0.05$ was considered statistically significant.

Results

Study Population

Between 2018 and 2023, a total of 93 patients meeting the inclusion criteria were included from all 16 participating centers, comprising the study population (database lock date: 22 December 2023). There were 51 females (54.8%) and 42 males (45.2%) and the median (Q1; Q3) age of the population was 40.3 (31.3; 51.7) years (5 patients were younger than 14 years). The full baseline demographic characteristics of the patients are summarized in Table 1. Overall, 37.6% of patients had comorbidities, the most common of which were thyroid disease (37.6%), dyslipidemia (22.9%), and hypertension (20.0%). Only one-third of patients (28.9%) were taking concomitant medications for these comorbidities. Up to 46.2% of patients had

Table 1 Baseline Demographic Characteristics of Patients

Characteristic	Value[A]
Age – years	
Mean (SD)	41.3 (13.9)
Median (Q1; Q3)	40.3 (31.3; 51.7)
Min–max	8.7–67.4
Patients <14 years, n (%)	5 (5.4)
Sex, n (%)	
Male	42 (45.2)
Female	51 (54.8)
Anthropometric data, mean (SD)	
Weight – kg	74.4 (16.0)
Height – cm	166.8 (9.5)
BMI – kg/m^2	26.7 (5.3)
Ethnicity, n (%)	
Europe	84 (90.3)
Middle East	3 (3.2)
Central and South America	6 (6.5)
Employment status[B]	
Active	78 (87.6)
Inactive	11 (12.4)

(*Continued*)

Table 1 (Continued).

Characteristic	Value[A]
Residence, n (%)	
Rural (<5000 inhabitants)	10 (10.8)
Semi-urban (5000–19,999 inhabitants)	11 (11.8)
Urban (>20,000 inhabitants)	72 (77.4)
Place of residence, n (%)	
Madrid	49 (52.7)
Badajoz	15 (16.1)
Barcelona	13 (14.0)
Seville	6 (6.5)
Navarra	6 (6.5)
Guadalajara	4 (4.3)
Living with mammalian pets, n (%)[C]	55 (59.1)
Dog	33 (60.0)
Cat	26 (47.3)
Horse	1 (1.8)
Rabbit	1 (1.8)
Smoking habits, n (%)	
Non-smoker	61 (65.6)
Ex-smoker	20 (21.5)
Current smoker	12 (12.9)
No. of cigarettes per day, mean (SD)[D]	9.1 (6.0)
No. of years smoking, mean (SD)	16.3 (8.1)
Number of packs/years, median (Q1; Q3)	6.8 (2.1–18.1)

Notes: [A]Valid percentages are shown in case of missing data; [B]A total of 4 missing values were reported (n = 89); [C]Percentage of each item calculated on a total of 55 patients; [D]Mean calculated on a total of 12 smoker's patients.
Abbreviations: BMI, body mass index; Q1, first quartile; Q3, third quartile; SD, standard deviation.

other relevant comorbidities, with gastroesophageal reflux (27.9%), obesity (27.9%) and anxiety (23.3%) being the most common, for which the majority of patients (75.6%) were not taking concomitant medications.

Characteristics of Asthma

Regarding asthma characteristics, the median (Q1; Q3) time from diagnosis of severe asthma to initiation of AIT was 1 (0.5–3.0) year. Up to 32 patients (34.4%) had experienced severe asthma exacerbations and 33 (35.5%) had received at least one course of systemic corticosteroids in the last year. The median (Q1; Q3) cumulative total corticosteroid dose (in prednisone equivalents) over the last year was 210 (150; 520) mg. Notably, no patients were hospitalized for severe asthma complications in the year prior to AIT initiation (Table 2). Almost all patients had rhinitis (96.8%), with about half of the cases being perennial (54.4%) and most being moderate (64.4%) and persistent (65.6%) (Supplementary Table S3). The median (Q1; Q3) asthma control score was 21.0 (18.0; 23.0) in adults (ACT) and 21.0 (17.0; n.d.) in children <14 years of age (CAN), indicating good asthma control (Supplementary Table S4). Patients with severe asthma had overall normal lung function. The mean (SD) blood eosinophil count was 392.7 (266.8) cells/μL, and the mean (SD) serum total IgE level was 609.1 (768.4) kU/mL.

Pre-Immunotherapy and Immunotherapy Treatment

Before starting AIT, most patients (94.6%) received inhaled corticosteroids (ICS) or a maintenance combination, mainly high-dose corticosteroids in combination with long-acting beta agonists (LABA) (76.3%). Up to 67.7% of patients received maintenance medications, most commonly anti-leukotrienes (92.1%) and long-acting muscarinic antagonists (LAMA) (46.0%). Similarly, 36.6% of patients used rescue short-acting bronchodilators (SABA) or ICS/LABA inhalers

Table 2 Characteristics of Severe Asthma

Characteristic	Value[A]
Time from asthma diagnosis to date of AIT initiation, median (Q1; Q3) – yr	6 (1.5–16.0)
Time from severe asthma diagnosis to date of AIT initiation, median (Q1; Q3) – yr[B]	1 (0.5–3.0)
Seasonal predominance of symptoms, n (%)	30 (32.3)
Severe asthma exacerbations in the last year, n (%)[C]	32 (34.4)
Allergens	17 (53.1)
Infection	4 (12.5)
Drugs	2 (6.3)
Unknown	9 (28.1)
Number of cycles of systemic glucocorticoids received in the last year, n (%)	
0	60 (64.5)
1	18 (19.4)
2	8 (8.6)
3	4 (4.3)
4	1 (1.1)
5	1 (1.1)
12	1 (1.1)
Total cumulative corticosteroid dose in the last year (prednisone), median (Q1; Q3)	210 (150; 520)
Number of visits to the emergency department in the last year, mean (SD)[D]	1.9 (2.2)
Number of admissions in the last year, mean (SD)	0 (0.0)

Notes: [A]Valid percentages are shown in case of missing data; [B]Four patients diagnosed after baseline (n = 89); [C]Percentage of each item calculated on a total of 32 patients; [D]Mean calculated over the number of patients with at least one glucocorticoid cycle.
Abbreviations: Q1, first quartile; Q3, third quartile; SD, standard deviation; yr, years.

in the last 4 weeks before starting AIT, with salbutamol 100 µg being the most common (73.5%). Fifteen patients (16.1%) were receiving concomitant biologic therapy, including 14 (93.3%) treated with omalizumab (6 of whom received AIT with native extracts and 8 with polymerized extracts) and 1 patient (6.7%) treated with mepolizumab (who was receiving AIT with polymerized extracts).

Most patients (91.4%) received immunotherapy via the subcutaneous route, with treatment predominantly following a perennial schedule (95.7%) using mainly native (46.2%) or chemically modified (41.9%) allergen extracts. In terms of allergen type, 42 patients (45.2%) received AIT against animal epithelia (Table 3). The most common allergen was cat epithelium (n = 18), followed by dog epithelium (n = 6) and other animal epithelia, such as rabbit or horse (n = 3). In 15 cases, the specific animal source was not documented in the clinical records. Regarding the type of extract administered to these 42 patients, 32 received AIT with native extracts, 5 received AIT with chemically modified extracts. In 5 cases, the type of extract was not documented in the clinical records.

Table 3 Type of Allergen Immunotherapy

AIT characteristics	Frequency, n (%)
Administration schedule	
Pre-seasonal	3 (3.2)
Pre-coseasonal	1 (1.1)
Perennial	89 (95.7)
Route of administration	
Subcutaneous	85 (91.4)
Sublingual drops	2 (2.2)
Sublingual tablets	6 (6.5)

(*Continued*)

Table 3 (Continued).

AIT characteristics	Frequency, n (%)
Type of build-up phase	
Conventional	25 (26.9)
Grouped	37 (39.8)
Rush	29 (31.2)
Ultrarush	2 (2.2)
Type of AIT	
Native SCIT	43 (46.2)
Modified SCIT	39 (41.9)
SLIT	9 (9.7)
Not specified	2 (2.2)
Specific AIT by allergen	
Mites	27 (29.0)
Animals	42 (45.2)
Pollen	24 (25.8)
Molds	10 (10.8)
Occupational	1 (1.1)

Abbreviations: AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Safety

A total of 34 ARs were reported in 21 patients (22.6% of the total population), including 19 adults and 2 children. Of these patients, 14 (66.7%) experienced only one event, 4 (19.0%) experienced two events, and 3 (14.3%) experienced three or more. By type of AIT, ARs occurred in 17 patients (81.0%) who received SCIT—11 treated with a native allergen extract and 6 with a chemically modified extract—and in 4 patients (19.0%) who received SLIT tablets. By treatment schedule, ARs were reported in 7 patients (33.3%) on a conventional schedule, 9 (42.9%) on a clustered schedule, 4 (19.0%) on a rush schedule, and 1 (4.8%) on an ultrarush schedule.

With regard to LRs, a total of 18 events were reported in 15 patients (16.1% of the total population), including 14 adults and 1 child. Of these patients, 12 (80.0%) experienced a single LR, while 3 (20.0%) experienced two. By type of AIT, 11 LRs were reported in 10 patients (66.7%) who received SCIT—8 in patients treated with a native allergen extract and 3 in those treated with a chemically modified extract—and 7 LRs were reported in 5 patients (33.3%) who received SLIT tablets. Among those treated with SCIT, 3 patients (30.0%) experienced 4 immediate LRs—2 mild (2 patients) and 2 moderate (1 patient)—while 7 patients (70.0%) experienced 7 delayed LRs—5 mild (5 patients) and 2 moderate (2 patients). Among those receiving SLIT, 4 patients experienced 5 immediate LRs, and 1 patient experienced 2 delayed LRs. Of the LRs related to SLIT, 4 were grade 1 (3 patients), 1 was grade 2 (1 patient), and 2 were grade 3 (1 patient). A total of 12 LRs occurred during the initiation phase (11 patients, 73.3%) and 6 during the maintenance phase (5 patients, 33.3%). By treatment schedule, LRs were reported in 6 patients (40.0%) on a conventional schedule, 5 (33.3%) on a clustered schedule, 3 (20.0%) on a rush schedule, and 1 (6.7%) on an ultrarush schedule. In 9 of the 15 patients (60.0%), no intervention was needed, and AIT continued unchanged.

Regarding SRs, a total of 16 events were reported in 8 patients (8.6% of the total population), including 7 adults and 1 child. Of these patients, 3 (37.5%) experienced a single SR, 3 (37.5%) experienced two, 1 (12.5%) experienced three, and 1 (12.5%) experienced four. All patients who experienced ≥1 SR received SCIT with a native cat epithelium allergen extract, except for one patient who received SCIT with a chemically modified mite allergen extract. By type of AIT, all SRs occurred in patients receiving SCIT—5 treated with a native allergen extract and 3 with a polymerized extract. Six of these patients (75.0%) experienced 13 immediate SRs, while 2 patients (25.0%) experienced 3 delayed SRs. In terms of severity, 3 patients (37.5%) experienced 4 grade 1 SRs, 6 patients (75.0%) experienced 9 grade 2 SRs, 1 patient (12.5%) experienced 2 grade 3 SRs, and 1 patient (12.5%) experienced 1 grade 4 SR. Twelve SRs occurred during the initiation

phase (5 patients, 62.5%), and 4 SRs occurred during the maintenance phase (3 patients, 37.5%). Symptomatic treatment was required in 6 patients (75.0%), including 5 (62.5%) treated with systemic corticosteroids, 4 (50.0%) with antihistamines, 4 (50.0%) with adrenaline, 4 (50.0%) with rescue inhalers, and 1 (12.5%) with other inhalers. Six of the eight patients (75.0%) continued AIT with a modified regimen. Only three patients suspended treatment. The safety results are summarized in Table 4.

Throughout the study period, a total of 17 temporary treatment interruptions were reported in 15 patients (16.1%). The main reasons were physician decisions unrelated to safety or efficacy (20.0%) and other factors (66.7%), such as

Table 4 Adverse Reactions by Type of Allergen Immunotherapy

	Local Reactions		Systemic Reactions	
	No. Patients (%)	**No. Reactions**	**No. Patients (%)**	**No. Reactions**
Total reactions	15 (16.1)	18	8 (8.6)	16
Adults	14 (15.0)	17	7 (7.5)	14
Pediatric	1 (1.1)	1	1 (1.1)	2
Number of reactions[A]				
0	78 (83.9)	0	85 (91.4)	0
1	12 (12.9)	12	3 (3.2)	3
2	3 (3.2)	6	3 (3.2)	6
≥3	0 (0.0)	0	2 (2.1)	7
Type of immunotherapy causing the event[B]				
SCIT, native extract	8 (53.3)	8	5 (62.5)	12
SCIT, chemically modified extract	3 (20.0)	3	3 (37.5)	4
SLIT	4 (26.7)	7	0 (0.0)	0
Phase of treatment[B]				
Initiation phase	11 (73.3)	12	5 (62.5)	12
Maintenance phase	5 (33.3)	6	3 (37.5)	4
Treatment regimen[B]				
Rush	6 (40.0)	6	6 (75.0)	12
Conventional	10 (66.7)	12	3 (37.5)	4
Type of local/systemic reaction[B]				
SCIT				
Immediate (<30 min)	3 (20.0)	4	6 (75.0)	13
Delayed (≥30 min)	7 (46.7)	7	2 (25.0)	3
SLIT				
Immediate (<30 min)	4 (26.7)	5	0 (0.0)	0
Delayed (≥30 min)	1 (6.7)	2	0 (0.0)	0
Number of immediate reactions[B]				
1	2 (13.3)	2	2 (25.0)	2
2	1 (6.7)	2	2 (25.0)	4
≥3	0 (0.0)	0	2 (25.0)	7
Number of late reactions[B]				
1	7 (46.7)	7	1 (12.5)	1
2	0 (0.0)	0	1 (12.5)	2
Size of LR with SCIT, mean (SD)[C]	8.5 (3.5)	6	N/A	N/A
Classification of immediate LR with SCIT[B]				
Mild (<5 cm)	2 (13.3)	2	N/A	N/A
Moderate (5–10 cm)	1 (6.7)	2	N/A	N/A
Classification of delayed LR with SCIT[B]				
Mild (<10 cm)	5 (33.3)	5	N/A	N/A
Moderate (10–15 cm)	2 (13.3)	2	N/A	N/A

(*Continued*)

Table 4 (Continued).

	Local Reactions		Systemic Reactions	
	No. Patients (%)	**No. Reactions**	**No. Patients (%)**	**No. Reactions**
Classification of LR with SLIT[B]				
Grade 1	3 (20.0)	4	N/A	N/A
Grade 2	1 (6.7)	1	N/A	N/A
Grade 3	1 (6.7)	2	N/A	N/A
Classification of SR with SCIT[B]				
Grade 1	N/A	N/A	3 (37.5)	4
Grade 2	N/A	N/A	6 (75.0)	9
Grade 3	N/A	N/A	1 (12.5)	2
Grade 4	N/A	N/A	1 (12.5)	1
Severe reactions[B]	0 (0.0)	0	1 (12.5)	2
Type of severity				
Life threatening	0 (0.0)	0	1 (12.5)	1
Medically significant	0 (0.0)	0	1 (12.5)	1
Treatment of symptoms of systemic reactions[B]	3 (20.0)	3	6 (75.0)	14
Antihistamines	2 (13.3)	2	4 (50.0)	7
Systemic corticosteroids	0 (0.0)	0	5 (62.5)	9
Adrenaline	0 (0.0)	0	4 (50.0)	5
Rescue inhalers	0 (0.0)	0	4 (50.0)	8
Other				
Antibiotics	1 (6.7)	1	0 (0.0)	0
Inhalers	0 (0.0)	0	1 (12.5)	1
Factors associated with the adverse reaction[B,D,E]	1 (6.7)	1	2 (25.0)	2
Action taken[A]				
AIT maintained, unchanged	9 (60.0)	11	2 (25.0)	2
AIT maintained, regimen modified	4 (26.7)	5	6 (75.0)	11
AIT suspended	1 (6.7)	1	3 (37.5)	3
AIT maintained, different administration route	1 (6.7)	1	0 (0.0)	0
Previous systemic reactions with AIT[B]	2 (13.3)	3	4 (50.0)	8
Type of treatment for previous systemic reaction				
SCIT	1 (6.7)	2	4 (50.0)	8
SLIT (tablets)	1 (6.7)	1	0 (0.0)	0

Notes: [A]Percentages calculated on the total number of patients (n = 93); [B]Percentages calculated on the number of patients with local (n = 15) or systemic (n = 8) adverse reactions; [C]Mean calculated on the number of LR with SCIT (n = 6); [D]The patient with a LR had already similar episodes and had not slept with concern about starting immunotherapy; [E]The two patients with SR had poor asthma control and possible viriasis.

Abbreviations: AIT, allergen immunotherapy; LR, local reaction; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SR, systemic reaction.

patient choice, lack of vaccine stock, dosing delays, or inability to attend the treatment center. There were also 25 permanent treatment discontinuations in 23 patients (24.7%). The primary reasons were adverse reactions (21.7%), physician decisions not related to safety or efficacy (17.4%), and other causes (65.2%), including patient decision, lack of efficacy, loss to follow-up, or poorly controlled asthma (Supplementary Table S5).

Bivariate analyses to identify characteristics associated with the occurrence of SRs showed that the use of rescue SABA or ICS/LABA inhalers in the last 4 weeks ($p = 0.048$) and the level of asthma control (poorly controlled asthma; $p = 0.004$) were significantly associated with the occurrence of SRs (Figure 1).

No significant differences were observed between the incidence of SRs and patient age, type of immunotherapy — neither type of allergen extract nor route of administration—, or schedule.

Clinical Improvement with AIT

Significant improvements from baseline were observed in FeNO, with mean (SD) values decreasing from 51.0 (51.6) to 40.6 (49.8) ppb after 6 months of AIT ($p = 0.049$) and also of FEV_1, with mean (SD) values increasing from 92.4%

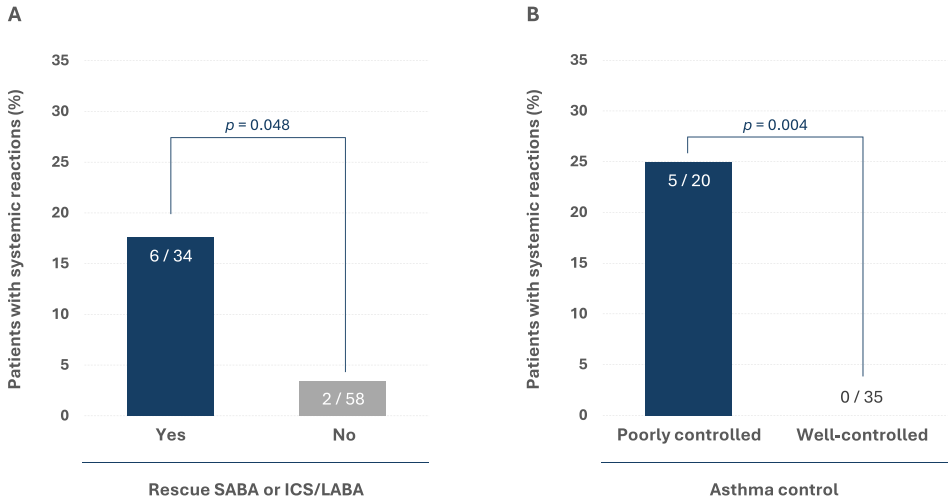

Figure 1 Variables associated with the occurrence of systemic reactions. (**A**) Use of rescue treatment with short-acting beta agonists (SABA) or inhaled corticosteroids (ICS)/long-acting beta agonists (ICS/LABA) (p = 0.048; Fisher's exact test). (**B**) Asthma control (p = 0.004)*. The number of positive patients out of the total number of patients analyzed in each group is indicated within the histogram bars.

(19.7) to 105.8% (18.8) of predicted value after 12 months of AIT (p = 0.028). Although a comparative analysis of the Mini-AQLQ quality of life questionnaire was not possible due to the small number of patients, numerical differences between baseline and post-AIT scores were assessed using paired data only. Mini-AQLQ scores were numerically higher at 1, 2, and 3 years after initiating AIT compared to baseline, suggesting a trend toward improved quality of life. While similar proportions of patients were on asthma maintenance therapy before and after starting AIT (68.8% vs 66.7%; p = 0.815), the proportion of patients not receiving rescue medication for asthma was significantly lower after starting AIT compared to the proportion before starting AIT (36.6% vs 22.6%; p = 0.019). There was also a decreasing trend in the number of patients using biologic treatments, from 15 patients before AIT, mainly omalizumab (n = 14), to none at five years (Figure 2). Immunotherapy was also associated with a 75.8% reduction in the number of emergency visits, which decreased from 62 before AIT initiation to 15 after treatment began (Figure 3).

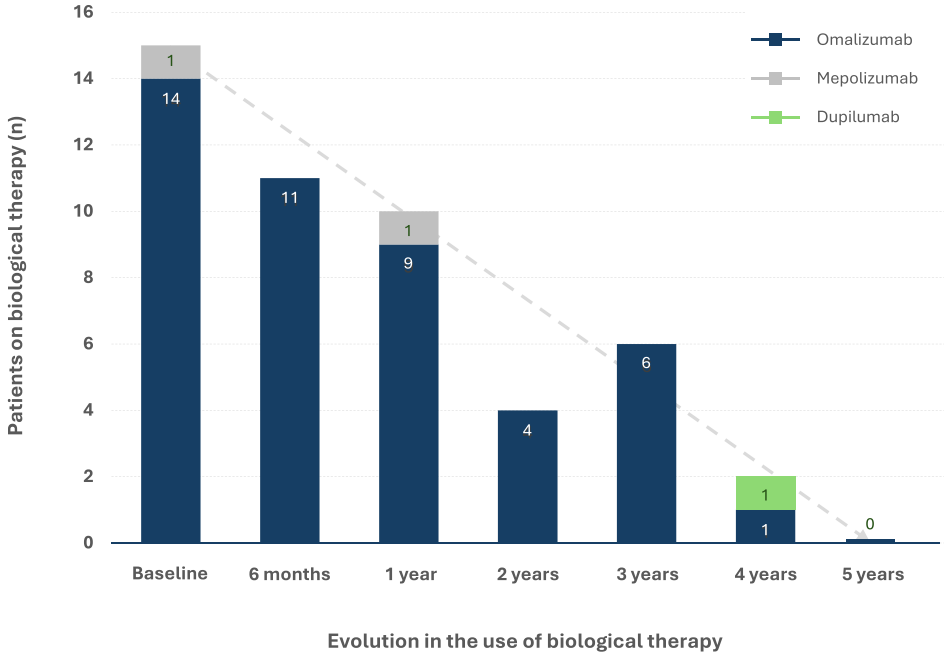

Figure 2 Effect of allergen immunotherapy (AIT) in the use of biologic treatments in the study population. A total of 15 patients were initially receiving concomitant biologic treatments, 14 of them omalizumab and only 1 mepolizumab. After 5 years of AIT, all patients were free of biologics.

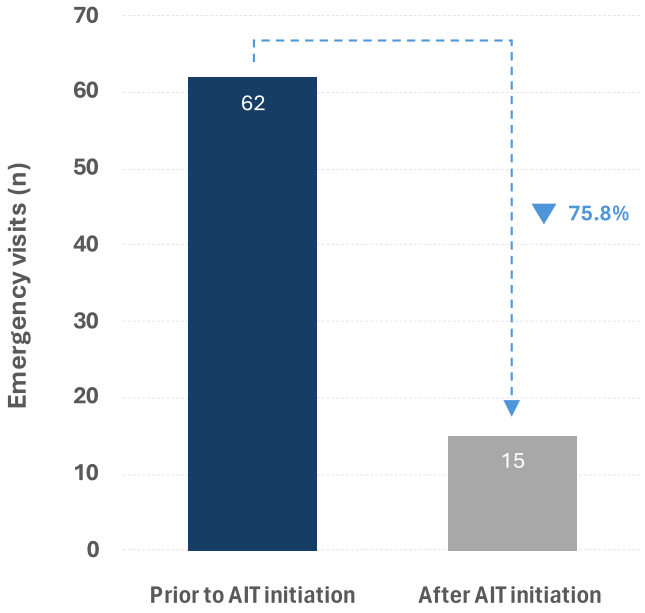

Figure 3 Effect of allergen immunotherapy (AIT) on the number of emergency room visits. The figure shows the total number of visits in the year before versus after initiation of AIT. A reduction of 75.8% in the total number of visits was observed, from 62 visits before the start of AIT to 15 visits after the start of AIT. The number of visits is indicated within the histogram bars.

Discussion

The role of AIT in the management of severe asthma has long been debated, as it is considered a major risk factor for adverse effects—particularly in patients receiving SCIT.[2,14,26,27] Nevertheless, robust evidence is lacking, especially from large, randomized trials, and further research on this topic is needed.[28]

Our results showed that patients with well-controlled severe asthma due to clinically relevant sensitization to one or more specific allergens achieved substantial clinical improvement after receiving AIT in a safe manner, regardless of the type of allergen extract, route of administration, or schedule. Most of the reported SRs were immediate and mild (up to 81% grade 1 and 2 according to WAO 2010 criteria), and occurred with SCIT, predominantly during the initiation phase and mainly on a rush schedule. Despite this, there were 2 serious SRs in 1 patient (1 grade 3 SR and 1 grade 4 SR) and treatment with epinephrine was required in 4 cases, which is a convenient reminder that there is a necessity for AIT, particularly SCIT, to be administered in a clinical setting with experienced personnel to manage adverse reactions, including anaphylaxis.[35] Importantly, most patients who experienced SRs continued AIT treatment, albeit on a different schedule; slightly more than one-third of patients eventually discontinued AIT treatment, with only 21.7% discontinuing due to side effects.

The present study supports the hypothesis that AIT may provide clinical benefits that largely outweigh the risks for patients with severe allergic asthma provided that the disease is controlled according to clinical criteria. Although there is evidence that uncontrolled asthma is a major risk factor for serious and fatal reactions to AIT, particularly SCIT,[2,14,26,27] the spectrum of SRs in patients with severe asthma remains poorly understood.[28] Further studies are needed to define and compare the overall risk of severe SRs in these patients with that of patients without severe asthma or no asthma.[36]

It is important to distinguish, particularly in the context of a real-world evidence study, between patients with 'difficult-to-treat' asthma, often related to extrinsic factors such as poor treatment adherence or incorrect inhaler technique, and those with "severe treatment-refractory" asthma, where patients remain inadequately controlled despite continuous monitoring and optimized treatment within specialized asthma units. However, considerable heterogeneity in definitions exists across different countries.[37] Due to this variability and the retrospective nature of our study, we were unable to accurately differentiate between these two patient subpopulations. Accordingly, patients were categorized, following the GINA guideline definitions, based on treatment with high-dose ICS in combination with at least one additional controller medication, typically a LABA.

https://doi.org/10.2147/JAA.S546044

Despite the known differences in immunotherapy approaches compared to Europe, results from a recent retrospective cohort study of 65,855 American patients who received SCIT between January 2015 and December 2019, including 1072 patients with severe asthma, showed that there was no difference in the rates of grade 3 or 4 SRs between patients with severe asthma and those without asthma, or in the rates of total SRs between severe asthma and no severe asthma (the observed increase in total SRs between patients with and without asthma was driven by grade 1 and 2 SRs). Using binary logistic regression analyses, the authors found that only age (mean age [SD] of the population was 32.5 [20.4] years) was a statistically significant predictor of WAO grade (ie, grades 1 and 2 vs grades 3 and 4), such that the likelihood of having a SR with a WAO grade of 3 or 4 increased with age ($\beta = 0.012$, $p = 0.007$; odds ratio [OR] 1.013; 95% CI [1.003–1.022]). Notably, many patients with mild persistent, moderate, and severe asthma in this study had uncontrolled disease, suggesting that a history of severe asthma per se or a history of poorly controlled asthma is not associated with increased rates of grade 3 or 4 SRs and, according to the authors, may not necessarily be a contraindication to initiating SCIT. In our study, however, we did not find an association between patient age and the incidence of SRs, possibly due to the much lower proportion of pediatric patients in our population than in the American study (5.4% vs 33.6%).[38] The results of this study highlight the importance of disease control in patients with severe asthma to be candidates for AIT.

Asthma control does not always correlate with the severity of the underlying disease, but rather with the degree to which disease manifestations (ie, symptoms between episodes, lung function, and exacerbations) are absent or maximally reduced by therapeutic interventions and reflects how well treatment goals are being met and therefore the adequacy of asthma management.[39] Despite having well-controlled asthma at the start of the study, some patients experienced a loss of control during treatment. We found that patients with poorly controlled disease—indicated by a low score on the asthma control questionnaire—and those who required rescue medication (ie, SABA or ICS/LABA inhalers) in the four weeks preceding a scheduled immunotherapy dose were significantly more likely to experience SRs. This underscores the importance of regularly assessing asthma control—not only before initiating immunotherapy but also throughout the treatment period, especially during the designated interval prior to each scheduled dose. Overall, patients with allergic asthma who have difficulty in maintaining control despite medication or avoidance strategies, or who require high or multiple doses to do so, may be suitable candidates for AIT, provided their asthma is stable at the time of administration. Patients should therefore be asked to complete an ACT questionnaire and to report on the use and frequency of rescue medications —particularly short-acting bronchodilators and oral corticosteroids— in the 4 weeks prior to each immunotherapy administration, both as surrogates for disease control. The ACT questionnaire offers a straightforward and reliable tool for assessing asthma control, not only to confirm the therapeutic indication, but also before each scheduled AIT dose and throughout ongoing treatment. Nevertheless, physicians must be aware that there may be discrepancies between the patient's and healthcare professional's assessment of the patient's level of disease control, mainly due to the different understanding of the term "asthma control" between the two groups.[40] As recommended by current guidelines, a partnership between the patient and the health care provider is necessary to increase the patient's confidence in their role in correct self-assessment and self-management of the disease, and thus reduce asthma morbidity and, through shared decision making, improve outcomes.[41–43] Information on the use and frequency of rescue medications is an important objective factor in assessing the level of symptoms and therefore asthma control, as patients who require rescue medications are at increased risk of exacerbations and systemic reactions to aeroallergens, higher rates of hospitalization and, in the case of medication abuse, higher rates of death.[44,45]

In addition to being safe, our results showed that AIT in patients with severe controlled asthma has clinical benefits similar to those described in patients with mild to moderate asthma.[14,16,46] In particular, AIT resulted in significant improvements in lung function and, importantly, a significant reduction in the need for rescue asthma medication.

As the mechanism of action of the available biologics for the treatment of asthma —essentially targeting inflammation—, are complementary to that of the AIT, their combination appears to be a highly relevant approach for bringing the benefits of AIT to patients who are a priori not eligible for it. Evidence generated from different studies has shown that pretreatment with biologics enables initiation and continuation of AIT in patients with moderate-to-severe allergic asthma in a safe manner. The combined treatment has been shown to induce a significantly higher improvement of asthma control, which persists after cessation of the biological therapy, and also a reduction of the levels of maintenance pharmacotherapy.[15] In our study, all 15 patients on biologic therapy at baseline, largely omalizumab, were biologic-free

after 5 years of AIT. Although being aware of the relatively small number of patients on biologics, these results clearly evidenced the disease-modifying effects of AIT inducing the so-called "off-treatment asthma remission",[47] even in this difficult to treat population. It was also found that AIT was associated with a significant reduction in the mean number of emergency department visits per year. Due to the disease-modifying properties of AIT, sustained clinical benefit after discontinuation of immunotherapy has been widely reported, although there are currently no accurate diagnostic tools to predict which patients will achieve sustained clinical remission after discontinuation of AIT, and therefore the duration of treatment should be determined by the treating physician in conjunction with the patient, taking into account the risk-benefit ratio of treatment.[48]

The study has limitations that should be acknowledged, including its retrospective nature. In this respect, real-world retrospective database studies are considered complementary to prospective clinical trials, as the latter are subject to bias because patients selected for AIT may differ from other patients with allergy. In addition, retrospective studies have the advantage of generally allowing the observation of larger, more comprehensive patient populations over longer periods of time than clinical trials.[49–51] The study may have missing data for certain assessments or participants at specific visits, particularly during the COVID-19 pandemic. In addition, there was some variability in data collection between centers, which is an intrinsic limitation of this type of studies. Regarding the study population, the small sample size — particularly the low number of pediatric patients— precluded reliable subgroup analyses. As such, we do not intend to directly generalize our findings to the broader pediatric population, and further research involving larger pediatric cohorts is warranted. In addition, more than half of the patients were enrolled in centers located in Madrid, which may be a potential source of bias due to the presence of local specific allergens. Due to its retrospective nature, the study did not have a control group for direct comparison. Nonetheless, we understand that studies of this type constitute a valuable part of the evidence ecosystem, particularly for real-world insights, safety surveillance, and hypothesis generation, and can provide information about causal treatment effects by extrapolating expected outcomes in the missing untreated arm. As other authors have suggested, single-group studies rely on implicit or historical comparisons as a surrogate for an ideal comparison group. Despite these clear limitations, this type of studies still play an important role in generating new hypotheses to be tested by more formal, experimental study design.[52–56]

Conclusions

This study reinforces the favorable safety profile of AIT in patients with well-controlled severe allergic asthma when administered in a specialized clinical setting. The findings support the use of AIT as a viable therapeutic option in this population—even in those receiving concomitant biological therapy—provided asthma control is maintained. These results highlight the potential role of AIT beyond its traditional indications. However, given the limitations of the study cohort, further large-scale, long-term prospective studies are warranted to confirm these findings and to inform future asthma management guidelines.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials. Any other information related to this study is available from the corresponding author, upon reasonable request.

Ethics Approval and Informed Consent

The study protocol was approved by the Clinical Research Ethics Committee of Navarra in 2022 (EO_2022/15). All methods and analyses were performed in compliance with local legal and regulatory requirements, as well as generally accepted research practices described in the latest version of the Declaration of Helsinki and the International Conference of Harmonization-Good Clinical Practice Guidelines. All patients provided written informed consent to participate in the study. For participants under 18 years of age, informed consent was obtained from a parent or legal guardian. All data included in this study were collected as part of routine clinical practice and analyzed retrospectively. In compliance with Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, all data included in this study

were anonymized, the basic regulation on patient autonomy and rights and obligations regarding information and clinical documentation, as well as current and applicable regulations.

Consent for Publication

On behalf of all authors, AIT consents to publication of all materials contained in this submission.

Acknowledgments

The authors would like to thank the principal investigators of all the participating centers, Paula Galván Blasco, Alicia Habernau Mena, Alicia Enríquez Mata, Teresa Robledo Echarren, Irán Sánchez Ramos, Paula López González, Beatriz Nuñez Acebedo, Inés Torrado Español, Ignacio Esteban Gorgojo, Marcela Valverde Monge, Ana Rosado Ingelmo, and to the Medical Affairs Unit of LETI Pharma for their support.

Author Contributions

All authors have made a substantial contribution to the work described in this article, including conception, design, execution, acquisition of data, analysis and interpretation, or all of these; have been involved in drafting, revising, or critically reviewing the article; have given final approval of the version to be published; have agreed on the journal to which the article will be submitted; and agree to take responsibility for all aspects of the work.

Funding

There is no funding to report.

Disclosure

AIT has received consultancy and speaking honoraria from Allergy Therapeutics, ALK-Abelló, Diater, Glaxo, Inmunotek, InnoUp, ITAI, LETI Pharma, Probelte, and Roxall. She has participated in research projects sponsored by Allergy Therapeutics, ALK-Abelló, Diater, Inmunotek, InnoUp, and Roxall. She also reports payment from RTC2019-006977-1 (Retos-Colaboración 2019 del Ministerio de Ciencia e Innovación). IP 2020-2024 paid to her institution. JDR has received speaker honoraria from AstraZeneca, Bial, Chiesi, GlaxoSmithKline, and Sanofi, as well as research grants from AstraZeneca within the past three years. He has also received meeting travel assistance from Sanofi and Menarini. EGM has received consultancy and/or speaking fees from Allergy Therapeutics, ALK-Abelló, AstraZeneca, Diater, Faes Pharma, Gebro, GlaxoSmithKline, Sanofi, Inmunotek, LETI Pharma, Novartis, Roxall, and Stallergenes Greer. She has also participated in research projects sponsored by Allergy Therapeutics, ASAC, LETI Pharma, and Roxall. JDO has received consulting and speaking fees over the past three years from ALK-Abelló, AstraZeneca, Chiesi, GlaxoSmithKline, LETI Pharma, Novartis, Mundipharma, Sanofi, and TEVA. Over the past three years, LSR has received honoraria for speaking at meetings sponsored by Allergy Therapeutics, Sanofi, AstraZeneca, Stallergenes-Greer, and GlaxoSmithKline. She also reports payment for manuscript preparation from LETI Pharma. The authors report no other conflicts of interest in this work.

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