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Allergen-Specific Immunotherapy and Biologics

Long-Term Effect of Allergen Immunotherapy in Responder Local Allergic Rhinitis Patients: Symptom Control, and Prevention of Asthma and Allergic Sensitizations

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Keywords: allergen immunotherapy | asthma | local allergic rhinitis | long-term effect | prevention

ABSTRACT

Background: Clinical trials (CTs) have shown that allergen immunotherapy (AIT) is effective for local allergic rhinitis (LAR) while treatment is ongoing. However, its long-term effects remain unknown. This study investigates the long-term clinical and preventive effect of AIT in responder LAR patients.

Methods: LAR patients obtaining a clinical benefit from 1-year CT of subcutaneous AIT were enrolled in this 10-year follow-up study (AIT cohort). All completed a full 3-year AIT course and were followed for additional 7 years. A matched group of LAR patients who did not receive AIT (non-AIT cohort) was followed over the same period. Primary outcomes included nasal-ocular symptom scores (visual analogue scale, VAS), reliever medication use and medication-free days (MFD). Secondary outcomes were asthma incidence, asthma control (asthma control test, ACT), lung function (FEV_1), quality of life (QoL), emergency visits,

Abbreviations: ACT, asthma control test; AIT, allergen immunotherapy; AR, allergic rhinitis; DP, *Dermatophagoides pteronyssinus*; ER, emergency room; GP, grass pollen; HDM, house dust mites; HR, hazard ratio; ITT, intention-to-treat; LAR, local allergic rhinitis; LOCF, last observation carried forward; MCID, minimal clinically important difference; MFD, medication free days; NAC, nasal allergen challenge; NAC-M, nasal challenge with multiple allergens; NAC-S, nasal challenge with single allergen; OR, odds ratio; PP, *Phleum pratense*; QoL, quality of life; RDBPCCT, randomized double-blind placebo-controlled clinical trial; RQLQ, rhinitis quality of life questionnaire; RR, relative risk; SCIT, subcutaneous immunotherapy; sIgE, allergen-specific IgE; sIgG4, allergen-specific IgG4; SPT, skin prick test; VAS, visual analogue scale.

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new sensitizations detected by nasal allergen challenge (NAC), and the analysis of the minimal clinically important difference (MCID). Assessments were conducted at baseline and at years 1, 3, 5, 7, and 10.

Results: Sixty-six patients were included (AIT $n=32$; non-AIT $n=34$). The AIT cohort showed a sustained reduction in nasal-ocular symptoms from year 1 ($p<0.001$) and significantly more MFD from year 3 ($p<0.001$). Asthma developed in 40.7% of non-AIT vs. 8.0% of AIT patients ($p=0.021$). New sensitizations occurred in 38.2% of non-AIT and 6.3% of AIT patients ($p=0.002$). FEV_1 improved in the AIT cohort and declined in non-AIT ($p<0.001$). QoL and emergency visits also favored AIT.

Conclusion: AIT induces a sustained clinical improvement and prevents the onset of asthma and local sensitizations in responder LAR patients.

1 | Introduction

Local allergic rhinitis (LAR) is defined by a clinical history suggestive of allergy, a negative result in atopy tests (skin prick test (SPT) and serum allergen-specific (s)IgE) and a positive response to the nasal allergen challenge (NAC) [1]. LAR represents an independent disease phenotype affecting 16%–25% of non-atopic children and adults with chronic rhinitis [2, 3], and follows a natural course towards the aggravation and the association of comorbidities (especially asthma) [4]. A bronchial counterpart of LAR, known as local allergic asthma, has also been described [5, 6]. Moreover, 36% of LAR cases start during childhood, and the disease is associated with a significant quality of life (QoL) impairment and a reduced school and job performance [4].

Both LAR and atopic allergic rhinitis (AR) are characterized by the synthesis of sIgE in the nasal mucosa through the sequential switching of IgG-producing B cells [7]. After sensitizing resident mast cells, the remaining sIgE molecules reach the blood stream where they bind to IgE receptors expressed in circulating basophils [8]. AR patients synthesize enough sIgE to saturate peripheral basophils and to reach dermal mast cells, thus giving positive SPT results [7]. Conversely, the amount of sIgE produced by LAR individuals is not sufficient for basophil saturation, possibly because IL-9 (a less potent stimulus than IL-4) is the cytokine driving class switch recombination [9]. In any case, both AR and LAR are IgE-mediated conditions.

To date, five randomized double-blind placebo-controlled clinical trials (RDBPCCT) have evaluated the efficacy of allergen immunotherapy (AIT) in adult LAR patients [6, 10–13]. These studies include house dust mites (HDM) [10, 13], grass pollen (GP) [12] and birch pollen [6, 11] and investigate both subcutaneous [6, 10–12] and sublingual routes [13]. These RDBPCCT consistently demonstrate that AIT, while being administered, induces a significant improvement in nasal, conjunctival and bronchial symptoms, reduces the need for rescue medication, improves QoL, and increases the nasal and bronchial tolerance to the allergen. In AR, AIT is also considered a disease-modifying intervention, with sustained benefits after discontinuation [14]. A 3-year course of AIT may prevent the onset of asthma and allergic sensitizations. However, its long-term effects in LAR remain unknown.

The evaluation of asthma incidence and the development of new sensitizations require extended follow-up [14]. Thus, we conducted a 10-year prospective follow-up study in LAR patients who responded to a 1-year RDBPCCT of AIT and who received the same treatment for two additional years under an observational study. A matched cohort of LAR patients who declined AIT was followed in parallel. We evaluated a broad range of outcomes, including symptoms, severity, disease control, QoL, lung function, and asthma onset. We incorporated patient-reported outcomes, healthcare use, and serial NAC to monitor nasal allergen tolerance and new local sensitizations over time.

2 | Methods

2.1 | Study Design and Individuals

This study was designed as a prospective responder-enriched matched cohort. LAR patients completing one of two 1-year RDBPCCT conducted in the Allergy Unit of Hospital Regional Universitario of Malaga, Spain [10, 12], and showing clinical response to AIT, were invited to participate in this 10-year prospective follow-up study (AIT cohort). Response was defined as a ≥50% reduction from baseline in the combined symptom and medication score at month 12 (primary endpoint of the trials). These patients subsequently completed the recommended 3-year course of AIT, in accordance with clinical guidelines. A comparator cohort of patients who declined AIT (non-AIT cohort) was followed prospectively and matched 1:1 by gender, age, rhinitis severity and duration, asthma status, and allergen sensitization profile. Both cohorts were assessed under identical protocols between January 2014 and December 2024. The responder-enriched design was meant to evaluate the persistence of the clinical benefit after treatment discontinuation, a key component of the disease-modifying capacity classically attributed to AIT.

Individuals aged 18–55 years with moderate-to-severe GP- or HDM-driven LAR were eligible. LAR was defined as a clinical history suggestive of HDM or GP allergy in a patient with negative SPT and undetectable serum sIgE to any aeroallergen, and a positive response to the nasal challenge with *Dermatophagoides pteronyssinus* (DP) or *Phleum pratense* (PP) [1].

Exclusion criteria included positive nasal challenge to allergens other than DP or PP, severe and/or uncontrolled oncologic, metabolic, heart, respiratory (including asthma), inflammatory or systemic conditions, chronic therapy with oral β-blockers, hypersensitivity to subcutaneous immunotherapy (SCIT) components other than the allergen, inability to comply with procedures, and pregnancy.

All participants provided informed written consent. The study protocol was approved by the Local Ethics Committee and conducted according to the Declaration of Helsinki.

2.2 | Allergen Immunotherapy

Subjects in the AIT cohort were administered either GP-SCIT (Depigoid PP; Laboratorios LetiPharma, Spain) or HDM-SCIT (Pangramin Plus DP; ALK, Spain). Monthly SCIT doses (Depigoid 0.5 mL and Pangramin Plus 0.8 mL) were administered over 3 years: the first year during the RDBPCCT, and the remaining 2 years under an observational study.

Depigoid is a standardized, depigmented and polymerized extract adsorbed into aluminum hydroxide (1000 DPP/mL), containing 35 μg/mL of Phl p 5 [12]. Pangramin Plus is a standardized, aluminum hydroxide-adsorbed depot extract (1000 STU/mL), containing 2 μg/mL each of Der p 1 and Der p 2 [10].

2.3 | Symptomatic Treatment

The intake of symptomatic drugs for rhinitis, conjunctivitis and/or asthma as needed was permitted in both cohorts. Details are provided in the Supporting Information.

2.4 | Clinical Assessment

Assessments were performed at baseline and at the end of years 1 (end of trial), 3 (end of AIT), 5, 7, and 10 (end of follow-up). For the non-AIT cohort, baseline corresponded to the time of recruitment (Figure S1). A description of the tools used and the minimal clinically important difference (MCID) [15–17] for each variable is elaborated in the Supporting Information.

Primary endpoints:

1. Nasal-ocular symptoms (visual analogue scale [VAS]) [18]
2. Use of reliever medication for allergic nasal, conjunctival or bronchial symptoms, as recorded in the patient's diaries (medication score)
3. Medication-free days (MFD), defined as the number of days without intake of symptomatic medication over a year

Patients were instructed to record the use of reliever medication in diaries, which were systematically reviewed at each visit. Any discrepancies were clarified directly with the patient, and data were cross-checked with e-health records. Moreover, data from the regional electronic prescription system were reviewed to validate medication use.

Secondary endpoints:

1. Asthma incidence: asthma diagnosis was conducted according to GINA [19]. Further details are described in the Supporting Information.
2. Asthma control test (ACT) in asthmatics [17].
3. Lung function (FEV1, via forced spirometry) [16].
4. Rhinitis severity (modified ARIA classification) [20].
5. Patients' global perception of evolution: improved, no change or worsened.
6. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [15].
7. Emergency room (ER) visits prompted by nasal, ocular and asthma symptoms.
8. Onset of local sensitizations (detected by NAC).
9. Serum allergen-specific (s)IgG4 and allergen dose tolerated in the NAC.
10. Remission rate (post hoc analysis based on prospectively collected data): remission was determined only when the following criteria were met at ≥ 2 consecutive visits at years 2, 3, 5, 7, and 10:
    a. Clinical remission: symptom- and medication-free
    b. Immunological remission: negative NAC
    c. Complete remission: simultaneous clinical and immunological remission

2.5 | Nasal Allergen Challenge

Two protocols involving bilateral application of standardized allergen extracts (Laboratorios LetiPharma SL, Spain) were used for different outcomes.

A. Single-allergen nasal challenge (NAC-S) [21]: performed at all visits to assess the reactivity to the original sensitizing allergen. Four increasing concentrations of PP 30 HEP/mL or DP 100 HEP/mL (1:1000, 1:100, 1:10, and 1:1) were administrated every 15 min. For each visit, the maximal allergen concentration tolerated (MaxCAT) was recorded.

B. Multi-allergen nasal challenge (NAC-M) [22]: performed at baseline (for exclusion) and at year 3, 5 and 10 (for new sensitizations). This procedure involved sequential application of 4–5 allergens at 1:1 concentration every 15 min. All individuals were tested for *Olea europaea*, *Alternaria alternata* and *Parietaria judaica* (30 HEP/mL each). Additionally, PP and DP were used according to the patient's phenotype. Subjects exposed to furry animals were also challenged with dog or cat allergens (30 HEP/mL).

Monitoring procedures are detailed in the Supporting Information [23].

2.6 | Other Procedures

SPT was performed at baseline and at the end of the study, and serum sIgE and sIgG4 were measured at baseline, year 1, and year 10 (see Supporting Information).

2.7 | Statistical Analysis

Based on previous studies [24], a sample size of 24 patients per cohort was estimated to detect a 30% relative effect of AIT versus control, with an 80% power and a two-sided alpha of 0.05. An intention-to-treat analysis (ITT) using a last

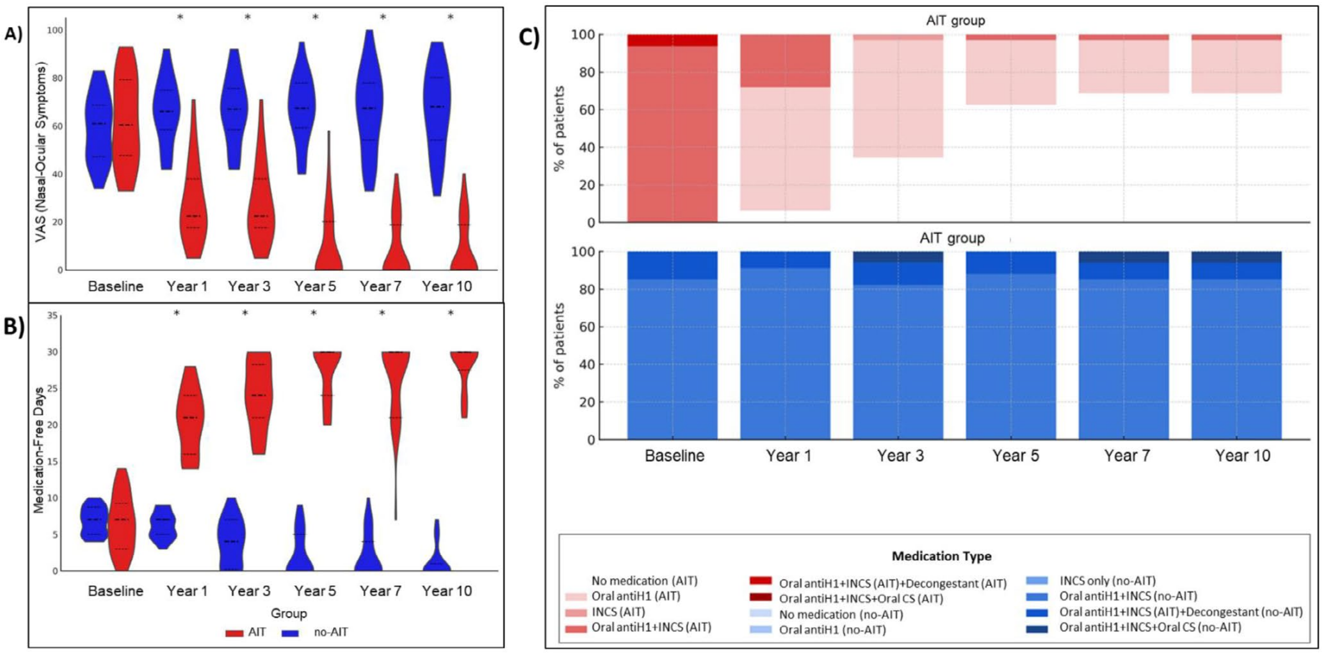

FIGURE 1 | Long-term evolution of nasal-ocular symptoms and use of reliever medication in AIT and non-AIT cohorts. (A) Nasal-ocular symptom scores over the study period assessed by visual analogue scale (VAS 0–100 mm). (B) Percentage of patients achieving a clinically relevant improvement in the symptom score defined a reduction of ≥ 23 mm in VAS, at each evaluation point. (C) Evolution of symptomatic medication use for rhinitis from baseline to year 10, shown as stacked bar charts for the AIT cohort (top) and no-AIT cohort (bottom). Color intensity reflects the different combinations of pharmacologic treatment. AIT, allergen immunotherapy; antiH1, oral H1 antihistamine; CS, corticosteroids; INCS, intranasal corticosteroid; VAS, visual analogue scale.

observation carried forward (LOCF) approach was applied to all outcomes.

Between-group comparisons used Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Within-group changes were analyzed with paired *t*-test or Wilcoxon signed-rank test. Categorical variables were compared using the chi-squared test. Bonferroni correction was applied for multiple comparisons. Treatment effect was calculated as: 100 − ([Active/Control] × 100).

Time-to-event was analyzed using Kaplan–Meier survival curves and the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated by Cox regression. Risk ratios (RR) with 95% CI were calculated for binary outcomes. p values reported are two-tailed, and $p \leq 0.05$ was considered significant. Analyses were performed using Prism 5.01 (GraphPad, San Diego, CA, USA) and R version 4.0.5.

3 | Results

3.1 | Baseline Characteristics

Sixty-six patients were included: 32 in the AIT cohort and 34 in the non-AIT cohort. Patients' disposition is shown in the Supporting Information (Figure S2). Consistent with the matched design, baseline characteristics were similar between groups (Table S1). Logistic regression revealed that asthma at baseline was significantly associated with prior-year ER visits (odds ratio (OR) = 38.25; 95% CI, 4.05–360.87; $p = 0.001$).

3.2 | Primary Endpoints

During the 7 years following AIT discontinuation, the AIT cohort showed a continued reduction in nasal-ocular symptoms (VAS), with significantly lower scores than the non-AIT cohort at every follow-up point (Figure 1A). MFD increased during the first two post-treatment years and remained stable through year 10, with significant between-group differences from year 3 onward (Figure 1B). Both outcomes showed large effect sizes (VAS: $r = -0.856$; MFD: $r = 0.893$; $p < 0.001$).

At baseline, > 85% of patients in both cohorts used oral H1 antihistamines and intranasal corticosteroids (see Supporting Information). In the AIT cohort, 34.4% were medication-free at year 3, rising to 68.8% at years 7 and 10, compared with 0% in the non-AIT group throughout the follow-up period. At year 10 the likelihood of being medication-free was significantly higher in the AIT cohort (RR = 0.01; 95% CI: 0.001–0.12; $p < 0.001$) (Figure 1C).

A summary of primary and secondary outcomes is presented in Table 1 and Figure S3.

3.3 | Secondary Endpoints

3.3.1 | Asthma Incidence and Emergency Room Visits

Among participants without asthma at baseline (25 in AIT, 27 in non-AIT), asthma developed in 2 (8%) and 11 (40.7%) patients, respectively, by year 10. Kaplan–Meier analysis showed a significant

TABLE 1 | Baseline-to-year 10 comparison of primary and secondary outcomes.

	Non-AIT cohort	AIT cohort	Difference AIT vs. non-AIT (range)	p	Effect size, RR, HR (95% CI)
	$N=34$	$N=32$			
Primary outcomes					
VAS year 10, median (range)	68 (31–95)	0 (0–40)	−68 (−31 to −45)	<0.001	$r=-0.856$
Change from baseline	+7 (−3 to 12)	−60.5 (−33 to −53)	−67.5 (−36 to −41)	<0.001	$r=-0.858$
MFD year 10, median (range)	0 (0 to 7)	30 (21 to 30)	+30 (21 to 23)	<0.001	$r=0.893$
Change from baseline	−7 (−4 to −3)	+23 (21 to 16)	+30 (28 to 32)	<0.001	$r=-0.856$
Medication for rhinitis (%)					
None (year 10)	0%	68.8%	+68.8%	<0.001[a]	RR = 47.727 (3.015–755.473)
Change from baseline	0%	+68.8%	+68.8%		
Oral antiH1 use (year 10)	100%	31.1%	−68.7%	<0.001	RR = 0.323 (0.196–0.533)
Change from baseline	0%	−68.7%	−68.7%		
INCS (year 10)	100%	3.1%	−96.9%	<0.001	RR = 0.046 (0.01–0.22)
Change from baseline	+14.7%	−90.7%	−105.4%		
Oral decongest. (year 10)	8.8%	0%	−8.8%	0.239	RR = 0.152 (0.008–2.823)
Change from baseline	−5.9%	−6.3%	−0.4%		
Oral CS (year 10)	5.9%	0%	−5.9%	0.493	RR = 0.212 (0.011–4.256)
Change from baseline	+5.9%	+0%	−5.9%		
Secondary outcomes					
Asthma incidence (%)	11/27 (40.7%)	2/25 (8.0%)	−24.8%	0.021	HR = 0.17 (0.038–0.765)
ACT Year 10, median (range)	22.5 (20 to 23)	25 (23 to 25)	+2.5 (3 to 2)	<0.001	$r=-0.806$
Median change from baseline	−0.5 (−2 to −1)	+2 (+1 to +1)	+1.5 (−1 to 0)	0.001	$r=-0.660$
ACT-MCID change from baseline	Non-AIT ($n=17$)	AIT ($n=8$)			
Improvement (≥2 points increase)	0%	55.6%	55.6%	0.002	RR = 19.8 (1.22–322.36)
Worsening (≥2 points decrease)	33.3%	0%	−33.3%	0.162	RR = 0.14 (0.009–2.21)
No clinically relevant change	66.7%	44.4%	−22.3%	0.371	RR = 0.70 (0.327–1.519)
Inhaled treatment for asthma year 10 (%)	52.9%	3.1%	−49.8%	<0.001	RR = 0.086 (0.017–0.424)
Change from baseline	32.3%	−18.8%	−51.1%		
FEV1% pred, year 10, median (range)	87 (77 to 101)	101 (91 to 113)	14 (14 to 12)	<0.001	$R=0.428$

(Continues)

TABLE 1 | (Continued)

	Non-AIT cohort	AIT cohort	Difference AIT vs. non-AIT (range)	*p*	Effect size, RR, HR (95% CI)
	N = 34	*N* = 32			
Change from baseline	−5 (−14 to 2)	11 (1 to 17)	16 (15 to 19)	< 0.001	*R* = 0.482
Physician-assessed severity of rhinitis (ARIA-modified) at year 10 (%)					
Asymptomatic	0%	59.4%	+59.4%		
Mild	0%	28.1%	+28.1%		
Moderate	41.2%	6.3%	−34.9%		
Severe	58.8%	6.3%	−52.5%		
Improvement from baseline, (%)	2.9%	90.6%	+87.7%	< 0.001	RR = 20.86 (4.34–100.27)
Patient-perceived clinical evolution year 10 (%)				< 0.001[a]	
Worsened	67.6%	6.3%	−61.3%		
No change	32.4%	0%	−32.4%		
Improved	0%	93.8%	+93.8%	< 0.001	RR = 64.698 (4.121–1015.804)
New sensitizations (NAC-positive) (%)	38.2%	6.3%		0.002	RR = 0.108 (0.022–0.528)
Grass pollen	14.7%	3.1%		0.198	RR = 0.187 (0.021–1.699)
Olea europaea pollen	20.6%	6.3%		0.090	RR = 0.257 (0.049–1.346)
D. pteronyssinus	14.7%	3.1%		0.198	RR = 0.187 (0.021–1.699)
Alternaria alternara	17.6%	0%		0.025	RR = ∞ (NA)

Note: All changes in primary and secondary efficacy outcomes were calculated as the difference between year 10 and baseline values (Y10—baseline), unless otherwise indicated. Negative values in VAS symptom scores and positive values in MFD or lung function indicate clinical improvement. Data on medication use were analyzed using unadjusted *p* values; the significance threshold was set at $p < 0.01$ after Bonferroni correction for five comparisons. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using 2 × 2 contingency tables. The difference in change from baseline to year 10 between the AIT and non-AIT groups was assessed using a *z*-test; a negative *z* value indicates a greater reduction in the AIT group. Effect size *r* was derived from the *z* statistic using the formula $r = z/\sqrt{N}$, and interpreted as small (0.10–0.29), moderate (0.30–0.49), or large (≥ 0.50) according to Cohen's classification.
Abbreviations: AIT, allergen immunotherapy; CI, confidence interval; OR, odds ratio.
[a]Fisher exact test.

difference in asthma-free survival between groups (log-rank, $p = 0.006$), with an absolute risk reduction of 32.7% in favor of AIT. Cox regression yielded a HR of 0.17 (95% CI, 0.038–0.765; $B = -1.775$; $p = 0.021$), indicating an 83% lower risk of asthma onset in the AIT cohort (Figure 2A). Time to first asthma-related ER visit was also significantly longer in the AIT group than in the non-AIT group (Figure 2B and Supporting Information).

3.3.2 | Asthma Control, Inhaler Use, and Lung Function

Asthmatics in both cohorts maintained ACT scores ≥ 20 points throughout the follow-up period. However, asthma control improved significantly in the AIT cohort by year 10 ($p < 0.001$), with a 2.5-point difference in favor of AIT. A MCID ≥ 2 points was observed in 62.5% of AIT patients, compared with none of the non-AIT group. Conversely, 35.3% of the latter experienced clinically significant worsening. Overall, AIT patients were nearly 20 times more likely to improve ($p = 0.002$; Figure 2C).

Despite comparable baseline inhaler use (Table S1), rates diverged markedly by year 10: 52.9% of non-AIT patients used inhalers vs. 3.1% of AIT subjects (absolute difference = −49.8%; $p < 0.001$), with significant between-group change from baseline (Δ = −51.1%; $p < 0.001$; *z*-test; Figure 2D).

Lung function improved in the AIT cohort, with an 11% increase in FEV1 (clinically and statistically significant [16]), while it slightly declined in the non-AIT group. At year 10, the between-group difference reached 16 percentage points in favor of AIT ($p < 0.001$; Figure 2E).

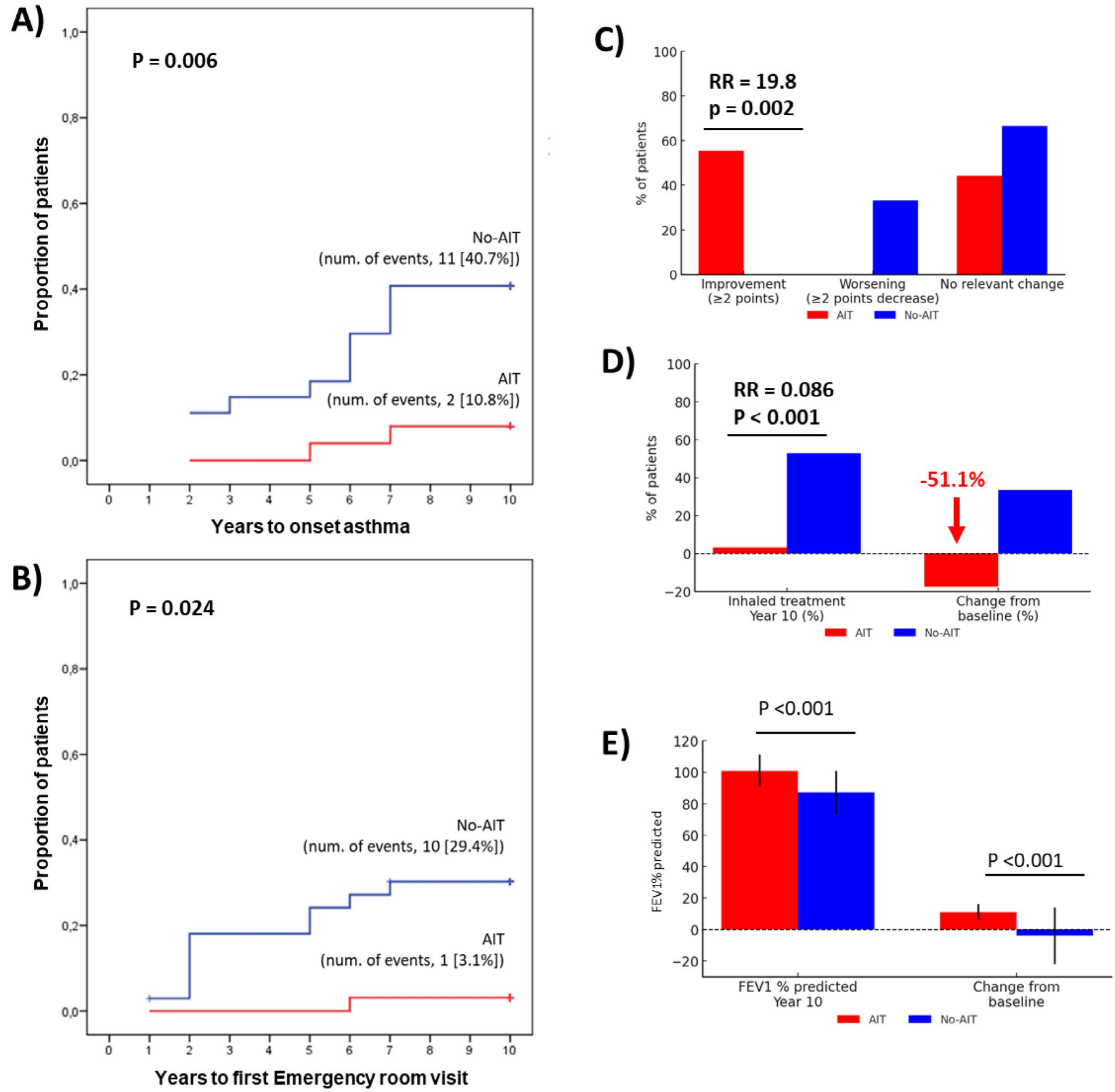

FIGURE 2 | Asthma evolution outcomes throughout the 10-year follow-up. (A) Time to asthma onset. The cumulative incidence of new asthma diagnosis was significantly lower in the AIT cohort compared to the non-AIT group ($p = 0.006$, log-rank test). (B) Time to first asthma-related emergency room (ER) visit. AIT-treated patients showed a significantly delayed occurrence of asthma-related ER visits ($p = 0.024$, log-rank test). (C) Asthma control at year 10, assessed by the asthma control test (ACT). A clinically meaningful improvement (≥ 2 points) was observed in 62.5% of AIT patients versus 0% in the non-AIT group, while 35.3% of non-AIT patients experienced clinically relevant worsening ($p = 0.002$; RR = 19.8). (D) Use of Inhaled medication. Although baseline use was comparable, year-10 inhaler use was markedly higher in the non-AIT cohort (52.9% vs. 3.1%), with a significant between-group difference in change from baseline (Δ = −51.1%, $p < 0.003$). (E) Lung function assessed by forced expiratory volume in 1 s (FEV_1, % predicted). AIT-treated patients exhibited an 11% improvement, while non-AIT patients showed a slight decline, resulting in a significant between-group difference of 16 percentage points at year 10 ($p < 0.001$).

3.3.3 | Quality of Life

Patients receiving AIT experienced a sustained improvement in both total and domain-specific QoL scores from year 1 onward, with all changes exceeding the MCID threshold of ≥ 0.5 points [15] (range: −1.21/−2.95 at year 1, and −2.06/−3.07 at year 10) (Figure 3A,B). Between-group differences were consistently significant ($p < 0.001$). At year 1, 96.9% of AIT patients reached the MCID across all domains (response rates: 62.5%–100%), an effect that persisted at year 10 (> 78%; Figure 3C). In contrast, no more than 12.5% of non-AIT patients achieved the MCID in any domain or time point.

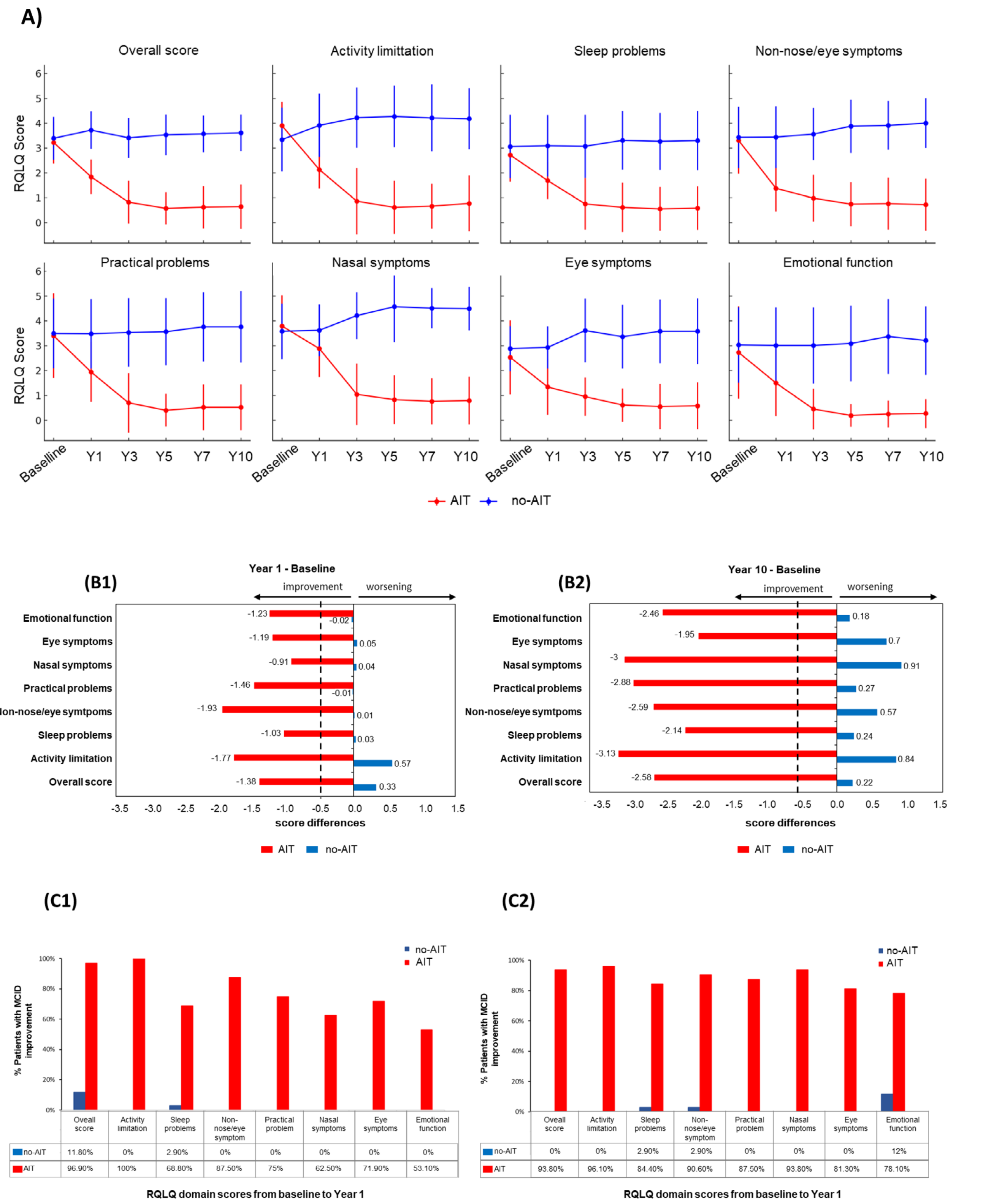

FIGURE 3 | Long-term impact of allergen immunotherapy on quality of life in patients with local allergic rhinitis. (A) Evolution of mean overall RQLQ scores at baseline and during the follow-up in patients receiving (red) and not receiving (blue) AIT. Mean scores and standard deviations are shown for each domain at baseline and during the follow-up (years 1, 3, 5, 7, and 10). p values were <0.001 for all intergroup comparisons. (B) Absolute change from baseline in each RQLQ domain at years 1 (B1) and 10 (B2) in patients receiving (red) and not receiving (blue) AIT. Negative values indicate clinical improvement. The dashed vertical line marks the threshold for the MCID, set at -0.5. All comparisons between AIT and non-AIT cohorts were statistically significant ($p<0.001$ for all domains). (C) Percentage of patients achieving a clinically relevant changes (≥ 0.5 points) in each RQLQ domain from baseline to years 1 (C1) and 10 (C2), stratified by treatment group (AIT vs. non-AIT). AIT, allergen immunotherapy; LAR, local allergic rhinitis; MCID, minimal clinically important difference; RQLQ, rhinitis quality of life questionnaire.

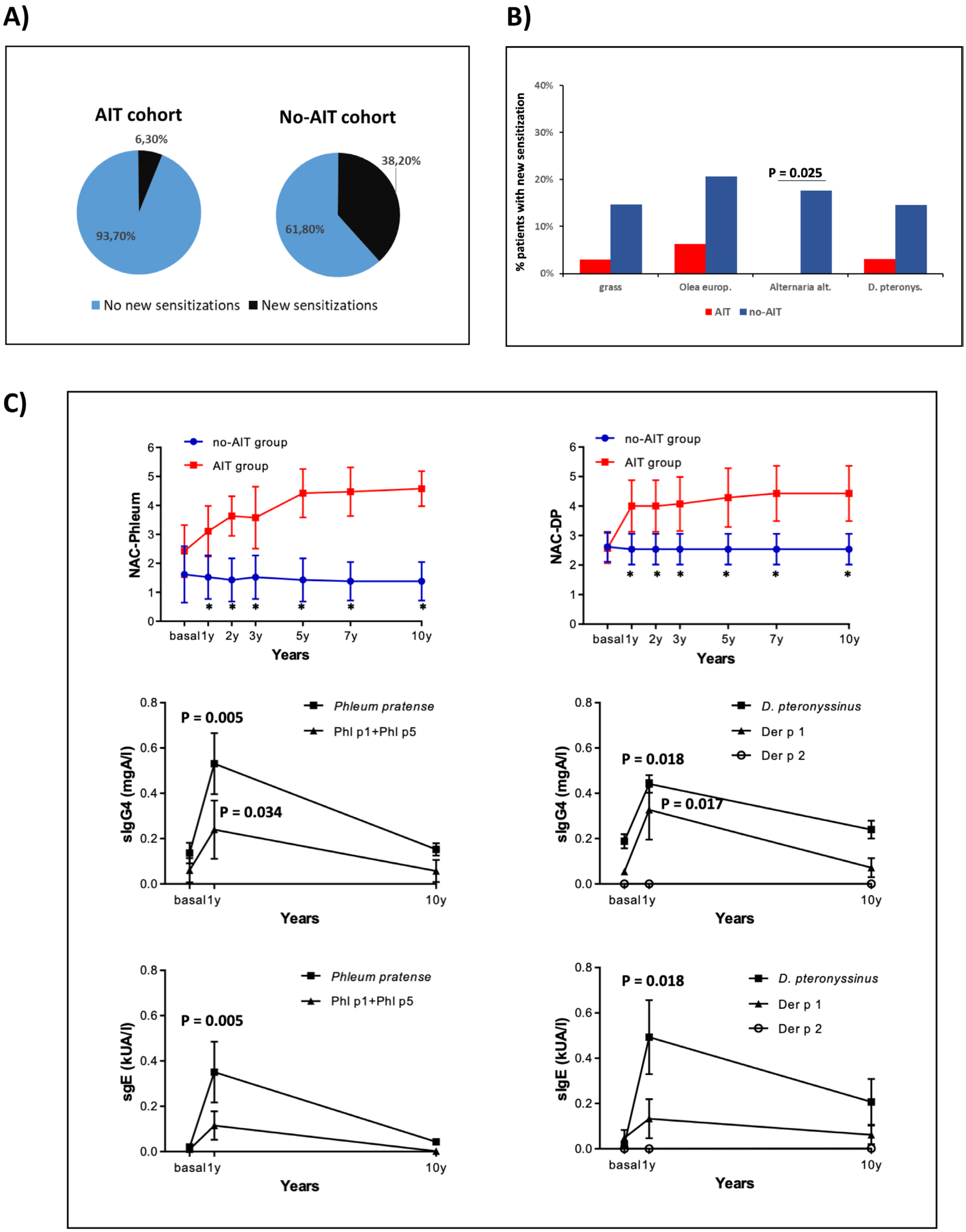

FIGURE 4 | Legend on next page.

FIGURE 4 | Prevention of new sensitizations and immunological evolution following allergen immunotherapy. (A) Incidence of new allergic sensitizations detected by multiple-allergen nasal challenge (M-NAC). (B) Proportion of patients developing new sensitizations to individual allergens. (C) Evolution of allergen-specific nasal tolerance and allergen-specific immunoglobulin responses. The two upper graphs represent NAC-S results (MAX CAT) to *Phleum pratense* and *Dermatophagoides pteronyssinuns* respectively. Between-group differences were statistically significant at all timepoints (*$p<0.001$). *Y*-axis values indicate allergen dilutions as follows: 1 = 1:1000, 2 = 1:100, 3 = 1:10, and 4 = 1:1. Lower panels show serum levels of allergen sIgG4 (mgA/l) and sIgE (kUA/l) to whole extracts and major components of *Phleum pratense* (Phl p 1 + Phl p 5) and *Dermatophagoides pteronyssinus* (Der p 1 and Der p 2) at baseline, year 1, and year 10.

3.3.4 | Onset of Local Sensitizations

During follow-up, NAC-M revealed new local sensitizations in 38.2% of non-AIT patients, vs. 6.3% of AIT patients ($p=0.002$), with more than 4-fold increased risk in the non-AIT group (RR = 4.08; 95% CI: 1.28–13.00; $p=0.009$). Among individual allergens, only *Alternaria alternata* showed significant between-group differences (0.0% vs. 17.6%; $p=0.025$) (Figure 4A,B).

3.3.5 | Nasal Tolerance and Immunological Response

NAC-S showed a progressive increase in MaxCAT values in the AIT cohort up to year 5, with sustained levels thereafter, while remaining low in the non-AIT cohort ($p<0.001$). Similar patterns were observed for both PP and DP. NAC negativity, defined as tolerance to the highest allergen concentration (1:1), was frequently achieved in AIT patients, but rarely in non-AIT individuals (Figure 4C).

In the AIT group, serum PP-, Phl p 1-, Phl p 5-, DP-, Der p 1- and Der p 2-specific IgG4 increased significantly at year 1 and returned to baseline at year 10. Conversely, sIgE showed a modest, transient increase at year 1—significant only for whole extracts and observed in two patients—and returned to baseline levels by year 10. No relevant changes were detected in the non-AIT group (Figure 4C).

3.3.6 | Rhinitis Severity

Physician-assessed severity improved progressively in the AIT cohort, with parallel improvements in patient-reported perception (Figure 5). At year 10, 90.6% showed clinical improvement and 93.8% reported subjective benefit, with strong physician–patient concordance ($\tau b=0.782$; $\rho=0.833$) (Table 1).

3.3.7 | Remission

Clinical, immunologic, and complete remission were achieved in 59.4%, 65.6% and 59.4% of AIT-treated patients, respectively, all of whom tested NAC-negative. No remission was observed in the non-AIT group (Figure S4).

4 | Discussion

This study demonstrates that LAR patients responding to AIT experience a progressive and sustained improvement in nasal and conjunctival symptoms, a reduced medication requirement and enhanced QoL, not only during treatment, but up to 7 years after discontinuation. Moreover, AIT exerts a preventive effect on the development of asthma and allergic sensitizations.

This work was prospectively designed as a responder-enriched matched cohort study. Patients in the AIT group had shown a clinical benefit by the end of the 1-year RDBPCCTs, and subsequently completed the recommended 3-year AIT course. In parallel, a contemporaneous matched cohort of LAR patients who declined AIT was followed under the same standardized protocol. While this design does not permit inferring conclusions about non-responder individuals, it directly addresses the persistence of clinical benefits after treatment discontinuation, which is a key component of disease modification. Our results should be interpreted considering that the comparator cohort was not randomized and that only individuals responding at year 1 received a 3-year course of AIT. Although these features reflect real-world conditions, they may introduce a residual confounding and limit the generalizability of results. Of note, relevant variables such as socioeconomic status or medication adherence could not be fully controlled.

AIT has long been regarded as the only etiological treatment for airway allergy due to its ability to redirect the adaptive immune response towards tolerance to the allergen [25], resulting in a decrease in symptoms and the use of reliever medication [26]. Notably, its effect may persist after treatment discontinuation if administered for at least 3 years [27], the minimum duration thought necessary to establish long-lived allergen-specific regulatory T cells [25, 28]. The ability of AIT to prevent rhinitis worsening and asthma onset supports its recognition as a disease-modifying intervention [29]. Moreover, the immunomodulatory effects may extend beyond allergen-specific lymphocytes, potentially preventing new sensitizations through trained immunity mechanisms in epithelial or antigen presenting cells [30].

Despite the proven efficacy during administration, evidence supporting the long-term or disease-modifying effect of AIT remains limited. Most available studies addressing these aspects are retrospective [31–33] or limited by a short follow-up period after discontinuation (1–3 years) [34, 35], a timeframe insufficient to capture outcomes like new sensitizations or new-onset asthma. Nevertheless, health-economic evaluations suggest long-term reduction in the utilization of healthcare resources [36], and some pediatric trials report a preventive effect on asthma up to 2 years after discontinuation [37]. The heterogeneity of AIT products, dosing regimens and routes further complicates interpretation, whereas the high cost of extended follow-up studies often limits their statistical power.

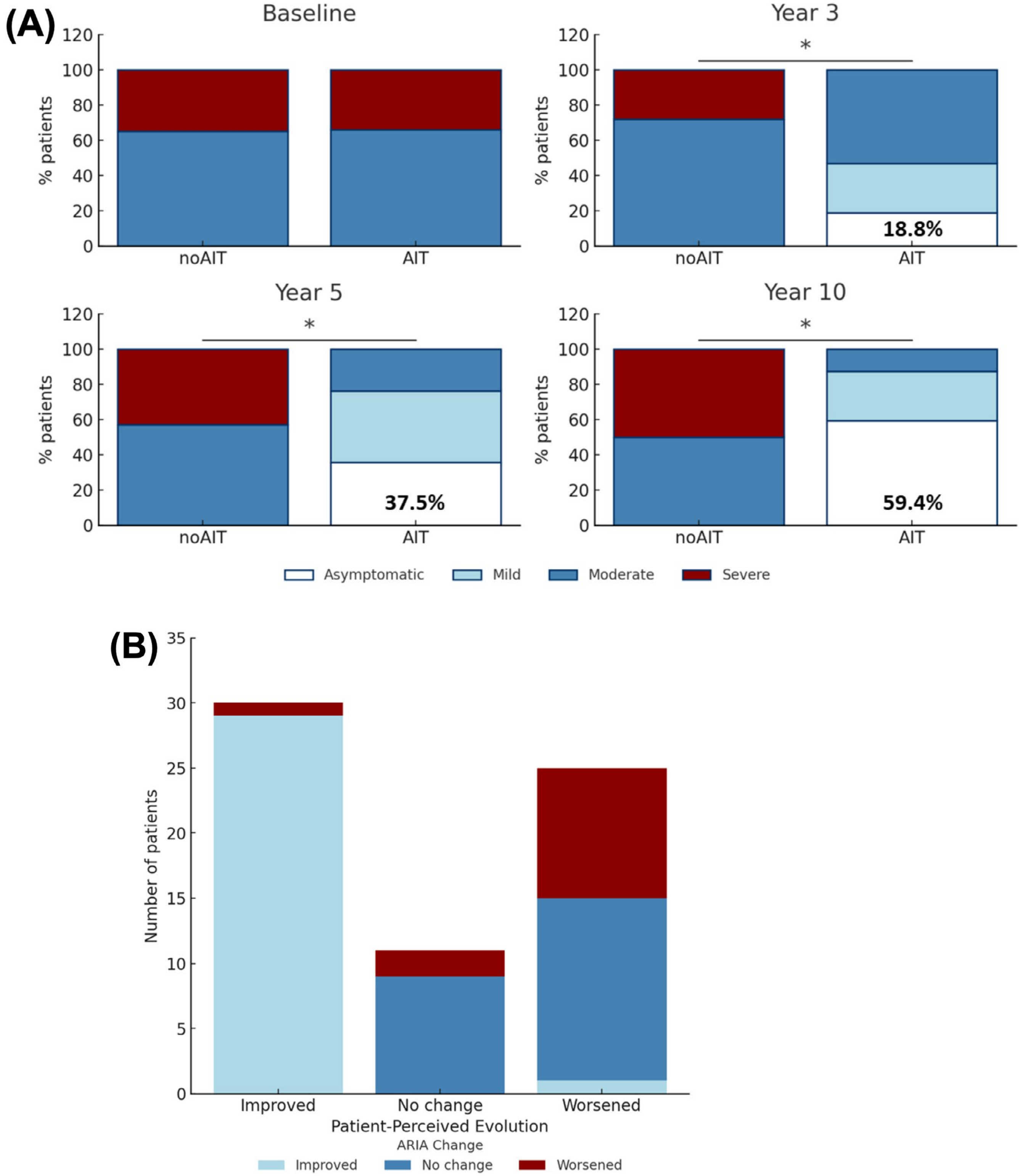

FIGURE 5 | Clinical evolution of rhinitis severity and concordance with patient-perceived change. (A) Rhinitis severity assessed by the physician using the modified allergic rhinitis and its impact on asthma (ARIA) classification at baseline, year 3, year 5 and year 10 in the AIT and non-AIT cohorts. (B) Concordance between physician-assessed rhinitis severity and patient-perceived evolution at year 10. Stacked bar charts show the distribution of ARIA-based changes (improved, no change, worsened) across patients-reported outcome categories. Strong agreement was observed Kendall's tau-$b = 0.782$ ($p < 0.001$), Spearman's rho $= 0.833$ ($p < 0.001$), * represents $p < 0.001$.

To our knowledge, this is the first prospective study to investigate the long-term effect of AIT in LAR patients. Both cohorts followed standardized evaluations of symptoms, medication use, healthcare utilization, QoL, disease severity, lung function, asthma incidence and new sensitizations, and patient-reported outcomes. Importantly, we incorporated the NAC, the gold standard for LAR diagnosis [21], to objectively assess changes in allergen tolerance over time.

Our findings show a robust and consistent benefit of AIT across all clinical endpoints. Treated patients exhibited sustained improvement in rhino-conjunctivitis symptoms, QoL and disease perception, together with decreased medication use. Interestingly, FEV1 increased regardless of asthma status, reinforcing the global airway concept [38]. Asthma control also improved, with reduced inhaler use and fewer ER visits.

Beyond symptomatic relief, AIT demonstrated preventive effects. New-onset asthma was significantly less frequent in AIT-treated patients, consistent with previous evidence from AR [29, 37], and now demonstrated for the first time in LAR. Similarly, fewer AIT-treated patients developed new allergic sensitizations, suggesting immunomodulation beyond allergen-specific T cells [30].

Interestingly, LAR patients treated with AIT did not only maintain the benefits post- discontinuation but showed progressive improvement over time in multiple variables (e.g., VAS, RQLQ, etc.). To our knowledge, no previous prospective study has shown this gradual post-treatment effect. In contrast, untreated LAR patients experienced worsening across most outcomes. This finding is consistent with a previous 10-year follow-up study conducted in a group of recently diagnosed LAR patients (disease duration 1–2 years), who experienced rapid progression within the first 5 years (e.g., more asthma cases and ER visits) [4]. In the present study, asthma prevalence at year 10 in the non-AIT group was higher than in [4] (50% vs. 31%). This difference likely reflects a more advanced disease stage at baseline (2–4 years of evolution) in the present work, and further supports the early initiation of AIT.

NAC results revealed a progressive increase in nasal tolerance in the AIT group, suggesting restoration of mucosal homeostasis as a key mechanism of long-term efficacy. Serum sIgG4 levels peaked at year 1 and declined thereafter, while clinical benefits persisted. This observation aligns with previous studies [25] supporting sIgG4's role as a transient biomarker of immune modulation rather than a direct mediator of long-term tolerance. Other mechanisms, including the induction of regulatory T cells [7], modulation of IL-10-producing group 2 innate lymphoid cells [28], and trained immunity [30], may also contribute to the persistent clinical benefit.

Remission analysis provided further insights into the long-term immunological impact of AIT. By year 10, nearly two-thirds of AIT-treated patients met criteria for both clinical and immunological remission, compared with none in the non-AIT group. This finding reinforces the concept of AIT as a disease-modifying intervention and supports the use of remission as a clinically relevant endpoint for future trials. While the concept of remission in severe asthma or chronic rhinosinusitis is often applied to subjects on biological therapy and/or testing positive for methacholine provocation [39, 40], LAR patients in our study were off treatment and did not react to intranasal allergen exposure. This fact highlights the true capacity of AIT to induce disease modification in airway allergy.

The lack of randomization in the comparator group represents a limitation of the study, whereas only AIT responders at year 1 were included. However, this selection reflects our objective: to analyze the persistence of the clinical benefit of AIT and its disease-modifying effect in patients who respond to the intervention. The matched design, standardized follow-up, and consistent effects across multiple domains strengthen the validity and clinical relevance of the findings. An ITT analysis with LOCF was applied to minimize potential attrition bias. This approach is particularly relevant considering that AIT failure rates in RDBPCCT are similar for AR and LAR patients (20%–30%) [10–13, 26, 27]. Additional limitations include a blinded design restricted to the first year in the AIT cohort, and the potential selection bias among the control patients derived from their refusal to SCIT. In any case, the latter reflects real-life shared decision-making processes. Finally, other study features (single-center nature focusing on moderate-to-severe GP- or HDM-driven LAR) limit the generalizability to other allergens, regions, or milder phenotypes. The question of whether the confirmation of a clinical response after 1 year should represent the major variable deciding the continuation of AIT for two additional years is beyond the scope of this study. Similarly, a responder-enriched matched-cohort study is not the optimal design to explore the baseline predictors of response or remission.

In summary, AIT in responder LAR patients provides long-term benefits extending beyond treatment discontinuation. These include not only sustained symptom control but also a preventive effect on asthma onset and new sensitizations, as well as the induction of clinical and immunological remission in a substantial proportion of responder subjects. Our findings support the role of AIT as a disease-modifying intervention in responder LAR patients and provide new evidence for its implementation in the management of this rhinitis phenotype. Early initiation of AIT may reduce the future burden of asthma and more severe allergic phenotypes. Further multicenter studies with broader inclusion criteria and evaluating immunotherapy with other allergens and administration routes are warranted to confirm and expand these results.

Author Contributions

C.M., M.J.T., I.E.-G. and C.R. designed the study and coordinated the work of the other authors. A.T.-M., L.Z.-F., T.I.G.-N., D.S.-T., M.J.T., I.E.-G. and C.R. recruited the participants and A.T.-M., L.Z.-F., I.E.-G. and C.R. conducted the clinical procedures. C.J.A., I.G.-E. and C.M. measured the specific immunoglobulins in patients' sera. C.R. analyzed the results. I.E.-G. and C.R. wrote the manuscript which was finally reviewed and approved by the other authors.

Conflicts of Interest

A.T.-M. has received honoraria for lecture fees from ALK, GSK and Astra Zeneca. I.E.-G. has received honoraria for lectures and advisory activities from HAL Allergy, Allergy Therapeutics, Inmunotek, LetiPharma, Diater, ALK, Allergopharma, Chiesi, Gebro, GSK, AstraZeneca, Sanofi, Novartis, Abbvie, Celltrion and Viatrix. C.R. has received honoraria for lectures from Gebro, GSK, Immunotek, and Roxal. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** all70153-sup-0001-AppendixS1.zip.