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TITLE: Local allergic rhinitis is an independent rhinitis phenotype: The results of a 10-years follow-up study.

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ABSTRACT

Background: The knowledge about the natural history of local allergic rhinitis (LAR) is limited. One unmet question is to demonstrate whether LAR should be considered the first step in the development of allergic rhinitis (AR) or an independent phenotype. The aim of this study was to prospectively evaluate the natural history of a population with LAR, the potential conversion to AR with systemic atopy, and the development of asthma during 10 years.

Methods: This is the second phase of a 10 year follow-up study of a cohort of 176 patients with LAR of recent onset and 115 age- and sex-matched healthy controls prospectively

evaluated from 2005 to 2016. Clinical-demographic questionnaire, spirometry, skin prick-test, and specific-IgE were evaluated yearly. Nasal allergen provocation tests (NAPT) with *D. pteronyssinus*, *Alternaria alternata*, *Olea europaea*, and grass pollen were performed at baseline, and after 5 and 10 years.

Results: After 10 years LAR patients experienced a significant and clinically relevant worsening of the rhinitis, with increase of emergency assistance, development of asthma, loss of allergen tolerance, and impairment of the quality of life. This worsening became significant after 5 years and progressed throughout 10 years.

A similar rate of development of AR with systemic atopy was detected in patients and controls (9.7% vs 7.8%, Log-rank $p=0.623$). In 5 patients conversion to systemic atopy occurred >10 years (3%).

Conclusions: LAR is a well-differentiated clinical entity with a low rate of development of systemic atopy, a natural evolution towards worsening and a risk factor for suffering asthma.

KEYWORDS: allergic rhinitis; asthma; local allergic rhinitis; natural history; nasal allergen provocation test; quality of life; systemic atopy

ABBREVIATIONS:

AR:	Allergic rhinitis
ARIA:	Allergic rhinitis and its impact on asthma
DP:	<i>D. pteronyssinus</i>
FHA:	Family history of atopy
LAR:	Local allergic rhinitis
NAPT:	Nasal allergen provocation test

OE:	<i>Olea europaea</i>
sIgE:	Specific IgE
SPT:	Skin prick test
VAS:	Visual analogue scale

INTRODUCTION

Local allergic rhinitis (LAR) is a clinical entity characterized by symptoms suggestive of allergic rhinitis (AR) in the absence of systemic atopy assessed by skin prick test (SPT) and determination of serum specific IgE (sIgE) (1,2). This is attributed to a localized allergic response in the nasal mucosa (1,2). LAR may affect patients from different parts of the world, ethnic groups and ages (3-12). Similarly to AR, the majority of patients are young non-smoking women with moderate-severe rhinitis with persistent and perennial symptoms (1). Nasal allergen provocation test (NAPT) is the gold standard for diagnosis, although the determination of nasal sIgE and the basophil activation test (BAT) have also demonstrated to contribute to the diagnosis (13,14). Although LAR patients have been managed with allergen avoidance measures and treated mainly with antihistamines and nasal corticosteroids, we have recently demonstrated the effectiveness and safety of specific allergen immunotherapy (AIT) with grass pollen (15) and *D. pteronyssinus* (16). These results show that LAR should be considered an indication for AIT, and reinforce the need of their diagnosis and etiological treatment.

One unmet question is whether LAR should be considered the first step in the development of AR, or an independent phenotype. In 2011 we published a preliminary study with the results of a 5-years follow-up of a cohort of 194 patients with LAR and 130 healthy controls

obtaining two interesting results: (i) increased persistence and severity of nasal symptoms, and new associations with conjunctivitis and asthma in nearly 30% of LAR patients; (ii) a rate of development of AR similar to healthy controls ($< 7\%$)(17).

However, a recent retrospective study performed in a small group of LAR patients (N=19) found a conversion to AR of 21% more than 7 years after the initial evaluation, suggesting that LAR might not be a stable phenotype and that conversion to AR may occur after longer time periods (18). These results may be influenced by several factors such as the small number of patients evaluated, the lack of a control group of healthy subjects, the retrospective design, irregular intervals between evaluations, and the different total evaluation time (1-20 years), therefore they need to be confirmed (19). We followed a large cohort of LAR patients and healthy controls over a 10-year period and confirmed that LAR is a well-defined and independent rhinitis phenotype with a low rate of long-term incidence of systemic atopy in adult patients, and a tendency towards worsening, with impairment of quality of life and development of asthma.

METHODS

Study subjects

We designed a 10-year follow-up study to investigate the natural history of LAR in a cohort of 194 LAR patients diagnosed between 2005 and 2006 in the Allergy Unit of Regional University Hospital of Malaga and 130 age- and sex-matched healthy controls (HC). All were ≥ 14 years old, with no immunological disease, and LAR had to have a recent onset (< 2 years) to avoid bias in the survival analysis. Eighteen LAR patients (9.3%) and 15 controls (11.5%) without systemic atopy dropped-out for work or personal reasons during the first 2 years and were excluded from the final analysis. Finally, 176 LAR patients and 115 controls completed the first 5 years of follow-up and were considered the study cohort. The baseline

demographic data of HCs, LAR patients and the outcome measures after 5-year have been previously published (17).

Self-administered demographic and clinical questionnaire, physical examination, spirometry, SPTs, and serum total IgE and sIgE measurements were performed yearly throughout the study. Single NAPT with *D. pteronyssinus* (DP), *Alternaria alternata* (AA), *Olea europea* (OE) and a mix of grass pollen were performed at the initial evaluation and after 5 and 10 years.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Malaga Ethics Committee. All participants and parents of patients younger than 16 years were informed and signed their corresponding informed consents/assents.

Demographic and Clinical Data

The main items explored in the demographic and clinical questionnaire (20) were: family history of atopy (FHA), smoking habits, domestic animals, rhinitis persistence and severity, comorbidities, subjective perception of disease evolution (disappearance/improvement/no change/worsening), health related to the rhinitis (excellent/very-good/good/unsatisfactory/bad), impairment of quality of life (none/mild/moderate/severe), and the use of medical emergency services due to severe symptoms of rhinitis and/or conjunctivitis or asthma attacks triggered by natural exposure to aeroallergens.

LAR was defined by the presence of a suggestive clinical history plus a positive NAPT response and a negative SPT and serum sIgE and classified as followed: (i) depending on the time of exposure it was divided into “perennial” or “seasonal”; (ii) depending on the persistence of symptoms based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (21) were classified as ‘intermittent’ (symptoms <4 days/week or <4 consecutive weeks), or ‘persistent’ (>4 days/week or >4 consecutive weeks); (iii) severity was graded following the modified-ARIA severity classification (21) according to the number of

impaired items (sleep, daily activities/sport/leisure, work/school performance, and troublesome symptoms) as ‘mild’ (0 items), ‘moderate’ (1-3 items), or ‘severe’ (4 items).

Comorbidities were defined as medical conditions existing simultaneously with rhinitis.

Asthma was defined by positive medical history of recurrent symptoms of wheezing, shortness of breath, dry cough, or chest tightness (22).

SPT and serum total IgE and sIgE

Systemic atopy was defined as one or more positive results in standard SPT or determination of serum sIgE with the most prevalent inhalant allergens in our area. The panel of allergens included: house dust mites (DP, *D. farinae*, *Lepidoglyphus destructor*), pollens (*Phleum*, *Lolium*, *Cupressus*, *Platanus*, OE, *Chenopodium*, *Plantago*, *Artemisia*, *Parietaria*, *Salsola kali*), molds (AA, *Aspergillus*, *Cladosporium*, and *Penicillium*) and animal epithelia (dog, cat and hamster) (ALK-Abelló Madrid, Spain). Serum total and sIgE levels were determined by fluoroenzyme immunosorbent assay (UNICAP; Pharmacia Diagnostics, Uppsala, Sweden). The cut-off value was 0.35 kU/l (sIgE).

Lung function tests

Flow-volume spirometry was performed with a Spirobank spirometer (Medical International Research, Rome, Italy) at baseline and every year throughout the survey. Decrease in FEV1 was expressed as percentage of the predicted value.

Nasal symptoms

The presence and intensity of individual nasal symptoms (nasal obstruction, rhinorrhea, itching, and sneezing) were recorded by visual analogue scale (VAS) of 100 mm. The total VAS was the sum of the four VAS scores (total range 0–400 mm).

Nasal allergen provocation test

The allergic response to NAPT with a single allergen was assessed at baseline and after 5 and 10 years of follow-up. NAPT was performed during an asymptomatic period at weekly

intervals (4,23). After a negative saline challenge to exclude nasal hyperreactivity, a bilateral NAPT was performed applying two puffs (100 μ L) of four increasing concentrations of freshly reconstituted freeze-dried allergen solution (ALK-Abelló, Denmark) at room temperature using a metered spray.

The panel of allergen used for NAPT included DP (*Der p1* 0.04, 0.4, 2 and 4 μ g/mL), AA (0.0025, 0.025, 0.125 and 0.25 μ g/mL), grass (0.001, 0.01, 0.05 and 0.1 μ g/mL), and OE pollen (0.006, 0.06, 0.3 and 0.6 μ g/mL). If a positive SPT was detected to an allergen not included in this panel, an additional evaluation was performed.

Responses were monitored using objective plus subjective parameters: acoustic rhinometry (SRE 2000 rhinometer, Rhinometrics, Lyngø, Denmark) and symptom scores, respectively.

Acoustic rhinometry was performed following the Guidelines of the Standardization Committee on Acoustic Rhinometry (24), measuring the volume of the nasal cavity that corresponds to the lower turbinate (vol 2–6cm) in each nostril. Symptoms of nasal obstruction, rhinorrhea, itching, sneezing and ocular symptoms were monitored at each time point by placing a vertical mark on a horizontal VAS of 100 mm. A positive NAPT was considered as an increase $\geq 30\%$ in the total VAS and a decrease $\geq 30\%$ in the total sum of vol 2-6cm of both nasal cavities compared with the baseline test (4,23). The response was monitored at baseline, 15min after saline challenge, 15min after each aeroallergen concentration, and 1h and 24h after the last concentration. The NAPT was stopped when a positive response occurred.

Statistical analysis

R (3.1.2) was used for statistical analysis. Continuous data are expressed as median and range, or mean and standard deviation, as indicated, and categorical data as percentages. The clinical and demographic data were compared between groups by χ^2 analysis and the Mann–Whitney U test. The survival distribution function without systemic atopy was

determined by Kaplan-Meier curves stratified by study group (LAR patients and HC). The probability of development of systemic atopy was the difference to 1.0. Multivariable Cox regression was applied to estimate hazard ratio (HR) with corresponding 95% CI of overall risk of systemic atopy by LAR status (yes, no) in all participants, and to control for confounding variables. Survival time was defined as the time from baseline measurement until systemic atopy diagnosis, any cause of drop-out, or end of study, whichever occurred first. Censored patients were considered with the survival time period until the last negative SPT. P values <0.05 were considered statistically significant.

RESULTS

Clinical evolution of LAR

At the onset of the disease, the mean age was below 30 in both groups and >60% were females, with a significantly ($p=0.018$) higher proportion of FHA in LAR (42%) than in HC (26%) (17). The majority of LAR patients had perennial rhinitis (73.9%) with persistent (64.8%), and moderate symptoms (59.7%). Conjunctivitis (52.3%) and asthma (18.8%) were the most frequent comorbidities (Table 1). From the study cohort of 176 LAR patients and 115 HC, 25 patients (14.2%) and 23 HC (20%) without systemic atopy dropped-out during the 6th to the 9th year of the study. Nine LAR patients dropped-out for work reasons, 16 LAR patients withdrew following medical recommendation of specific AIT due to bad clinical evolution, inadequately controlled with pharmacologic treatment. Five of these also developed asthma. Fourteen HC subjects dropped-out due to work; 9 were lost to follow-up. After 10 years of follow-up (mean $9.45y \pm 1.54$) we detected a significant worsening of the disease compared to baseline, with increases in the persistence (89%; $p<0.001$) and severity of nasal symptoms (42%; $p<0.001$) becoming significant after 5 years, which were sustained and slightly increased after 10 years. (Table 1). A progressive increase in the incidence of

asthma was detected from the initial evaluation, becoming significant after 10 years (from 18.8% to 30.7%; $p=0.009$). Conjunctivitis, the most frequent comorbidity, showed a progressive but not significant increase over time (Table 1).

The analysis of the use of medical emergency services showed a significant increase in the percentage of LAR patients who attended emergency departments (ED) and in the number of visits per patient. The percentage of patients attended in ED at initial evaluation (17.6%) increased significantly at 5th year (35.8%; $p=0.017$), and at 10th year (42.6%; $p<0.001$). Similarly, the initial number of visits/patient to ED (0.31 ± 0.799) increased significantly at 5th year (0.61 ± 1.082 ; $p=0.037$) and 10th year (0.68 ± 1.143 ; $p=0.007$) (Table 1).

Second-generation oral antihistamines and intranasal corticosteroids were the most frequent medical treatments used by LAR patients during the study. After 10 years there was a significant increase in the use of oral and ocular antihistamines, and a significant reduction in the use of intranasal decongestants. Patients showed a non-significant progressive increase in the use of oral and intranasal corticosteroids (Table 1).

Lung function explored by FEV1, which was normal at the initial evaluation (94.1%) showed a significant reduction after 10 years of follow-up (89.1%; $p=0.001$) (Table 1).

From the 5th to the 10th year of evolution there was a progressive and significant worsening in all clinical outcomes in terms of requirement of ocular antihistamines ($p=0.002$) and reduction of lung function ($p=0.001$) (Table 1).

Patient perception of LAR evolution is shown in Table 2. At final evaluation 42% of the patients reported a worsening of the disease, and 23% a progressive worsening in health perception related to rhinitis, with a significant decrease in “excellent health”, and significant increase in “unsatisfactory” and in “bad health” after 5 and 10 years. The percentage of “unsatisfactory health” increased significantly from the 5th to the 10th year ($p<0.001$). Similarly, the number of patients with impairment of quality of life significantly increased by

30.1% ($p < 0.001$) after 10 years, with a significant increase in the categories of “mild” and “moderate-severe” impairments after 5 and 10 years of evolution compared to initial evaluation, and without significant changes between 5 and 10 years (Table 2).

Nasal Allergic Response

After 10 years of follow-up, there was a significant increase in the percentage of LAR patients with polysensitization (52.8%) compared with baseline (36.4%; $p = 0.002$), and with 5 years of evolution (40.9%; $p = 0.025$). This increase induced a change in the predominant sensitization pattern, from monosensitization at baseline (63.3%) to polysensitization at the 10th year (52.8%). The most frequent nasal sensitizing allergens were DP (56.8%), and AA (39.8%). The distribution of nasal allergen sensitization is shown in Figure 1a.

Analysis of the concentration of allergen tolerated by LAR patients in the NAPT over time showed a significant reduction for DP ($p < 0.001$), AA ($p = 0.008$), grass pollen ($p = 0.002$), and olive pollen ($p = 0.002$) after 10 years compared to baseline (Table 3).

Analysis of the allergen concentration tolerated by LAR patients in NAPT showed a significant loss of tolerance to DP, AA, grass pollen, and olive pollen after 5 and 10 years of follow-up, compared to baseline. During the period from the 5th to the 10th year the loss of allergen tolerance progressed, being statistically significant for DP ($p = 0.040$) (Table 3).

Systemic atopy

After 10 years, 26 individuals developed systemic atopy detected by SPT or serum sIgE (17 LAR patients (9.7%), and 9 HC (7.8%)). There were no significant differences in the probability of developing systemic atopy between patients and HC (Log-rank $p = 0.623$) as shown by Kaplan-Meier curve in Figure 2. In a secondary analysis, we assessed the hazard risk of developing systemic atopy in LAR patients. The probability was significantly higher for patients with asthma associated with rhinitis (Figure 2a; Log-rank $p = 0.001$), and for

smokers (Figure 2b; Log-rank $p < 0.001$) at the beginning of the study compared to those without any of these factors. There were no significant differences for gender, age (≤ 25 years vs >25 years old), dwelling, sensitizing allergen, pattern of sensitization, persistence, or nasal symptom severity.

We further evaluated the effect of these demographic and clinical variables in LAR patients by a multivariable Cox regression finding significant associations between development of systemic atopy and smoking habit (Hazard ratio 8.858 [95% CI, 3.248-24.157], and asthma (hazard ratio 4.230 [95% CI, 1.626-11.004] at the beginning of the study. No confounding or modifying variables were detected in the multivariate logistic regression analysis.

The distribution of systemic allergen sensitization is shown in Figure 1b. The main sensitizing allergen in both groups of subjects was *D. pteronyssinus*, followed by *Alternaria alternata* in LAR, and by grass pollen in HC. Of the 50 systemic sensitization detected in both groups (37 in LAR patients and 13 in HC), 48 (96%) of them were identified as clinically relevant by clinical history and positive NAPT response. Two subjects had not clinically relevant SPT sensitization to dog epithelia extract (1 LAR and 1 HC).

DISCUSSION

To the best of our knowledge, this study represents the first long-term 10-year follow-up conducted to explore the natural history of LAR by following a large cohort of patients and healthy controls. In this study, after 10 years patients with LAR experienced a progressive worsening of rhinitis, reflected in both the doctor's evaluation and the patient's perceptions, with increased need for emergency assistance, development of asthma, loss of allergen tolerance, development of new local allergen sensitization, and impairment of the quality of life. This worsening was clinically relevant and statistically significant after 5 years (17) and 10 years of evolution, remarking the importance of the first 5 years in the natural evolution of

LAR patients and the tendency towards a more severe disease and association with asthma and conjunctivitis.

Clinical evaluation detected a significant increase in the presence of severe nasal symptoms from 18.8% to 42% after 10 years. During this period of follow-up LAR had a negative impact on lower airways with significant evolution towards asthma in 12% of patients after 10 years, doubling the percentage of patients attended in ED due to asthma attacks, and with reduction of lung function explored by FEV1%.

At this point it is important to remark that after 6-9 years of follow-up, 16 LAR patients with bad evolution and 5 of them with new development of asthma were retired from the study for ethical reasons, to give them the opportunity to initiate a specific treatment with allergen AIT, an etiologic treatment that has demonstrated to have a beneficial clinical and immunological effect on LAR patients in a double-blind placebo-controlled clinical trial (16). If these patients were not retired from the study the results of natural evolution of LAR patients would be even worse.

The frequent association between LAR and asthma (4,5,17) suggests a local allergic response in the bronchial mucosa of these patients. The results of a pilot study by our group detecting a clinical and inflammatory allergic response after bronchial provocation test with *D. pteronyssinus* (DP-BPT) in LAR-asthmatic patients support this hypothesis (25). However, functional studies are needed to investigate the underlying mechanisms of the bronchial allergic response.

The presence of sIgE in nasal (26) or bronchial secretions (27) is not sufficient to induce an allergic response by itself. A recent study in non-atopic asthmatic patients has detected sIgE in induced sputum able to bind Der p1 and p2 major allergens and to activate basophils, but unable to induce an allergic response after DP-BPT (27).

An important proportion of patients perceived a negative impact of LAR with worsening in their nasal symptoms (42%), health (23%), and quality of life (30.1%).

These results confirm that LAR is a relevant disease affecting the health and quality of life of adult patients with a natural tendency towards worsening and development of asthma and conjunctivitis in a high proportion of patients.

One of the main objectives of this study was to evaluate the incidence of *de novo* systemic atopy, by SPT and serum sIgE determination in a long-term follow-up study. The initial results of the first 5 years of follow-up showed a similar rate of development of AR with systemic atopy in LAR patients and HC (17). These results have been confirmed in the present study, with a similar rate of long-term development of AR in LAR patients (9.7%) and HC (7.8%). Although the number of LAR patients converting to AR was low, asthma and smoking at the onset of the disease were identified as risk factors for developing systemic sensitization.

One of the strengths of this study was the evaluation of LAR patients with a recent onset of the disease (≤ 2 years), avoiding the survival bias that would have excluded from the study subjects who had already developed systemic atopy in their natural evolution and which would therefore have underestimated the conversion or progression rate to systemic atopy.

A limitation of this study is that in our allergy department the age of the population evaluated starts at 14 years because of the patients referral system and therefore we did not have the opportunity to evaluate younger subjects. Whether LAR may evolve to systemic atopy more frequently in children than in adolescent and adults need to be explored in further studies. In addition, it would have been interesting to include a third group of subjects with systemic AR, in order to compare the evolution of LAR and AR in parallel. However, it was crucial to include in this study a group of HC to compare the rates of conversion to AR and the development of asthma. Given the need to include both LAR and HC, it was not possible to

include a third group of AR patients here, due to the additional economic and human cost this would incur.

In summary, the results of this first long-term 10-years follow up study confirm that LAR is a well-defined and independent rhinitis phenotype with a low rate of long-term incidence of AR with systemic atopy in adolescents and adult patients. LAR should not be considered a mild disease since it has a natural tendency towards worsening with significant impairment of quality of life, increases in the persistence and severity of nasal symptoms, the use of emergency assistance, and the development of asthma. The first 5-year period is a critical time point in this worsening natural evolution of LAR towards a more severe disease and association with asthma and conjunctivitis.

All these results, along with the beneficial effect of subcutaneous AIT in LAR demonstrated by double-blind placebo-controlled clinical trials with *D. pteronyssinus*-AIT (16) and in an observational study with *Phleum pratense*-AIT (15) remarks the importance of an early diagnosis and specific treatment of this entity as a clear example of personalized medicine.

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Table 1. Clinical evaluation of LAR at basal, 5 and 10 years

	basal	5 years	10 years	basal vs 5y p value	basal vs 10y p value	5y vs 10y p value
Number of patients (%)	176	176	151	NA	NA	NA
Seasonality of nasal symptoms, N (%)				0.258	0.164	0.792
Perennial	130 (73.9)	139 (79.0)	141 (80.1)			
Seasonal	46 (26.1)	37 (21.0)	35 (19.9)			
Persistence of nasal symptoms, N (%)				0.001	<0.001	0.625
Persistent	114 (64.8)	153 (86.9)	156 (88.6)			
Intermittent	62 (35.2)	23 (13.1)	20 (11.4)			
Severity of rhinitis, N (%)				0.001	<0.001	0.858
Mild	38 (21.6)	28 (15.9)	26 (14.8)			
Moderate	105 (59.7)	79 (44.9)	76 (43.2)			
Severe	33 (18.8)	69 (39.2)	74 (42.0)			
Co-morbidities, N (%)						
Asthma	33 (18.8)	43 (24.4)	54 (30.7)	0.195	0.009	0.189
Conjunctivitis	92 (52.3)	106 (60.2)	109 (61.9)	0.133	0.067	0.743
Food allergy	3 (1.7)	4 (2.3)	4 (2.3)	-	-	-
Drug allergy	2 (1.1)	2 (1.1)	2 (1.1)	-	-	-
NSAID Hyp.	4 (2.3)	4 (2.3)	4 (2.3)	-	-	-
Hymenoptera allergy	2 (1.1)	3 (1.7)	3 (1.7)	-	-	-
Atopic dermatitis	4 (2.3)	4 (2.3)	6 (3.4)	-	-	-
Urticaria-AE	2 (1.1)	2 (1.1)	0 (0.0)	-	-	-
Hypothyroidism	6 (3.4)	8 (4.5)	8 (4.5)	-	-	-
High blood pressure	4 (2.3)	4 (2.3)	4 (2.3)	-	-	-
Emergency assistance						
Patients, N (%)	31 (17.6)	63 (35.8)	75 (42.6)	0.017	<0.001	0.190
Rhinitis or conjunctivitis, N (%)	11 (6.4)	24 (13.9)	20 (11.4)	0.001	0.091	0.519

Asthma attack, N (%)	20 (11.4)	39 (22.2)	41 (23.3)	0.007	0.003	0.799
Number of visits/patient (mean±SD)	0.31±0.799	0.61±1.082	0.68±1.143	0.037	0.007	0.519
Rhinitis medical treatment, N (%)						
Antihistamines						
Oral	163 (92.6)	171 (97.2)	173 (98.3)	0.053	0.011	0.474
Ocular	65 (36.9)	75 (42.6)	104 (59.1)	0.276	<0.001	0.002
Corticosteroids						
Intranasal	137 (77.8)	140 (79.5)	145 (82.4)	0.696	0.285	0.497
Systemic	9 (5.1)	11 (6.3)	14 (8.0)	0.645	0.281	0.534
Decongestant						
Oral	10 (5.7)	9 (5.1)	5 (2.8)	0.814	0.187	0.275
Intranasal	9 (5.1)	2 (1.1)	2 (1.1)	0.032	0.011	1.000
NSAIDs	11 (6.3)	2 (1.1)	0 (0.0)	0.011	0.002	0.156
Lung function test*						
FEV1	94.1 ± 10.7	93.2 ± 9.7	89.1±10.1	0.464	0.001	0.001

“-”: Not performed; “*”: data are expressed as mean % predicted ± SD; AE: angioedema; AR: allergic rhinitis with systemic atopy; LAR: local allergic rhinitis; N: number of subjects; NSAID: non steroidal anti-inflammatory drugs; NSAID Hyp: non steroidal anti-inflammatory drug hypersensitivity;

Table 2. Patient perception of LAR evolution

	Baseline	5 years	10 years	basal vs 5y p value	basal vs 10y p value	5y vs 10y p value
Clinical Evolution, N (%)						0.421
Disappearance	NA	0 (0)	0 (0)	NA	NA	
Improvement	NA	58 (33)	47 (26.7)	NA	NA	
Worsening	NA	65 (36.9)	74 (42.0)	NA	NA	
No change	NA	53 (30.1)	55 (31.3)	NA	NA	
Health perception, N (%)	NA	31 (17.6)	40 (22.7)	NA	NA	0.232
Health impairment						
Excellent	141 (80.1)	121 (68.7)	114 (64.8)	0.015	0.001	0.428
Very Good	23 (13.1)	30 (17.0)	25 (14.2)	0.297	0.756	0.463
Good	12 (6.8)	11 (6.3)	9 (5.1)	0.829	0.500	0.645
Unsatisfactory	0 (0)	10 (5.7)	19 (10.8)	0.002	<0.001	<0.001
Bad	0 (0)	4 (2.3)	9 (5.1)	0.123	0.002	0.158
Impairment of QoL, N(%)						
Yes	97 (55.1)	146 (83.0)	150 (85.2)	0.001	<0.001	0.560
Mild	57 (32.4)	89 (50.6)	87 (49.4)	0.001	0.001	0.831
Moderate-severe	40 (22.7)	57 (32.4)	63 (35.8)	0.043	0.007	0.500
Moderate	38 (21.6)	50 (28.4)	55 (31.3)	NP	-	-
Severe	2 (1.1)	7 (4.0)	8 (4.5)	NP	-	-

NA: not applicable; NP: not performed; QoL: Quality of life

Table 3. Changes over time in concentration of allergen tolerated (mean $\pm$ standard deviation) by LAR patients in nasal allergen provocation test

Allergens	Baseline	5 years	10 years	basal vs 5years p value	basal vs 10years p value	5years vs 10years p value
<i>D. pteronyssinus</i>	1.33 $\pm$ 0.82	0.93 $\pm$ 0.84	0.91 $\pm$ 0.86	<0.001	<0.001	0.004
<i>Alternaria alternata</i>	0.09 $\pm$ 0.05	0.08 $\pm$ 0.06	0.08 $\pm$ 0.06	0.009	0.008	0.568
Grass pollen	0.04 $\pm$ 0.02	0.04 $\pm$ 0.02	0.03 $\pm$ 0.02	0.018	0.003	0.067
<i>Olea europea</i> pollen	0.26 $\pm$ 0.13	0.21 $\pm$ 0.13	0.20 $\pm$ 0.14	0.008	0.002	0.083





