

## REVIEW

## Local allergic rhinitis: Implications for management

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## Funding information

This work was supported by the Institute of Health "Carlos III" of the Ministry of Economy and Competitiveness (National Health Ministry FIS PI11/02619, FIS PI12/00900, FIS PI14/0864, "Rio Hortega" funding scheme CM17/00140, and "Rio Hortega" funding scheme CM17/00141); Andalusian Regional Ministry Health grant (PI-0346-2016), and grants cofunded by European Regional Development Fund (ERDF): RiRAAF RD07/0064 and ARADyAL RD16/0006/000).

## Summary

A significant proportion of rhinitis patients without systemic IgE-sensitisation tested by skin prick test and serum allergen-specific IgE (sIgE) display nasal reactivity upon nasal allergen provocation test (NAPT). This disease phenotype has been termed local allergic rhinitis (LAR). LAR is an underdiagnosed entity affecting children and adults from different parts of the world, with moderate-to-severe symptoms, impairment of quality of life and rapid progression to symptom worsening. LAR is a stable phenotype and not merely an initial state of AR. Allergic rhinitis and LAR share many clinical features including a positive NAPT response, markers of type 2 nasal inflammation including sIgE in nasal secretions and a significant rate of asthma development. LAR should be considered as a differential diagnosis in those subjects of any age with symptoms suggestive of AR but no evidence of systemic atopy. Although LAR pathophysiology is partially unknown, in some patients sIgE can be demonstrated directly in the nasal secretions and/or indirectly via positive responses in basophil activation test (BAT). LAR can coexist with other rhinitis phenotypes, especially AR. The diagnosis currently relies on the positivity of NAPT to a single or multiple allergens. NAPT has high sensitivity, specificity and reproducibility, and it is considered the gold standard. BAT and the measurement of nasal sIgE can also contribute to LAR diagnosis. LAR patients benefit from the same therapeutic strategies than AR individuals, including the avoidance of allergen exposure and the pharmacotherapy. Moreover, several recent studies support the effectiveness and safety of allergen immunotherapy for LAR, which opens a window of treatment opportunity in these patients.

## 1 | INTRODUCTION

Chronic rhinitis is an inflammatory disorder of the nasal mucosa which negatively affects quality of life and is responsible of significant work and school absenteeism.<sup>1</sup> The condition is often classified as allergic rhinitis (AR) and non-allergic rhinitis (NAR).<sup>1,2</sup> AR constitutes a relatively homogenous phenotype resulting from IgE-sensitisation to environmental allergens.<sup>1</sup> Conversely, NAR comprises a heterogeneous group of diseases where immune-mediated inflammation is not always apparent.<sup>1,3</sup> AR patients are by definition positive for skin prick test (SPT) and/or serum specific (s)IgE.<sup>4</sup> Nevertheless a

significant proportion of healthy subjects also display positivity for either test, demonstrating the need for a correlation between symptoms and allergen exposure.<sup>5</sup> A nasal allergen provocation test (NAPT) can help determining the clinical relevance of IgE-sensitisation in this setting.<sup>6</sup> Interestingly, some patients with seasonal or perennial rhinitis display positive NAPT with negative SPT and serum sIgE. This disease phenotype is termed local allergic rhinitis (LAR), and does not fit into the AR/NAR dichotomy.<sup>7,8</sup> Both AR and LAR are associated to positive NAPT responses,<sup>9</sup> markers of type 2 nasal inflammation including sIgE in nasal secretions<sup>10</sup> and a significant rate of asthma development.<sup>11</sup> In this review, the clinical implications

of local allergy will be discussed with emphasis on the management of non-atopic rhinitis patients with positive NAPT.

## 2 | DEFINITION AND AETIOLOGIC CLASSIFICATION

In the past, non-infectious rhinitis has been classified as allergic and non-allergic (NAR) based on the clinical history and the results of SPT and serum sIgE. However, after the description of LAR it became apparent that these systemic tests do not always detect the nasal allergic inflammation, and the classical aetiologic classification of rhinitis was updated (Figure 1).

Local allergic rhinitis (LAR) is a clinical rhinitis phenotype characterised by the presence of nasal symptoms of AR in non-atopic patients with negative skin prick test (SPT), undetectable specific IgE (sIgE) in serum against inhalant allergens, but with positive NAPT<sup>12-16</sup> and good response to allergen-specific immunotherapy.<sup>17,18</sup>

Regarding the endotype, LAR symptoms are believed to originate by a localised allergic response in the nasal mucosa exhibiting a type 2 nasal inflammation,<sup>19-21</sup> including the presence of nasal sIgE (NsIgE).<sup>20-24</sup> The phenotyping and endotyping of patients with LAR is discussed in detail in the following sections.

## 3 | ENDOTYPING LAR: THE ROLE OF THE MUCOSA

The immunopathology of LAR is not well understood. In 20%-40% of patients with positive NAPT but absent systemic sensitisation, sIgE has been found in nasal secretions.<sup>9,10,20-22</sup> Nevertheless the source of this sIgE is not clear. The synthesis of high-affinity antibodies is induced in germinal centre (GC) B cells in a process involving class switch recombination (CSR) from IgM to the definitive isotype (eg IgG or IgA).<sup>25</sup> This step is followed by the somatic hypermutation of the variable regions of the antibody to increase the affinity for its cognate antigen.<sup>25</sup> On the other hand, direct CSR to IgE (eCSR) in GC is less efficient than CSR to the other isotypes.<sup>26</sup> Moreover, IgE-producing B cells display impaired somatic hypermutation at GC which lead them to experience high levels of apoptosis before exiting the secondary lymphoid tissues.<sup>27</sup> To preserve high-affinity IgE immune responses, memory IgG-producing B cells have developed the capacity to undergo sequential CSR to IgE upon re-exposure to the allergen.<sup>26</sup> Of note this phenomenon can occur in the peripheral tissues, like the respiratory mucosa of patients with airway allergy.<sup>28,29</sup> (Figure 2). IgE synthesised at the mucosal level may enter the blood stream via the lymphatic vessels, and ultimately bind circulating basophils or be distributed to peripheral tissues to

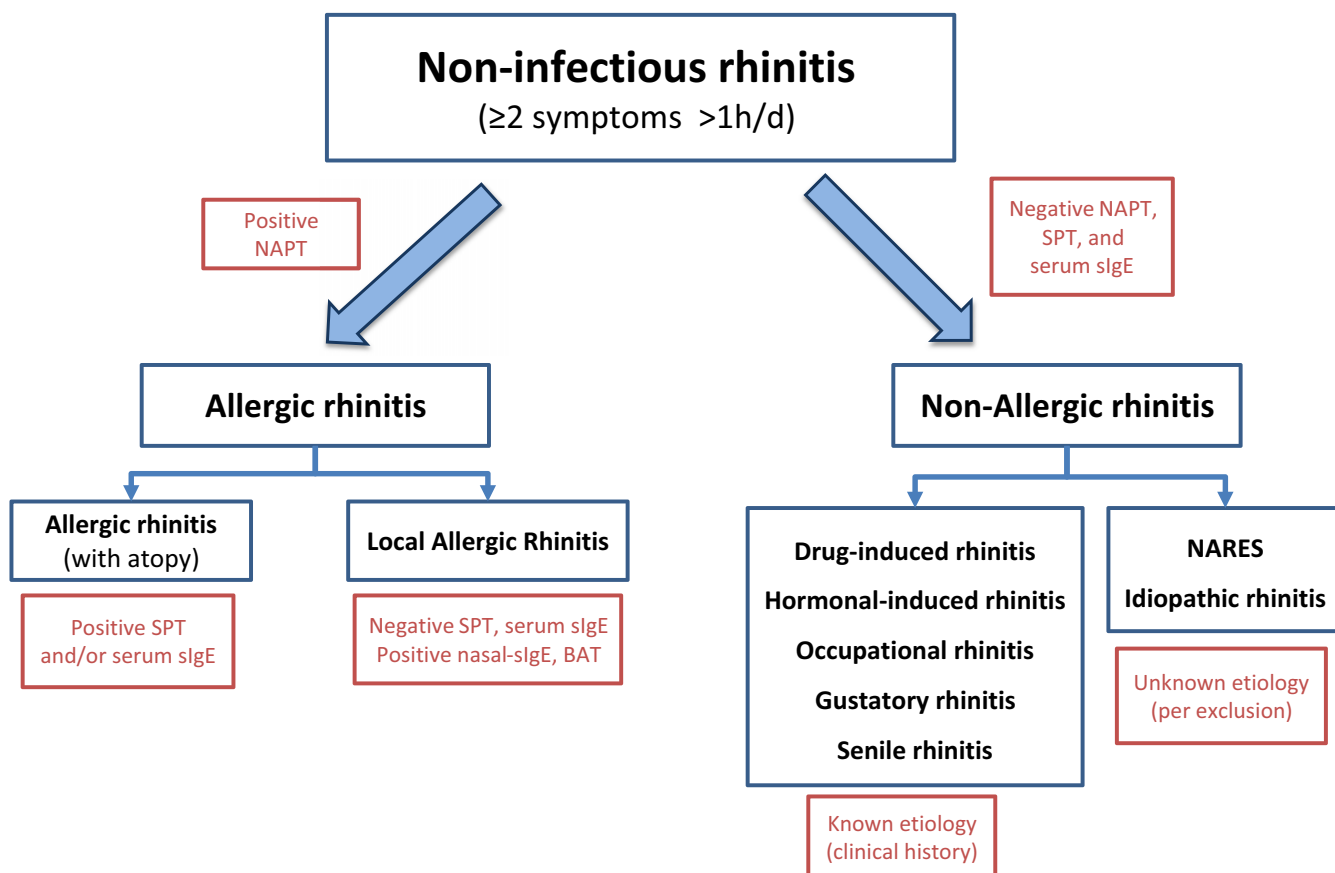


**FIGURE 1** Aetiologic classification of non-infectious rhinitis. The main diagnostic characteristics of each aetiologic group are represented in red squares. BAT, basophil activation test; NAPT, nasal allergen provocation test; NARES, non-allergic rhinitis with eosinophilia syndrome; sIgE, specific IgE; SPT, skin prick test

sensitise resident mast cells.<sup>30,31</sup> Importantly, markers of sequential  $\epsilon$ CSR were found in the bronchial mucosa of asthmatic patients regardless of their atopic status.<sup>32</sup> In this regard, it is tempting to speculate that in LAR individuals IgE produced at the mucosal level can be enough to sensitise nasal effector cells, but not to reach skin mast cells or to be detected at a free state in serum. Of note, 40% of house dust mites-LAR individuals display positive IgE-mediated basophil activation test (BAT) responses to house dust mites,<sup>33</sup> suggesting that in those patients mucosal IgE has been able to reach the blood stream.

## 4 | PHENOTYPING LAR: CLINICAL MARKERS AND COMORBIDITIES

### 4.1 | Clinical phenotypes of LAR

Local allergic rhinitis and AR patients share several demographic and clinical features. The typical LAR patient is a young non-smoking woman, with moderate-to-severe rhinitis and persistent/perennial symptoms, commonly associated to comorbidities such as conjunctivitis and asthma. Nasal itching and watery rhinorrhea are the most frequent LAR symptoms and house dust is the most common trigger.<sup>11</sup> Although LAR is more frequent in young adults,<sup>11</sup> data from different studies show that children,<sup>11,34-36</sup> and elderly individuals<sup>37</sup> may also be affected. Compared with patients with NAR, LAR subjects are significantly younger, with family history of atopy and more severe symptoms.<sup>8,38</sup>

### 4.2 | Environmental allergens

Data available from several studies have identified a few allergens as main symptom triggers in most LAR individuals. They include house dust mite (HDM), grass and olive tree pollens,<sup>12-14,20-23</sup> and moulds.<sup>11,37</sup> However, little is known about the role that other less common allergens can play in LAR.

The mite *D. pteronyssinus*, has been identified as the main individual allergen inducing nasal allergic reactivity in both young adults and elderly patients with AR or LAR. Interestingly, allergic reactivity to the mould *Alternaria alternata* is more frequent in LAR subjects, whereas allergy to pollen and animal dander is more typical of AR individuals.<sup>11,13,37,38</sup>

Although the possibility of an occupational-LAR has not been yet thoroughly investigated, the pathophysiological and diagnostic aspects of LAR could be applied in the investigation of occupational rhinitis with negative SPT and serum sIgE and a clear occupational history.<sup>39</sup>

### 4.3 | Local allergic rhinitis and asthma

There are multiple similarities in the pathophysiological features of allergic and non-allergic asthma,<sup>40,41</sup> including the cellular infiltrate of the bronchial mucosa in non-allergic asthma largely resembles that of allergic asthma,<sup>42</sup> and the expression of cytokines such as IL-4, IL-5 and IL-13 is similarly increased in both asthma phenotypes.<sup>40,42</sup>

Current published data suggests that bronchial symptoms are common in LAR patients.<sup>11,20,21</sup> In these studies, typical symptoms of asthma are self-reported by 20%-47% of LAR patients. Moreover, long-term follow-up studies in these patients show an increase of lower airway symptoms after 10 years of evolution of the disease, with a significantly higher proportion of patients requiring a visit to the hospital due to wheezing and dyspnoea.<sup>43</sup>

Evidence also suggests that IgE may play a relevant role in asthma regardless of the atopic status, and several studies have demonstrated that asthmatic individuals without systemic atopy also display local synthesis of IgE, increased expression of  $\epsilon$  heavy-chain germ line, local  $\epsilon$ CSR and up-regulated expression of the high-affinity receptor for IgE (Fc $\epsilon$ RI) in the bronchial mucosa.<sup>32,40</sup> A study reported functional HDM-specific IgE in sputum samples from non-allergic asthma patients after bronchial provocation with *D. pteronyssinus*.<sup>44</sup> However, the role of allergens as triggers of bronchial symptoms in LAR patients was not sufficiently clarified in this study because the

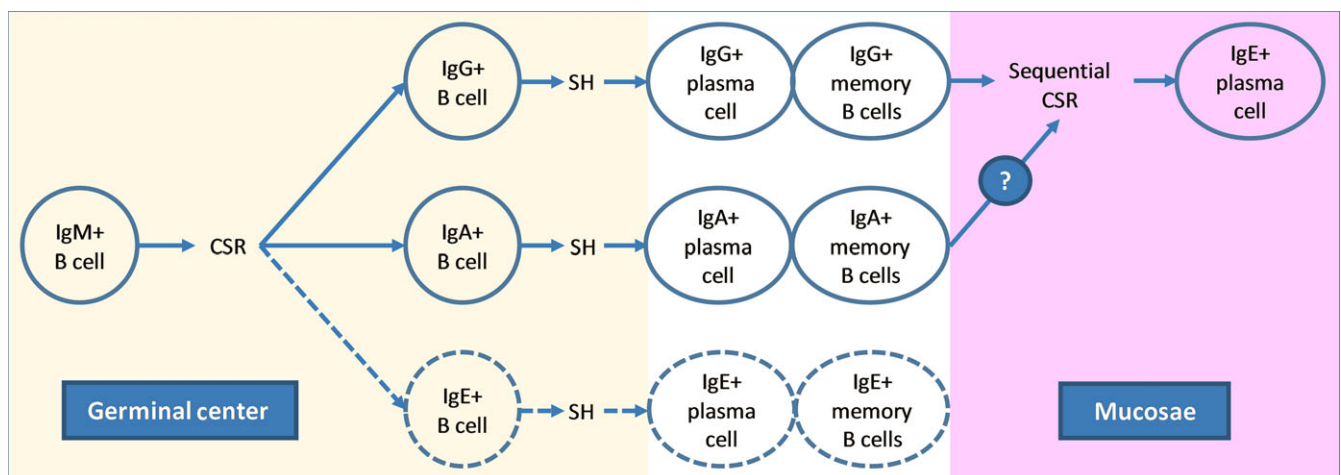


**FIGURE 2** Synthesis of specific IgE. High-affinity IgE production by IgG+ plasma cells/memory B cells in the mucosae following class switch recombination to IgE (CSR)

patients did not always experience a clinical response after the inhalation of the allergen.<sup>44</sup> Another study including patients with LAR and asthma confirmed by methacholine test, found that 53% of the individuals displayed positive responses to HDM upon bronchial provocation with a significant increase in methacholine PC<sub>20</sub> 24 hours after the allergen challenge.<sup>45</sup> These observations strongly suggest that a lower airway equivalent of LAR may exist, but studies with larger cohorts are required for definitive conclusions.

#### 4.4 | Local allergic rhinitis and conjunctivitis

Patients with LAR frequently display eye symptoms such as ocular itching and burning, tearing and red eye during natural exposure<sup>11</sup> or during NAPT.<sup>8,11,16</sup> Ocular symptoms are more common in pollen-reactive LAR patients than in those sensitised to HDMs.<sup>8,11</sup> However, it is still not clear if the involvement of the conjunctiva in LAR is a true ocular sensitisation or an activation of nasal-ocular reflexes after allergen exposure in the nose.<sup>46</sup> The conjunctival epithelium hosts a robust population of immune cells, such as mast cells and T and B lymphocytes,<sup>47</sup> and in allergic conjunctivitis resident B cells produce IgE that sensitise conjunctival mast cells.<sup>48</sup> Whether conjunctival sensitisation in addition to nasal-ocular reflexes work synergistically in LAR patients to induce ocular symptoms is not sufficiently investigated.

### 5 | CLINICAL RELEVANCE AND EARLY DIAGNOSE

#### 5.1 | Natural evolution and quality of life

Since the first studies in LAR, one important question for the investigators was if LAR could be a temporary or incomplete rhinitis phenotype, which would evolve towards AR in a short period of time. Recently, a long-term 10-years follow-up study has confirmed that LAR is an independent phenotype of rhinitis, and not a first step in the development of AR as initially was suggested.<sup>49</sup> This follow-up study underwent in a cohort of 194 LAR patients and 130 healthy controls reviewed yearly for 10 years demonstrated a low rate of incidence of AR with systemic atopy (9.7%) in patients with LAR, and importantly, similar to healthy controls (7.8%)<sup>43,50</sup> (Figure 3). After 10 years, LAR patients experienced a significant increase of severe rhinitis from 19% to 42% and a negative impact on lower airways, with 12% of onset asthma, doubling the percentage of patients with asthma attacks attended in emergency departments, and a decrease of lung function explored by FEV1%.<sup>43</sup> Moreover, 42% of patients self-reported a worsening of the disease, 23% a negative impact on health, and 30% an impairment of their quality of life.<sup>43</sup> These results confirm LAR as a relevant respiratory disease with chronic course and natural progression towards worsening, decrease in allergen tolerance, need for emergency assistance, impairment of the quality of life, and development of asthma and new nasal sensitisations.<sup>43</sup> During the first 5 years after disease onset, there is a significant increase of rhinitis severity with

progressive impairment of quality of life.<sup>50</sup> This worsening is accompanied by a higher incidence of asthma and conjunctivitis, which causes an increased number of visits to the emergency department.<sup>50</sup> LAR continues worsening during the subsequent second 5 years, but importantly, at a much lower rate.<sup>43</sup>

#### 5.2 | Prevalence and clinical impact

Different epidemiological and clinical studies have demonstrated that LAR is an underdiagnosed entity, affecting individuals from different countries, ethnic groups and age ranges.<sup>13,14,34-37,51-53</sup> A recent systematic review including 46 studies involving 3230 patients (1685 AR and 380 non-atopic rhinitis), and 165 healthy controls has explored the frequency of nasal reactivity towards allergens among AR and NAR patients.<sup>38</sup> In this study, the prevalence of LAR in non-atopic rhinitis patients was 24.7% if only SPT or serum IgE was used to rule out atopy, and 56.7% when both systemic diagnostic test were negative. In children, the prevalence of LAR in this study was 16.1%,<sup>38</sup> slightly lower than in elderly patients (21%).<sup>37</sup> However the heterogeneity of the NAPT protocols used, the criteria for patient selection, the age groups, the examined allergens, the tools to measure the nasal response, and the cut-off point to determine a positive NAPT result,<sup>38</sup> limits the direct comparison (Figure 4), and makes necessary a multi-centre study with a uniform protocol to evaluate the prevalence and real clinical impact of LAR in rhinitis patients.

#### 5.3 | Local allergic rhinitis in children

Allergic rhinitis is a highly prevalent disease in the paediatric population, and tends to increase with age, raising from 3.4% at 4 years of age to more than 30% at age 18 in some studies.<sup>54</sup> An important proportion of LAR subjects develop their first symptoms during childhood. In the past years several publications have highlighted the importance of considering LAR as a major differential diagnosis in children, and the importance of evaluating the target organ by means of NAPT to rule out or confirm the diagnosis. In the systematic review mentioned above,<sup>38</sup> nasal allergen reactivity in children under 16 years old with NAR was 16.1% (95% CI, 9.5-24.0).<sup>7,24,36,38,55-57</sup>

Recent studies analysing LAR in paediatric populations include close to 270 children altogether, with either perennial or seasonal symptoms, with ages ranging from 4 to 18 years, with a prevalence of positive NAPT ranging from 0% to 66.6% (Table 1). Fuiano and col.<sup>24</sup> evaluated the local production of IgE in 36 individuals with ages ranging from 4 to 18 years; in those patients NAPT with *Alternaria* was performed, with 64% displaying positive responses. Another study in Thailand with 25 children with NAR aged 8-18 years did not find any positive response to nasal provocation with HDM.<sup>55</sup> Some recent studies in different geographical areas have shown a rate of positivity from 25% to 66.6% of children undergoing a NAPT to several allergens. Summarising, LAR is an important differential diagnosis in children and must be ruled out in children with typical AR symptoms and negative SPT/IgE.

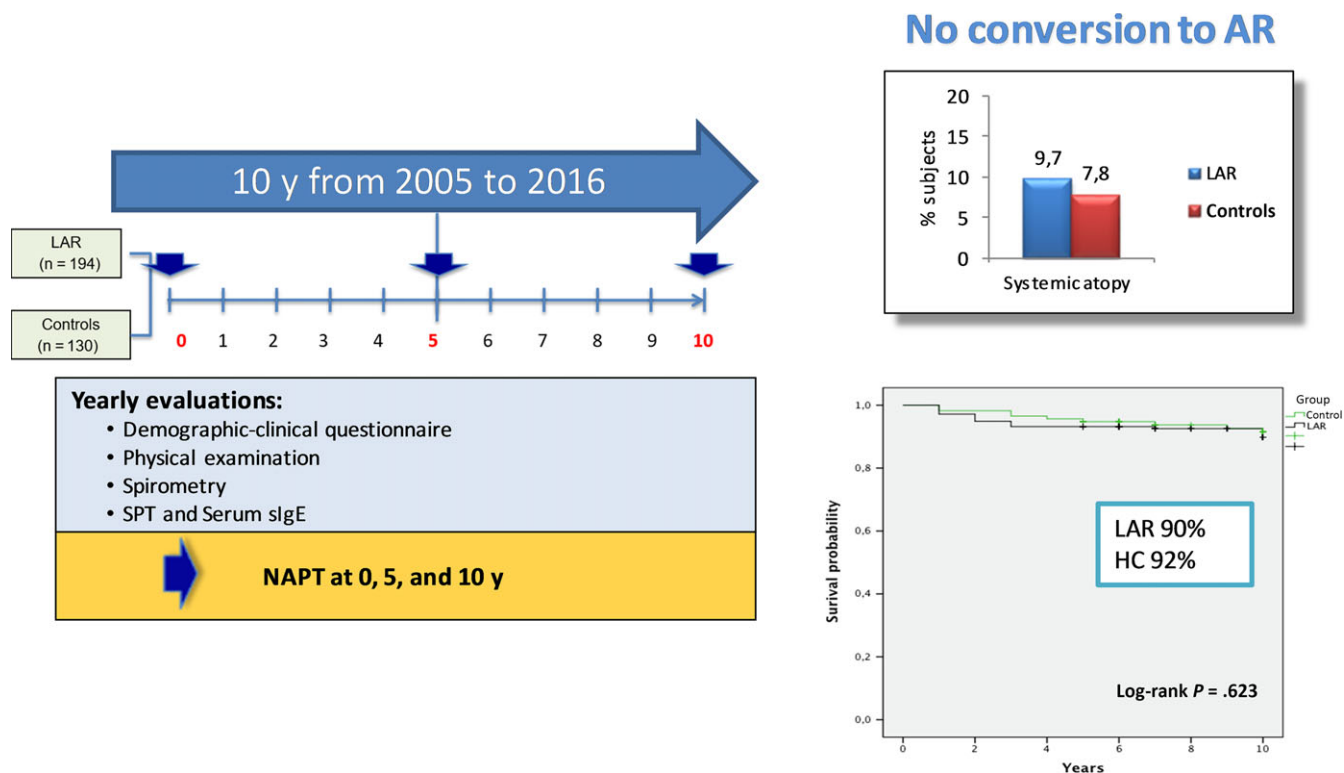


**FIGURE 3** Natural evolution of local allergic rhinitis. This figure shows the main results of 10-years follow-up study of a cohort of 194 LAR patients and 130 healthy controls. Yearly evaluations included demographic-clinical questionnaire, physical examination, spirometry, skin prick test and serum determination of specific IgE. Additionally, at baseline, at 5th and at 10th year of evolution nasal allergen provocation tests (NAPT) were performed. The low and similar rate of development of allergic rhinitis (AR) with atopy in LAR patients and healthy controls (9.7% vs 7.8%,  $P = .623$ ) confirmed LAR is an independent and well-defined rhinitis phenotype

## 6 | CLINICAL RELEVANCE TO DIFFERENTIATE BETWEEN LOCAL ALLERGIC AND NON-ALLERGIC RHINITIS

In several European health systems, the evidence of systemic atopy is considered the main referral criteria to Allergy Units.<sup>58</sup> This fact limits the chances of LAR individuals to be evaluated by a specialist and to obtain an accurate diagnosis. Moreover, the use of a rhinitis allergological work-up limited to STP and measurement of serum sIgE,<sup>2,4</sup> results in a significant rate of misdiagnosis of both adult and paediatric rhinitis patients, as it classifies the LAR individuals as non-allergic rhinitis phenotype.<sup>8,38</sup>

In this regard, the implementation of NAPT protocols in the evaluation algorithms of rhinitis is crucial for the identification of LAR individuals,<sup>9</sup> and it may also help to determine the clinical relevance of an IgE-sensitisation in rhinitis patients with systemic atopy.

As mentioned above, the development of systemic atopy is not a common phenomenon in LAR individuals.<sup>43</sup> Nevertheless, LAR tends to a rapid worsening with progressive impairment in quality of life. Of note, the first 5 years after the disease is established is the critical period for the increase of rhinitis severity, the onset of comorbidities, and the higher need of emergency assistance due to asthma and conjunctivitis attacks.<sup>43,50</sup>

The identification of the trigger eliciting rhinitis may help establishing avoidance measure to control the symptoms. Moreover, recent studies have demonstrated that allergen immunotherapy with HDM<sup>18</sup> and grass pollen<sup>17</sup> are efficient and safe therapeutic options for patients with LAR. In this regard, it is crucial to identify LAR individuals shortly after the disease is established, in order to initiate adequate therapeutic strategies to control the symptoms and to potentially prevent the onset of comorbidities.

## 7 | DIAGNOSTIC TOOLS IN LOCAL ALLERGIC RHINITIS

Local allergic rhinitis has to be considered as a differential diagnosis in those subjects with symptoms suggestive of AR but no evidence of systemic atopy.<sup>3,10</sup> In the evaluation of LAR patients, always a detailed clinical history must be conducted, including assessment of comorbidities such as ocular and bronchial symptoms. Also, the age of onset of symptoms, urban/rural dwelling, family history of atopy, smoking habit, the pattern and severity of nasal complaints and the evolution of the disease as the onset should be specifically interrogated (Figure 5).<sup>11</sup> Later on, a thorough exploration of the nasal cavity via nasal endoscopy or CT scan when needed must be performed to rule out chronic rhinosinusitis among other nasal disorders. If the detection of atopy is

**FIGURE 4** Positive nasal allergen provocation test (NAPT) among patients initially diagnosed as having non-allergic rhinitis (NAR). The diamond represents a pooled summary estimate of the probability of positive NAPT (From Hamizan AW, Rimmer J, Alvarado R, Sewell WA, Kalish L, Sacks R, et al.<sup>38</sup>

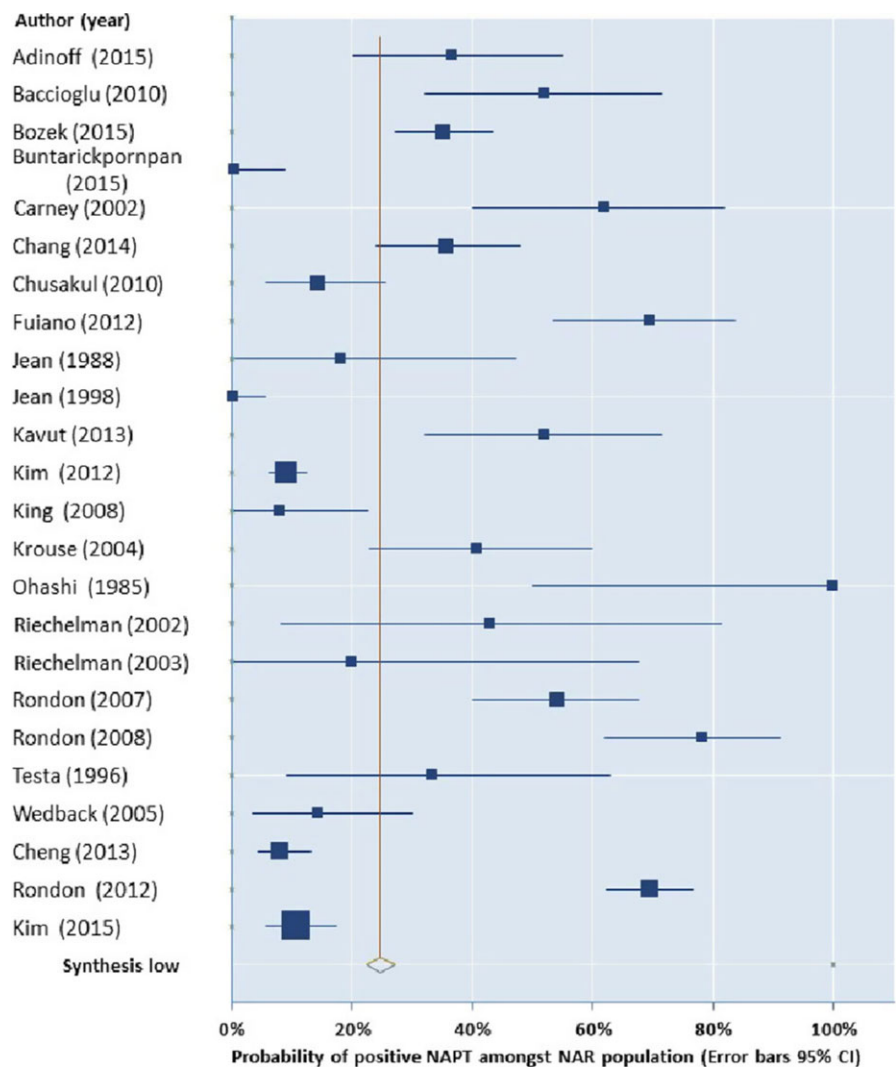


**TABLE 1** Local allergic rhinitis in children

| Author                | Year | Country  | Study group                 | Age             | Allergen                 | Positive response NPT (n, %) |
|-----------------------|------|----------|-----------------------------|-----------------|--------------------------|------------------------------|
| Fuiano et al          | 2012 | Italy    | 36 NAR (perennial)          | Children 4-18   | Alternaria               | 23/36 (64%)                  |
| Buntarickporpan et al | 2015 | Thailand | 25 NAR (perennial)          | Children 8-18   | DP                       | 0/25 (0%)                    |
| Blanca-López et al    | 2016 | Spain    | 61 NAR (seasonal)           | Adults/children | Phleum                   | 37/61 (61%)                  |
| Duman et al           | 2016 | Turkey   | 28 NAR (seasonal/perennial) | Children 5-16   | DP,DF, grass mix         | 7/28 (25%)                   |
| Zicari et al          | 2016 | Italy    | 18 NAR (perennial)          | Children 6-12   | DP,DF, lolium            | 12/18 (66.6%)                |
| Krajewska-Wojtyś A    | 2016 | Poland   | 121 NAR (seasonal)          | Children 12-18  | Phleum, artemisia, birch | 73/121 (52.5%)               |

positive (SPT/sIgE) and there is a concordance with the clinical history, the diagnosis of AR has been reached. In the case of LAR patients, the classical approach is insufficient and leads to misdiagnosis, so the response of the target organ to an allergen challenge must be evaluated.<sup>10</sup> NAPT is currently the gold standard for LAR diagnosis, along with the detection of sIgE in the nasal secretions<sup>10,11,16,20,21,45</sup> or a positive basophil activation test (BAT).<sup>33,59</sup> NAPT has the capability of differentiate between allergic (AR and LAR) and non-allergic individuals (healthy controls and NAR), as well as between relevant and no-relevant allergen sensitisation in atopic subjects.<sup>38,60</sup> Previous to

NAPT a nasal challenge with saline is recommended to rule out non-specific nasal hyperreactivity.<sup>6,8-11,15-18</sup>

Nasal allergen provocation test is a sensitive, specific and reproducible technique although is time-consuming and requires and trained personnel. To decrease the number of visits that are required, there is a protocol of nasal challenge with multiple allergens that identifies patients without nasal reactivity, shortening the diagnostic work-up.<sup>9</sup> Also, it has been recently demonstrated that LAR subjects respond to purified allergens (83% of LAR patients challenged with nOle e 1) as was previously shown in AR.<sup>59</sup>

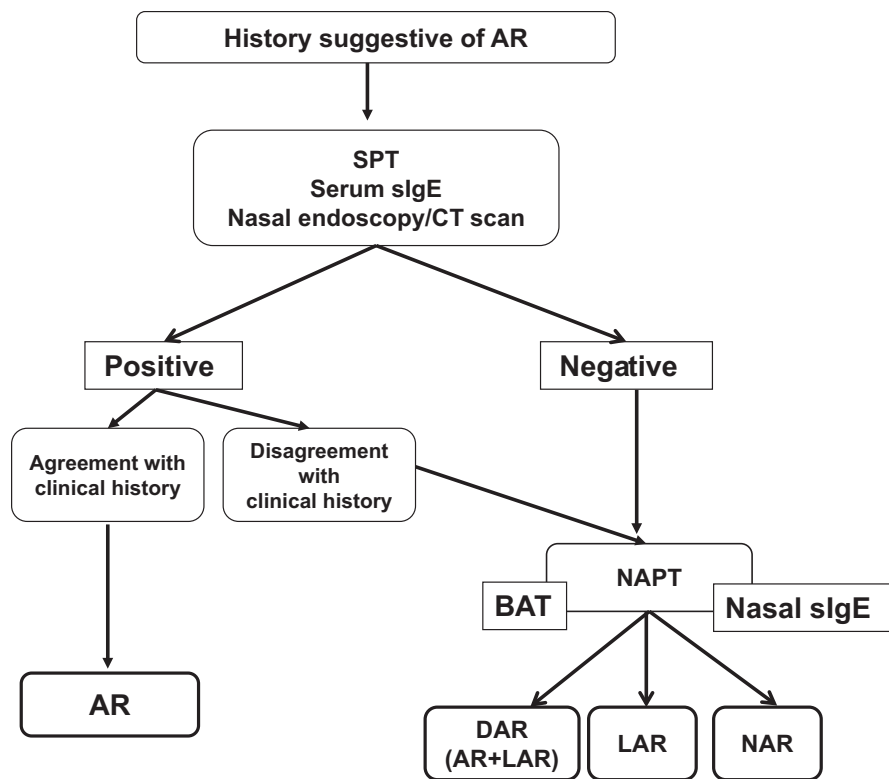


**FIGURE 5** Diagnostic algorithm of rhinitis. AR, allergic rhinitis; BAT, basophil activation test; CT, computed tomography; DAL, dual allergic rhinitis; LAR, local allergic rhinitis; NAPT, nasal allergen provocation test; NAR, non-allergic rhinitis; sIgE, specific Immunoglobulin E; SPT, skin prick test

Nasal allergen provocation test reproduce the allergic response in a controlled way.<sup>60</sup> Of note, when recording the clinical history it is common to observe that allergic patients (LAR and AR) recognise natural exposure to allergens as the trigger of their respiratory symptoms, exhibiting the same clinical response after controlled exposure by NAPT. On the other hand, NAR patients usually recognise more frequently unspecific triggers such as chemical irritants and temperature changes than AR and LAR patients.<sup>11</sup>

There are some patients who show perennial symptoms but positive SPT to seasonal allergens only (grass, olive tree pollen). Preliminary data from our group showed that a percentage of these patients had a positive NAPT to perennial allergens (HDM, *Alternaria*). This rhinitis phenotype has been called dual allergic rhinitis (DAR), to reflect that both local and systemic sensitisation coexist in the same patient.

At this point is important to remember that the existence of specific IgE in serum or nasal secretion (at a free state) or bound to the mast cells receptors (among other cells) in the skin (as measured by SPT) is only indicative of sensitisation, but it is not enough to diagnose a patient of airway allergy.<sup>6,10,24,61</sup>

In a proportion of LAR individuals, sIgE in the nasal secretions is detected, but the sensitivity of this measurement largely relies on the technique utilised to collect the nasal sample. With the nasal lavage, the quantification of sIgE is very specific (>90%) but shows very low sensitivity (22%-40%).<sup>20-23,59</sup> Other techniques such as nasal brushing<sup>62</sup> or sinus packs<sup>63</sup> have been shown useful in nasal detection of sIgE but still need to be tested in LAR. Recently, a minimally-invasive method of direct detection of NsIgE using an automated immunoassay has been evaluated in patients with LAR to

*Dermatophagoides pteronyssinus* (DP).<sup>64</sup> The detection of NsIgE was performed by direct application of the solid phase of a commercial DP ImmunoCAP®, obtaining in LAR patients 42.86% sensitivity with the highest specificity.<sup>64</sup> Therefore, this study demonstrates the feasibility of the detection of NsIgE to DP in LAR using a simple, commercialised device with high specificity.

Basophil activation test is a useful tool for LAR diagnosis as shown in several studies in patients with sensitisation to DP and olive tree pollen.<sup>33,59</sup> In LAR patients reactive to DP BAT has 50% sensitivity,<sup>33</sup> and it is higher in subjects sensitised to *Olea Europaea* (66%) upon nasal provocation.<sup>59</sup> In both cases the specificity was >90%. The specific IgE mechanism of basophil activation in LAR has been demonstrated by performing BATs with wortmannin pretreatment, showing negativisation of positive results when wortmannin was added to the assay.<sup>33</sup>

In conclusion, NAPT is still the most reliable tool for LAR diagnosis, and can be supported by finding a positive NsIgE and/or BAT. A detailed clinical history and nasal exploration must be performed as well.

## 8 | THERAPEUTIC MANAGEMENT: PRESENT AND FUTURE

### 8.1 | Where are we now?

In the daily practice, most LAR patients are given health education, allergen avoidance measures and are treated with symptomatic treatment including oral antihistamines and intranasal corticosteroids in

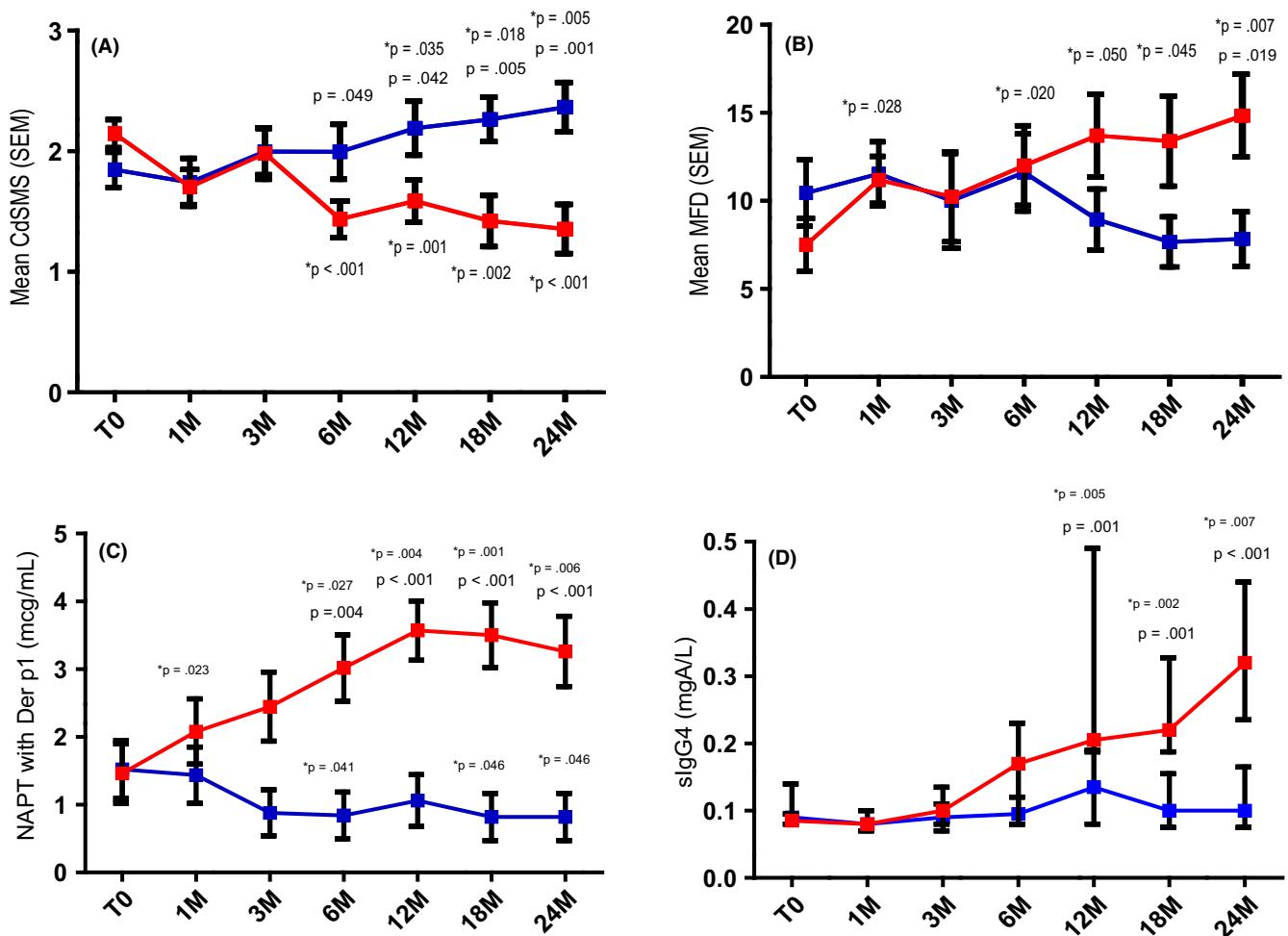


**FIGURE 6** Clinical and immunological changes during treatment with subcutaneous allergen-specific immunotherapy with *D. pteronyssinus* (DP-SCIT) vs placebo: (A) Combined daily symptoms–medication score (CdSMS). (B) Medication free days (MFD). (C) Nasal tolerance to Der p1 (mcg/mL). (D) Serum levels of specific IgG4 (sIgG4) to DP (mgA/mL). Blue line: placebo group; red line: DP-SCIT group. Similar results were obtained in the observational study with grass pollen-SCIT vs symptomatic medication, and in the randomised double-blind placebo-controlled clinical trial with *Phleum pratense*-SCIT vs placebo

line with the *Allergic Rhinitis and its Impact on Asthma* (ARIA) guidelines and criteria.<sup>4,65,66</sup> However, allergen avoidance is not always feasible, and symptomatic treatment is unable to stop the natural progression of LAR towards clinical worsening and development of comorbidities over time.<sup>43,50</sup> In AR, patients who do not respond to symptomatic pharmacotherapy, allergen immunotherapy (AIT) is indicated. AIT is highly effective, safe and confers long-term clinical benefit after discontinuation of treatment in adequately selected patients.<sup>67</sup> AIT is the only aetiological treatment for AR and asthma with disease modifying effect and can change the natural course of the disease.<sup>2,4,66,68–72</sup> This fact together with the clinical and immunologic similarities between AR and LAR, made investigators to focus their efforts in evaluating the potential of subcutaneous allergen immunotherapy (SCIT) for treating LAR individuals.

The first approach was an observational study to compare the safety and efficacy of 6 months of preseasonal grass-SCIT vs symptomatic medication in patients with moderate-severe seasonal LAR due to grass pollen.<sup>17</sup> The promising results obtained have been

recently confirmed by a 2-years randomised double-blind, placebo-controlled clinical trial (RDBPCT) with SCIT with *D. Pteronyssinus* (DP-SCIT),<sup>18</sup> a 2-years RDBPCT with *Phleum pratense* (Phl-SCIT),<sup>73</sup> and a 2-years RDBPCT with *Betula verrucosa* pollen (Bet-SCIT).<sup>74</sup> These studies provided evidence for the short-term and sustained clinical effect of SCIT in LAR patients.<sup>7,17,18,75</sup> The beneficial clinical effect of SCIT resulted in a significant improvement of symptoms and medication scores (Figure 6A), severity of rhinitis and an increase in the number of medication free days (Figure 6B). This improvement became significant after 6 months of treatment and progressed throughout the study, achieving the greatest clinical benefit at the end of the trial.<sup>17,18,75</sup> These results have been reproduced in recent RDBPCT with Phl-SCIT<sup>73</sup> and Bet-SCIT.<sup>74</sup> The RDBPCT with *Phleum*-SCIT has also demonstrated the beneficial effect of SCIT on ocular symptoms, asthma control and quality of life compared to placebo.<sup>75</sup>

The effect of SCIT on allergen tolerance and levels of specific IgG in serum in LAR patients was also investigated. In the three

studies, SCIT induced a strong, progressive and dose-dependent increase of allergen tolerance starting at the 3rd month of treatment (Figure 6C). Of note, 30% of patients treated with 6 months grass-SCIT,<sup>17</sup> 50% treated with 2-years DP-SCIT,<sup>18</sup> and 56% treated with 2-years Phl-SCIT<sup>75</sup> tolerated the maximum concentration of the intranasal delivered allergen at the end of the study thus being negative for the post-SCIT NAPT.

Subcutaneous allergen immunotherapy induces a progressive dose-dependent increase in serum sIgG4 levels throughout the study in LAR patients, which became significant after 6 months (Figure 6D). The origin of this increase might be related to the capacity of SCIT to generate IL-10-producing Treg and IgG4-producing Breg,<sup>76,77</sup> but future studies need to be performed to evaluate in depth the immunologic effect of SCIT in LAR. Immune mechanisms studies will also underscore relevant surrogate and predictive biomarkers of LAR.

These results confirm that SCIT is a clinically effective treatment for LAR, related to a significant increase in allergen tolerance, and to a positive impact on the quality of life.

## 8.2 | Future therapeutic options

Besides the classical subcutaneous and sublingual routes, the intralymphatic, intradermic or epicutaneous administration of allergen are under investigation for airway allergy.<sup>78</sup> To date, none of these routes have been specifically tested in LAR individuals. Recently the efficacy of intranasal AIT was reported in a mouse model of allergic asthma.<sup>79</sup> Because LAR is defined by a localised immune response in the nasal mucosa, it would be interesting to develop intranasal AIT strategies for LAR and to compare their clinical and immunological effects with those produced by SCIT.<sup>17,18,75</sup>

Omalizumab is an anti-IgE humanized monoclonal antibody (mAb) approved for severe allergic asthma<sup>80</sup> and chronic urticaria.<sup>81</sup> Several studies on asthma indicate a beneficial effect of omalizumab over the concomitant rhinitis.<sup>82,83</sup> Mepolizumab, reslizumab and benralizumab are humanised mAbs directed against the IL-5 pathway.<sup>84</sup> Yet these drugs have been shown efficient for eosinophilic asthma,<sup>84</sup> their effects over nasal allergy have not been investigated. Dupilumab is a human mAb targeting the IL-4/IL-13 pathway approved in the US for severe atopic dermatitis,<sup>85</sup> but whose effects over airway allergy remain to be clarified. Of note, omalizumab and mepolizumab showed promising results for chronic rhinosinusitis with nasal polyps.<sup>86</sup> Even though cost-efficiency limits the use of biologicals for nasal allergy, it can be expected that some of these drugs have a beneficial effect in LAR patients.

## 9 | CONCLUSIONS

Since the last 15 years growing evidence indicates that nasal reactivity to allergens can occur in the absence of systemic atopy. Even though a multicenter cross-sectional study is missing, published literature suggests that LAR might account for a significant proportion of

individuals previously diagnosed of NAR. Yet LAR immunopathology remains to be defined, several evidences indicate an IgE-mediated mechanism; namely, some patients display detectable sIgE in nasal secretions and positive BAT responses, and SCIT is efficient in the majority of LAR individuals. It is also necessary to study the long-term effects of SCIT in LAR, especially over the onset of conjunctivitis and asthma.

In any case, the concept of local allergy has important implications for the clinical management of individuals with rhinitis, as negative SPTs and/or serum sIgE do not exclude *per se* nasal reactivity to environmental allergens. In this regard, it is crucial to implement NAPT protocols in the diagnostic algorithms of rhinitis patients, at least until the *in vitro* tests become ready for the clinical practice. LAR rapidly evolves towards the clinical worsening and the association to asthma and conjunctivitis implying that an early diagnosis and the initiation of specific therapies are crucial for controlling the disease and potentially preventing its comorbidities.

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**How to cite this article:** Campo P, Eguiluz-Gracia I, Bogas G, et al. Local allergic rhinitis: Implications for management. *Clin Exp Allergy*. 2019;49:6–16. <https://doi.org/10.1111/cea.13192>