Curr Treat Options Allergy (2015) 2:54–63
DOI 10.1007/s40521-014-0042-9

Specific Immunotherapy (L Cox, Section Editor)

Local Allergic Rhinitis: Is There a Role for Systemic Allergy Immunotherapy?

Carmen Rondón, MD, PhD[1,*]
Paloma Campo, MD, PhD[1]
Natalia López-Blanca, MD, PhD[2]
María José Torres, MD, PhD[1]
Miguel Blanca, MD PhD[1]

Address
[*,1]Allergy Unit, Regional University Hospital of Malaga, IBIMA, UMA, Malaga, Spain
Email: carmenrs61@gmail.com
[2]Allergy Unit, Infanta Leonor Hospital, Madrid, Spain

Published online: 10 January 2015

This article is part of the Topical Collection on *Specific Immunotherapy*

Keywords Allergen · Allergic rhinitis · Immunotherapy · Local allergic rhinitis · Nasal allergen provocation test

Opinion statement

Allergen immunotherapy (AIT), the etiologic treatment of allergic rhinoconjunctivitis and allergic asthma, has been shown to be an effective and safe treatment in patients with allergic respiratory disease. The efficacy of AIT in reducing symptoms and medication requirements has been demonstrated not only during treatment but also after it is discontinued. AIT is the only treatment that has the ability to modify the natural course of allergic rhinoconjunctivitis and asthma. In recent years, a new entity—local allergic rhinitis (LAR)—has been reported, which is characterized by the presence of a local allergic response to inhalant allergens, with negative skin tests and no detection of specific IgE antibodies in the peripheral blood. Patients had a nasal-specific response after nasal allergen challenge and a nasal Th2 inflammatory response with specific IgE antibodies, and showed clinical improvement with the classical treatment for allergic rhinitis (antihistamines and nasal corticosteroids). Ongoing evidence indicates that these patients benefit from subcutaneous AIT and supports this indication for LAR.

Key points

1. LAR is a new phenotype of allergic rhinitis characterized by the presence of a localized allergic response in the nasal mucosa with negative skin test and no detection of serum-specific IgE antibodies in the peripheral blood.
2. It is an underdiagnosed/misdiagnosed respiratory disease that may affect patients from different countries and among different ethnic and age groups, showing a tendency

toward worsening of the disease and a risk of developing asthma.
3. Patients with LAR commonly have persistent rhinitis, with moderate to severe nasal symptoms associated with conjunctivitis and/or asthma and impairment of their quality of life.
4. AIT is the etiological treatment of allergic respiratory disease and has the ability to modify its natural course. According to ARIA guidelines, it is indicated in moderate to severe persistent or intermittent allergic rhinitis and/or allergic asthma.
5. The efficacy and safety of subcutaneous allergen-specific immunotherapy for grass pollen and *Dermatophagoides pteronyssinus* has been demonstrated in adults with LAR.

Introduction

Allergic rhinitis (AR) is a global health problem, adversely affecting quality of life, and frequently associated with asthma, conjunctivitis, and rhinosinusitis [1]. Thus, the early diagnosis and effective management of AR can improve patients' quality of life and their clinical evolution.

In the past decade, a new phenotype of AR has been described, characterized by the presence of a localized allergic response in the nasal mucosa, with the absence of atopy assessed by conventional diagnostic tests such as skin-prick testing (SPT) and/or determination of serum-specific IgE (sIgE) [2••, 3, 4••, 5]. This entity has been identified as local allergic rhinitis (LAR), or entopy [4••, 6, 7].

The immunological characteristics of LAR include in situ production of serum-specific IgE (sIgE) antibodies to inhalant allergens, a Th2 pattern of mucosal inflammatory response during natural exposure to aeroallergens, and a positive NAPT with release of inflammatory mediators [2••, 3, 4••, 8–11]. LAR affects more than 45 % of patients previously diagnosed with non-allergic rhinitis (NAR) [2••, 8, 9, 12, 13]. It is now considered a new phenotype of allergic rhinitis and is included in the AR group in the latest etiological classification of rhinitis [3, 4••, 14••].

The characterization of LAR has generated several important questions concerning its prevalence and natural evolution, the influence of environmental factors, and the role of immunotherapy. The evidence of a localized allergic response in patients with non-atopic rhinitis suggests that allergen-specific immunotherapy would be beneficial in these patients. This article review the latest work carried out on LAR, with a particular emphasis on the clinical and immunological effects of systemic AIT in LAR.

Immunological characteristics of LAR

There is sufficient evidence supporting the contention that LAR is a localized IgE-mediated allergic respiratory disease. The primary difference between classical systemic AR and LAR is that, in the former, the specific IgE is circulated in peripheral blood and can be detected in the sensitized mast cells of the skin (SPT), and is also a free antibody circulating in sera, whereas in LAR, it cannot be detected. The reasons, however, remain unknown.

Various studies have demonstrated that patients with LAR have a Th2 allergic inflammatory response, driven by nasal production of specific IgE [8, 9, 15, 16] and nasal accumulation of eosinophils, mast cells, and CD3+/CD4+ T cells [8, 9, 15–17], as well as a positive response to nasal allergen provocation tests (NAPT) [2••, 8, 9, 12, 13]. The immediate and late phases of the allergic response to NAPT have been measured in LAR patients through the monitoring of symptoms, acoustic rhinometry, and the release of inflammatory mediators [10, 11].

Th2 allergic nasal inflammatory response

In LAR, as in AR, the natural exposure to inhalant allergens is associated with a nasal Th2 IgE response. Increased levels of eosinophils, basophils, mast cells, CD3+ T cells, and CD4+ T cells have been detected by flow cytometry studies in nasal lavage [8, 9]. T cells may contribute to the recruitment of eosinophils and to the production of the IgE antibodies in patients with LAR.

In the past, the hypothesis that an inflammatory mechanism might be involved in the pathophysiology of non-allergic rhinitis, however, has been controversial. Various histological studies have found a Th2 inflammatory pattern in patients with NAR compared to healthy individuals, with increased numbers of mast cells, eosinophils, IgE^+ B cells [15], and T cells [16], although these findings have not been reported by others [18, 19]. The reason for these apparently contradictory results may be the great heterogeneity of NAR, including patients with a different pathogenesis, predominantly inflammatory in some cases [15, 16], possibly including patients with LAR, and including neurogenic mechanisms in patients with IR [18, 19].

Local production of sIgE and pro-inflammatory mediators

Although the detection of nasal sIgE to *D. pteronyssinus* was reported by Huggins and Brostoff in 1975 [20] in a group of rhinitis patients with positive NAPT to *D. pteronyssinus* and negative SPT and serum sIgE, it was not until 2007 that nasal sIgE during natural exposure to an allergen was reported [8].

Over the years, researchers have demonstrated the presence of sIgE antibodies in nasal secretions of LAR patients during periods of natural exposure to aeroallergens [8, 9], after nasal challenge [10, 11, 21•], and during periods of non-exposure to aeroallergens [10, 11]. Cellular studies have found the expression of epsilon germline gene transcripts and mRNA for the epsilon heavy chain of IgE in B cells of the nasal mucosa [22]. In patients with negative skin-prick tests, a Th2 inflammatory pattern, with increased numbers of IgE+B cells, mast cells, and eosinophils, has been detected [15].

The presence of free light chains (FLCs) of IgE in the nasal mucosa and nasal secretions of patients with AR and NAR [23] suggests that these FLCs could play a role in IgE-mediated hypersensitive immune responses with the involvement of mast cells. Further investigation is needed to elucidate the presence of FLCs in patients with LAR and to establish whether FLCs have an adjuvant or independent role in patients with IgE-mediated allergic disorders.

In a recent study, Gómez et al. [24••] demonstrated that 50 % of subjects with LAR to *D. pteronyssinus* had a positive and highly specific basophil activation test (BAT), supporting the concept that LAR is an IgE-mediated allergic disease and providing a new diagnostic tool. These results have been replicated in larger populations and with other allergens such as olive tree pollen [25••]. The peripheral basophil activation in LAR may be due to the spillover of locally synthesized sIgE into the circulation, with basophils the primary effector cells [26•].

The kinetics of the immediate and late phases of the allergic response after NAPT has been studied in LAR subjects sensitised to grass pollen and *D. pteronyssinus* (DP) [10, 11]. In these studies, the time course of clinical symptoms, reduction in nasal patency, and local production of sIgE and pro-inflammatory cytokines was evaluated [10, 11]. Tryptase and eosinophil

cationic protein (ECP) were chosen as specific markers of mast cell and eosinophil activation. Patients had an immediate or dual response to NAPTs, accompanied by release of tryptase, ECP, and sIgE in nasal secretions. In these patients, we did not observe isolated late responses [10, 11].

The kinetic curve of tryptase showed a strong correlation with nasal symptoms of itching and sneezing, with different patterns for immediate versus dual-responders. The maximum level of tryptase was detected at 15 minutes, decreasing over time, and normalizing at six hours in immediate responders and at 24 hours after challenge in dual-responders [10, 11].

Eosinophilic cationic protein stored in the granules of eosinophils and secreted after cell activation has been used as a specific marker for eosinophil activation in late responses to NAPT in subjects with allergic rhinitis, showing a significant increase from four to nine hours after the challenge [27, 28].

In patients with LAR, the release of ECP was detected 15 minutes after the NAPT, with a progressive increase, reaching the maximum nasal concentration at 24 hours after provocation in both immediate and dual-responders [10, 11]. The maximum levels of ECP and sIgE to grass pollen and *D. pteronyssinus* were recorded at 24 hours after the challenge, the final time point of the evaluation period. Whether nasal production of ECP and/or sIgE continues to increase after this time point must be explored in further studies.

The detection in some patients of basal levels of nasal sIgE during non-exposure periods, which progressively increased from 1 to 24 hours after allergen challenge, supports the existence of persistent local production of sIgE in nasal mucosa that rapidly increases after allergen-specific stimulation [10, 11].

In these kinetic studies, a significant correlation was observed between the increase in nasal levels of tryptase and ECP and the intensity of nasal symptoms. These correlations were more pronounced in LAR patients sensitized to grass pollen between tryptase and nasal itching and rhinorrhea, and between ECP and nasal obstruction [10].

Positive response to NAPT

The diagnosis of LAR is based largely on the demonstration of a positive response to NAPT and/or local synthesis of sIgE [4••]. The NAPT reproduces the allergic reaction, allowing us to study the immediate and late allergic response demonstrating both the presence of local allergen-specific IgE and the triggering of the response by the allergen. The NAPT is considered the gold standard in the diagnosis of LAR, and has proven to be a highly sensitive, specific, and reproducible test, with a higher sensitivity than that associated with the detection of nasal-specific IgE antibodies [8, 9, 12]. This technique requires well trained-personnel, it is time-consuming, and it is not available in many centers. A multiple-allergen NAPT (NAPT-M) approach in a single session has been designed in order to shorten the procedure without impairing the specificity, sensitivity, and reproducibility of the test [29••].

Several studies have shown that from 47 % to 66 % of patients previously diagnosed with idiopathic rhinitis or NAR were found to have LAR with positive NAPT responses measured objectively by acoustic rhinometry [8–11, 13], anterior rhinomanometry [12], and nasal secretion of sIgE and inflammatory mediators [8–11], and by subjective nasal and ocular symptoms [8–13, 14••].

Natural history

What is the natural history of LAR? Should it be considered a risk factor for asthma? These are important clinical question that were posed after LAR was first described. Whether this entity is a first step in the development of AR with systemic atopy or represents a distinct phenotype is currently under investigation.

In a retrospective study performed in 180 patients who were initially diagnosed with NAR between 2000 and 2004 and were reevaluated three to seven years later, the development of de novo sensitization was detected by means of skin-prick testing, serum-specific IgE, or both in 24 % of the patients [30]. However this study did not differentiate between NAR and LAR patients.

In a follow-up study evaluating the natural history of LAR over a 10-year period in a cohort of 149 patients with LAR and 130 healthy controls, the results of the first five years of the study showed similarly low rates of conversion to systemic atopy in both patients and controls, suggesting that LAR is an entity well-differentiated from AR [31••]. Furthermore, after five years of follow-up, a worsening of rhinitis was detected, with a significant impairment in quality of life, an increase in the persistence and severity of nasal symptoms and in the use of emergency assistance, as well as new associations with conjunctivitis and asthma. After five years, conjunctivitis had increased by 7.9 % and asthma by 5.6 %. [31••]. Although these results must be validated after the completion of 10 years, the data show that LAR has a natural tendency toward worsening, with the appearance of new cases of asthma, although not evolving toward AR with systemic atopy.

Phenotype and clinical relevance

Although prevalence data in the general population are lacking, various publications have reported that LAR may affect more than 47 % of patients previously diagnosed with NAR [8–13, 14••], and up to 25 % of patients with rhinitis referred to a specialist for allergological study [2••].

In recent years, several studies have shown that LAR is a common underdiagnosed/misdiagnosed respiratory disease that may affect patients from different countries and among different ethnic and age groups [2••, 10–12, 21•, 32•, 33•].

Although data in childhood populations are limited, it has been suggested that LAR should be included in the differential diagnosis of rhinitis in children. In a recent study in children with perennial rhinitis and negative SPT, the authors found positive responses to NAPT with Alternaria in 30 of 36 children (83 %) [21•]. In another study including 110 adult patients with LAR, participants reported onset of the disease in childhood in 36 % of cases [2••].

A recent study evaluated the clinical phenotype of patients with LAR in a comparative analysis of a large number of subjects with LAR, AR, and NAR [2••]. Patients with LAR and AR exhibited a similar demographic-clinical phenotype: a young woman, non-smoker, with severe persistent perennial rhinitis frequently associated with conjunctivitis and asthma, and with *D. pteronyssinus* as the main sensitizing aeroallergen [2••].

Therapeutic options in local allergic rhinitis

The management of allergic rhinitis includes patient education, allergen avoidance measures (when possible), pharmacotherapy, and AIT. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have proposed a new classification of allergic rhinitis and an initial treatment strategy based on the duration and intensity of symptoms and patient lifestyle limitations [1, 34••, 35].

Given the clinical-immunological similarities between patients with LAR and those with AR, it is reasonable to think that LAR patients would benefit from the same pharmacological treatment, including antihistamines, inhaled corticoids, and IgE antagonists, for nasal as well as bronchial symptoms.

In fact, the majority of patients with LAR are currently being treated with education, allergen avoidance measures, and pharmacological treatment with intranasal corticosteroids and oral antihistamines, according to the ARIA criteria [8, 9], and showing a similar response in terms of symptom relief and management of the disease [8, 9, 31••]. Allergen avoidance is not always suitable, however, and the efficacy of environmental avoidance measures is not well-established. In addition, intranasal corticosteroids and oral antihistamines cannot prevent progression of the disease.

AIT is the only treatment that has the ability to modify the natural course of the allergic disease in addition to providing a reduction in symptoms and the use of medication [36–38].

According to ARIA guidelines, allergen immunotherapy is indicated in children and adults with moderate to severe persistent or intermittent AR and/or allergic asthma [1, 34••, 35–38]. The long-term clinical effect of AIT and its potential role in preventing the development of asthma in patients with AR has been recognized in the ARIA [1, 34••, 35] and Global Initiative for Asthma (GINA) guidelines [39].

Is there a role for systemic AIT in local allergic rhinitis?

The first steps – observational study

The evidence of a localized allergic response in patients with non-atopic rhinitis suggests that allergen-specific immunotherapy would be beneficial for these patients. As discussed previously, patients with LAR often complain of persistent rhinitis with moderate-severe symptoms, frequently associated with conjuctivitis and asthma. Apart from the natural history, there is a worsening of the disease, with a tendency toward persistent and severe nasal symptoms, increased emergency assistance, and development of conjunctivitis and asthma [31••]. For these reasons, a proportion of these patients require continous pharmacological treatment with nasal corticosteroids and oral antihistamines for the relief of their symptoms [8, 9, 31••].

In order to evaluate the potential role of AIT in local allergic rhinitis, an initial observational study was conducted by Rondón et al. in 2011 [40••]. In this study, 20 adult patients (aged 19–45 years) with moderate or severe LAR

sensitized to grass pollen were evaluated. Ten patients were treated for six months with a pre-seasonal course of grass-specific subcutaneous immunotherapy (SCIT) and with rescue medication in the spring (active group), and 10 patients received rescue medication only (control group) [40••].

In the active group, the six-month course of pre-seasonal SCIT involved a six-week up-dose up-titration, followed by monthly subcutaneous administration of a standardized extract of a mixture of six grass pollens (*Dactylis*, *Festuca*, *Lolium*, *Phleum*, *Poa*, and *Secale* species), administered from September through March. Skin-prick tests, NAPT responses, and determination of levels of grass pollen-specific serum IgG and IgE to *Lolium* and *Phleum* species were performed at 1, 3, 6, and 12 months after beginning SCIT in order to evaluate the immune response. Seasonal symptoms and medication scores from April through June were recorded at baseline and after one year. The results of this study showed that grass SCIT was a safe and effective treatment that induced immunological changes and clinical improvement in patients with LAR. The patients who received SCIT showed significant improvement in nasal tolerance to the allergen compared with the control group, with higher threshold concentrations of grass pollen in NAPTs after 6 and 12 months of treatment, and a negative response to NAPT in 3 of 10 patients (30 %). Significant increases in *Lolium*- and *Phleum*-specific serum IgG antibodies were also detected. A significant reduction in symptoms and rescue medication, and an increase in the number of medication-free days, was observed in the active group compared with the control group. No systemic adverse reactions were observed in the active group. Although a placebo effect may have been present in this study, the important increase in nasal tolerance to NAPT and the increase in serum levels of *Lolium* and *Phleum*-specific IgG antibodies are objective parameters indicative of the beneficial effect of SCIT [40••].

The results of this study show that SCIT with grass pollen is a safe and effective treatment in subjects with LAR, with significant improvement in nasal tolerance to NAPTs and clinical response to natural exposure to the allergen [40••].

New questions – from observational to interventional studies

In light of the interesting results of the observational study, research was conducted in the form of a randomized double-blind placebo-controlled (DBPC) clinical trial to investigate the efficacy and safety of subcutaneous AIT with *D. pteronyssinus* and grass pollen in patients with LAR [41••].

The first DBPC parallel-group phase II clinical trial of subcutaneous AIT with *D. pteronyssinus* (SCIT-DP) conducted in LAR patients proved that SCIT-DP was an effective and well-tolerated treatment [41••] In this phase II clinical trial, 36 subjects with LAR were randomized to receive SCIT (Pangramin Plus *D. pteronyssinus* [ALK]) or placebo for 24 months. SCIT-DP produced significant clinical improvement, with a reduction in symptom and medication scores and an increase in the number of medication-free days, as well as an objective improvement in nasal tolerance to NAPT-DP, compared to placebo, with negative responses to

NAPT-DP in 50 % of the patients. This first DBPC phase-II study provides an indication for AIT in LAR [41••].

Compliance with Ethics Guidelines

Conflict of Interest

Carmen Rondón has had travel/accommodations expenses covered or reimbursed by EAACI.
Paloma Campo has had travel/accommodations expenses covered or reimbursed by EAACI.
Maria José Torres has had travel/accommodations expenses covered or reimbursed by EAACI.
Miguel Blanca has had travel/accommodations expenses covered or reimbursed by EAACI.
Natalia López-Blanca declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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