



Is the evidence of local allergic rhinitis growing?

Carmen Rondón, Ibon Eguiluz-Gracia, and Paloma Campo

Purpose of review

To examine the recent advances on epidemiological studies, diagnostic approach and clinical management of local allergic rhinitis (LAR) in adults and children.

Recent findings

Evidence about LAR is growing especially in pediatric and Asian populations. The prevalence of LAR is lower in Asian countries compared with western countries in both children and adults. LAR is considered a chronic condition and an independent rhinitis phenotype that affects up to 26.5% of nonatopic rhinitis patients. The disease rapidly progress toward the clinical worsening with associated onset of asthma and conjunctivitis, which further impairs patient's quality of life. Nasal Allergen Provocation Test is the diagnostic gold standard that can be complemented by basophil activation test and the detection of specific IgE in nasal secretions. Allergen immunotherapy induces a significant and early improvement in both clinical symptoms and quality of life in LAR patients.

Summary

LAR is a common entity, with different prevalence depending on geographical locations. LAR has to be considered in the process of differential diagnosis in children and adults with rhinitis. Diagnosis of LAR is crucial in order to start an etiologic treatment such as allergen immunotherapy, which has proven to be very effective in these patients.

Keywords

allergen immunotherapy, basophil activation test, local allergic rhinitis, nasal allergen provocation test, nasal specific IgE

INTRODUCTION

Local allergic rhinitis (LAR) is a new phenotype of allergic rhinitis that in the past years has caused an enormous interest and discussion among researchers and clinicians interested in the allergic response of the upper airway. In the last decade, an important effort was made in order to increase the knowledge about LAR in terms of pathophysiology, diagnosis and treatment. Still, many aspects of LAR are not well known.

Recently, a significant number of articles have been published, many of them focused on prevalence of LAR within allegedly nonallergic rhinitis (NAR) patients, especially in Asian countries. It is noteworthy that several of these publications are focused in paediatric populations, increasing the prior evidence that LAR frequently started in childhood [1[■]]. Also, there have been important developments in terms of diagnosis and treatment of the disease. In that sense, recent data supports the fact that allergen immunotherapy (AIT) is the treatment of choice for LAR patients, not only those sensitized to house dust mites (HDM) [2] but also to grass [3,4[■]] and birch pollen [5]. This article will summarize and emphasize the recent developments in this field.

DEFINITION AND CLINICAL CHARACTERISTICS

Local allergic rhinitis is considered an independent phenotype defined by perennial or seasonal rhinitis symptoms, absent systemic atopy measured by skin prick test (SPT) and/or serum allergen-specific IgE (sIgE) and positive nasal allergen provocation test (NAPT) [6–10]. This condition is believed to arise from a localized allergic response in the nasal mucosa, including the synthesis of sIgE [6,11,12]. Epidemiological studies show that LAR is a common disease, which often commences during childhood [13–15] and persists throughout life [16]. A 10-year follow-up study has shown that LAR is a stable rhinitis phenotype not evolving to systemic atopy

Allergy Unit, Hospital Regional Universitario de Malaga-IBIMA, ARA-DyAL, Malaga, Spain

Correspondence to Carmen Rondón, MD, PhD, Laboratorio de Investigación, Hospital Civil, pabellón 5, sótano, Plaza del Hospital Civil, 29009 Malaga, Spain. Tel: +34 951290313; fax: +34 951290302; e-mail: carmenrs61@gmail.com

Curr Opin Allergy Clin Immunol 2018, 18:342–349

DOI:10.1097/ACI.0000000000000456

KEY POINTS

- Evidence of LAR is growing, especially studies performed in children and in Asian countries. Prevalence of LAR is lower in Asian countries compared with western countries.
- LAR is a well differentiated clinical entity with a natural evolution towards worsening and involvement of lower airway.
- Nasal allergen provocation test, detection of nasal sIgE and basophil activation test are the three main diagnostic tools.
- Allergen immunotherapy is an etiologic and clinically effective treatment for LAR.

over time [17,18]. Large population studies investigating LAR prevalence are lacking. Nevertheless, published literature supports that up to 26.5% of adults and children classified in the NAR group fulfil diagnostic criteria for LAR [8,19,20]. LAR is a disease largely unrecognized [19,21], especially because of the poor implementation of NAPT in the diagnostic algorithm of many centres [22,23].

Allergic rhinitis and LAR share many features including seasonal or perennial symptoms, a type-2 nasal inflammation and the response to oral antihistamines or intranasal corticosteroids [19,24]. Moreover, both rhinitis phenotypes respond similarly to AIT [2,3,4⁵]. The allergens triggering rhinitis symptoms are also similar in both cases, although moulds are more frequent in LAR, and cat and dog dander prevail in allergic rhinitis [19,24,25].

Our group has recently identified several differential characteristic of LAR compared with NAR such as the predominance of younger, nonsmoker and female patients, the higher severity of symptoms, and the family history of atopy [24]. Among the different NAR phenotypes [26], nonallergic rhinitis with eosinophilia syndrome (NARES) is the condition showing more similarities with LAR, including a type 2 nasal inflammation in the absence of systemic atopy [27]. Nevertheless, the proportion of NARES individuals who fulfil criteria for LAR diagnosis is currently unknown, as many studies on NARES do not include a NAPT in their investigation protocol [28,29].

RECENT EVIDENCE OF LOCAL ALLERGIC RHINITIS IN DIFFERENT GEOGRAPHICAL LOCATIONS

Clinical and epidemiological studies have demonstrated that LAR affects individuals from different

countries, ethnic groups and ages. Studies were started in United States by Huggins and Brostoff [30] and later on mostly in Western countries. However, the most recent studies in both children and adults have been performed in Asian populations, which give important information about prevalence of LAR in genetically diverse patients. Table 1 summarizes the publications regarding LAR prevalence in adults and children.

In this section, we analyse in depth the characteristics/quality of the prevalence studies undertaken in adult and paediatric population, unmet needs and lines for further researches.

Recent evidence of local allergic rhinitis in adult populations

Studies performed in adults show that significant differences in the prevalence and the demographic features of LAR patients might exist between geographical areas (Table 1). Still, many aspects remain unknown in this regard, and the cause of these differences is not clear. Some of the reasons could be for instance: variations in the allergen exposure between geographical areas with distinct climates, environmental factors (air pollution, temperature or humidity), age or genetic differences.

Recent data have shed some light into the possible influence of environmental exposure to allergens on LAR development [31]. This study found a high proportion of LAR among individuals with seasonal rhinitis and absence of atopy in two different geographical areas with high concentration of grass, which demonstrates that LAR is not a mild form of allergic rhinitis limited to areas with low allergenic load.

In terms of age differences, the prevalence of LAR in elderly rhinitis patients [16] is slightly lower (21%) than in young adults (26%) [25,32³³]. In the study by Bozek *et al.* [16] performed in 219 patients over 65 years, HDM were the main allergen in LAR patients as seen in younger adults of the same geographical area [32³³]. On the other hand, older LAR patients were more frequently current or former smokers, had more commonly a family history of atopy, and had milder symptoms as compared with young adults with LAR.

In terms of geographical/genetic differences, three recent studies performed in Asian countries, have showed a lower prevalence of LAR (7.4–18.9%) compared with western countries [33–35], and that HDM is the most common allergen. In the Jung [34] study, LAR patients had longer duration of disease, tended to be older and had higher medication score than allergic rhinitis patients.

Table 1. Summary of studies in local allergic rhinitis in adult and paediatric populations

Author	Year	Country	Study groups	Group age	Allergens	Positive NAPT response (n, %)
Carney <i>et al.</i>	2002	UK	21 IR (perennial)	Adults	DP/DF, epithelia, grass	13/21 (61.9%)
Wedback <i>et al.</i>	2005	Sweden	15 IR (seasonal)	Adults	Birch, Timothy	7/15 (46.7%)
Rondon <i>et al.</i> [6]	2007	Spain	50 IR (perennial)	Adults	DP	27/50 (54%)
Rondon <i>et al.</i>	2008	Spain	32 IR (seasonal)	Adults	Grass, olive	21/32 (65.6%)
Cruz Niesvaara	2012	Spain	30 IR (perennial)	Adults	DP	19/30 (63.3%)
Rondon <i>et al.</i>	2012	Spain	158 IR (seas/perennial)	Adults	DP, alternaria, pollens, epithelia	110/158 (69.6)
Cheng <i>et al.</i>	2013	China	147 IR (perennial)	Adults	DF	12/147 (8.1%)
Chang <i>et al.</i>	2014	Korea	62 IR (perennial)	Adults	DP	22/62 (35.5%)
Bozek <i>et al.</i> [16]	2015	Poland	131 IR (perennial)	Adults >65 years	DP, pollens, moulds, cat	46/131 (35.1%)
Klimek <i>et al.</i>	2015	Germany	2 IR (perennial)	Adults	Alternaria	2 (case report)
Jang <i>et al.</i> [33]	2015	Korea	110 IR (perennial)	Adults	DP	12/110 (10.9%)
Refaat <i>et al.</i>	2015	Egypt	40 IR (perennial)	Adults	DP	25/40 (62.5%)
Blanca-Lopez <i>et al.</i> [31]	2016	Spain	52 NAR (seasonal)	Adults	<i>Phleum</i> spp.	28/52 (53.8%)
Jung <i>et al.</i> [34]	2017	Korea	81 NAR (perennial)	Adults	DF	6/81 (7.4%)
Venegas-Díaz <i>et al.</i>	2017	Spain	80 NAR (seas/perennial)	Adults	DP/salsola/cupressus	21/80 (26.25%)
Krajewska-Wojtyś <i>et al.</i>	2017	Poland	84 NAR (perennial)	Adults	DP/alternaria/cat	21/84 (25%)
Tao <i>et al.</i> [35]	2018	China	79 NAR (seas/perennial)	Adults	Pollen/DP	15/79 (18.9%) local IgE, no NAPT
Fuiano <i>et al.</i> [36]	2012	Italy	36 NAR (perennial)	4–18	Alternaria	23/36 (64%)
Adinoff <i>et al.</i>	2015	EEUU	30 IR (seasonal/ perennial)	Adults/ Children	Tree, weed, Timothy, cat	11/30 (36.7%)
Buntarickporpan <i>et al.</i>	2015	Thailand	25 NAR (perennial)	8–18	DP	2/54 (3.7%)
Duman <i>et al.</i> [39]	2016	Turkey	28 NAR (seas/perennial)	5–16	DP, DF, grass mix	7/28 (25%)
Zicari <i>et al.</i> [37]	2016	Italy	18 NAR (perennial)	6–12	DP, DF, Lolium	12/18 (66.6%)
Prieto <i>et al.</i>	2016	Spain	45 NAR (perennial)	10–20	HDM, pollens, epithelia	30/45 (66%)
Krajewska-Wojtyś <i>et al.</i> [32**]	2016	Poland	121 NAR (seasonal)	12–18	<i>Phleum</i> spp., artemisia, birch	73/121 (60.3%)
Blanca-Lopez <i>et al.</i> [31]	2016	Spain	9 NAR (seasonal)	7–18	<i>Phleum</i> spp.	4/9 (44.4%)
Ha <i>et al.</i> [15]	2017	Korea	64 NAR (perennial)	1–18	DP	5/64 (7.8%)

DF, *Dermatophagoides Farinae*; DP, *Dermatophagoides pteronyssinus*; IR, idiopathic rhinitis; NAPT, nasal allergen provocation test; NAR, nonallergic rhinitis; seas: seasonal.

Local allergic rhinitis in paediatric population

Most studies analysing LAR in paediatric populations have appeared in the last 3 years (Table 1), with close to 400 children recruited. Similarly to what has been observed in adults, prevalence of LAR is higher in Western countries (range 36.7–66.6%) [13,31,32**,36,37] compared with Asian [15,38,39]. A study performed in Thailand in 54 NAR children showed that only 3.7% had LAR by NAPT [38], being 25% in Turkey [39] and 7.8% in Korea [15]. House dust mites is also the most common allergen in Asian countries [15,38], although grass is also relevant in Turkey [38].

The largest study has been performed in 121 NAR children with seasonal rhinitis in Poland [32**], where LAR to several pollens (*Phleum* spp.,

Artemisia spp. and birch) was confirmed in 17 (16.6%), 6 (5.9%), and 9 (8.9%) patients, respectively, by NAPT. In the study by Zicari *et al.* [37], 12 out of 18 children (66.7%) had a positive response to at least one NAPT: 6 to HDM (33.3%), 5 to grass (27.8%) and 1 to both allergens (5.6%).

ADVANCEMENTS IN LOCAL ALLERGIC RHINITIS DIAGNOSIS

NAPT is the diagnostic gold standard for LAR [6,11,12]. This technique has an optimal sensitivity and specificity profile for the disease [6,8,19] and displays a high level of reproducibility [7,17,18]. It is a very well tolerated technique as severe adverse reactions are extremely uncommon (0.04%) (Rondon,

unpublished data: The preliminary results of this study have been presented in the Annual Congress of the European Academy of Allergy and Clinical Immunology; Munich, Germany; 20–26 May 2018).

The assessment of NAPT response should always include both symptom evaluation and an objective measurement using acoustic rhinometry among other methods [40]. Recently a position statement from the European Academy of Allergy and Clinical Immunology progressed in the standardization of key aspects of NAPT including the challenge protocol, and the allergen concentrations to administer [23]. On the other hand, NAPT consumes a significant amount of time and human resources, and requires trained personnel [23,40]. To decrease the number of visits needed to reach the final diagnosis, our group developed a protocol to perform NAPT with multiple allergens in one session [41]. This approach achieved a 75% reduction in the total number of visits required for NAR patients, and a 55% reduction in the case of LAR individuals [41].

Since the description of LAR, several authors have put significant effort to detect sIgE in the nasal secretions (NsIgE) as a mean to diagnose LAR [42]. Different methods have been described to collect and process nasal secretions, including sample lio-philization [43]. Overall, these techniques display a sensitivity of ~30%, even when a nasal challenge precedes the collection of the sample [6,11,12]. This low sensitivity might be because of the dilutional effect or to the extensive sample processing before quantification. On the other hand, the detection of

NsIgE is highly specific, and it serves as confirmatory test for LAR diagnosis [24]. Recently our group has described an automated, minimally invasive method to detect NsIgE with reduced sample manipulation [44]. In this method, the solid phase of the commercial ImmunoCAP is placed for 10 min in the nasal mucosa after NAPT. The solid phase is subsequently processed according to the ImmunoCAP automated procedure. Nasal ImmunoCAP showed a sensitivity of 44% for the diagnosis of LAR because of *Dermatophagoides pteronyssinus* sensitization [44]. This increased capacity probably derives from the lower manipulation of the sample, as the binding of NsIgE to the allergen occurs in the nasal cavity.

The development of noninvasive in-vitro diagnostic tests will help increasing the recognition of the disease. In this regard, our group has pioneered the implementation of basophil activation test (BAT) for LAR diagnosis [45]. In a group of 16 individuals with LAR because of *D. pteronyssinus* sensitization, the BAT displayed a sensitivity of 50%. In four of the BAT-positive patients, the IgE-mediated activation of basophils was confirmed by wortmannin pretreatment [45]. In another study, including 12 LAR patients because of *Olea europaea* sensitization, the BAT with the whole pollen extract showed a diagnostic sensitivity of 66%, and of 33% when using the pollen's major allergen, *Ole e 1* [46]. Although these results require confirmation in larger studies and for other allergens, the implementation of BAT appears as a promising approach for LAR diagnosis (Fig. 1).

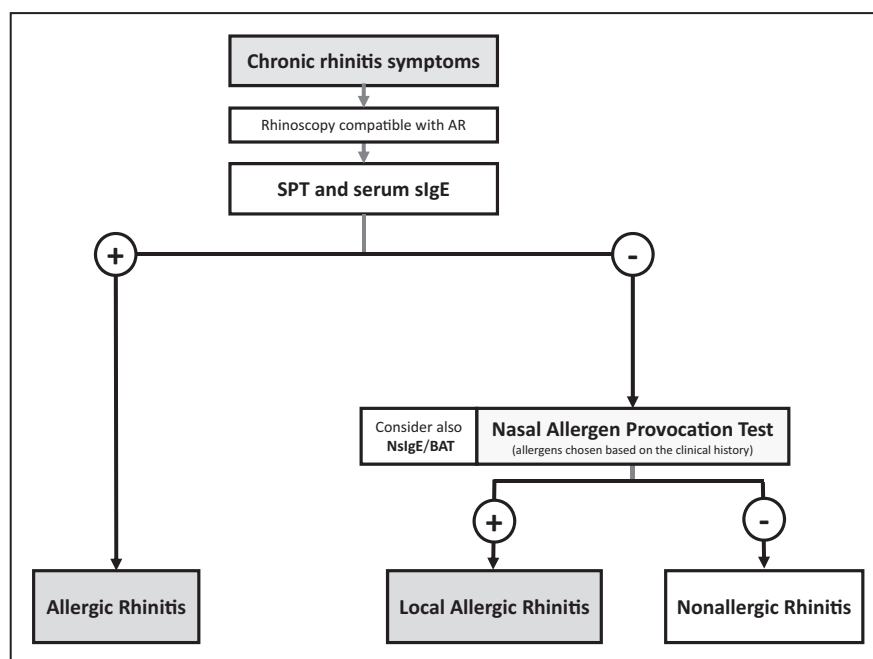


FIGURE 1. Diagnostic algorithm of local allergic rhinitis. AR, allergic rhinitis; BAT, basophil activation test; NsIgE: nasal allergen-specific IgE; sIgE: allergen-specific IgE; SPT, skin prick test.

NATURAL EVOLUTION

The clinical similarities between LAR and allergic rhinitis [25,32²²,47] led investigators to suggest that LAR constituted the initial state of allergic rhinitis. An early retrospective study including 19 LAR individuals reported a significant conversion rate to systemic atopy [48]. However, this study has important limitations including the small number of patients, the lack of a healthy control group or the irregular intervals between evaluations [48]. Recently, the first 10-year follow-up study of a cohort of 194 LAR patients and 130 matched healthy controls indicated that LAR is an independent rhinitis phenotype, which tends to worsen and to associate comorbidities over time [18]. During the first 5 years after disease onset, the severity of rhinitis significantly increases with progressive impairment of quality of life, a higher incidence of asthma and conjunctivitis, and more frequent visits to the emergency department [17]. LAR continues worsening during the subsequent second 5 years, but importantly, at a much lower rate [18]. Both allergic rhinitis and NAR are well known risk factors for the development of asthma [56]. The frequent association of nasal, ocular and bronchial symptoms in LAR patients supports the concept of one airway one disease [56] and remark the role of respiratory mucosa in the initiation and progression of the disease.

The development of systemic atopy was low and comparable between LAR patients (9.7%) and healthy controls (7.8%) indicating that LAR and

allergic rhinitis are two independent phenotypes [18] (Fig. 2). During the first 10 years of evolution, LAR severity increases from 19 to 42%, and the allergen concentration tolerated in NAPT decreased. Moreover, there was a 12% incidence of asthma, the percentage of severe asthma attacks attended in emergency departments doubled, and the FEV1% decreased [18]. Additionally, the patients self-reported a clinical worsening (42%), with negative impact on health (23%), and clinically relevant impairment of quality of life (30%). These results define LAR as a chronic respiratory disease naturally progressing towards the worsening and the development of asthma and new nasal sensitizations [18]. This prospective study also identifies the first 2–4 years of LAR evolution as a window of opportunity for early intervention and prevention of future complications [17,18].

ALLERGEN IMMUNOTHERAPY IN LOCAL ALLERGIC RHINITIS

Allergen immunotherapy is the etiological treatment for airway allergy and has the ability to modify the natural course of the disease [49–54]. In the last years, researchers have focused their interest in exploring the potential benefit of subcutaneous specific immunotherapy (SCIT) in patients with LAR, especially after knowing the natural tendency of LAR towards the clinical worsening and the onset of asthma [17,18,48].

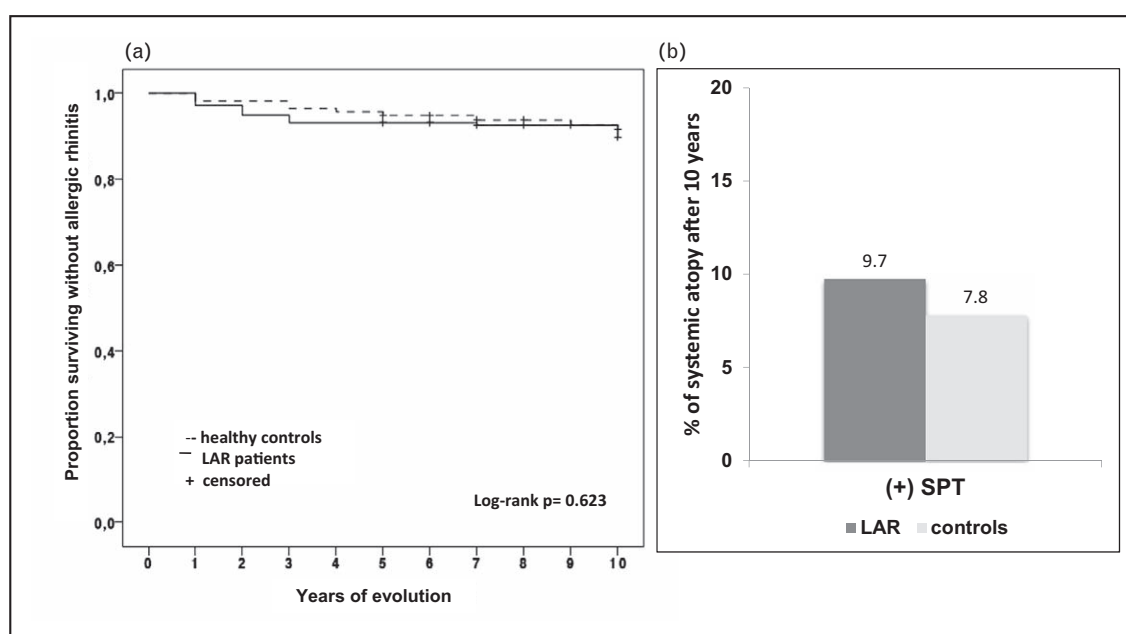


FIGURE 2. (a) Kaplan–Meier curves showing surviving proportion of local allergic rhinitis patients (continuous line) and healthy controls (dotted line) without systemic atopy after 10 years of follow-up. (adapted from [18]). (b) Incidence of allergic rhinitis in LAR patients (dark gray bar) and healthy controls (light gray bar) after 10 years of follow-up.

Table 2. Summary of allergen immunotherapy study characteristics in local allergic rhinitis

Study ID	Total N	Study design	Comparator	Allergen	Immunotherapy product	Extract characteristics	AIT duration
Rondon <i>et al.</i> [3]	20	Observational	Medication	Grass mix pollen: <i>Dactylis</i> , <i>Festuca</i> , <i>Lolium</i> , <i>Phleum</i> , <i>Poa</i> , and <i>Secale</i> species	Pangramin Plus (ALK-Abello, Madrid, Spain)	Allergen adsorbed in aluminum hydroxide	6 months
Rondon <i>et al.</i> [2]	36	RDBBC	Placebo	<i>D. pteronyssinus</i>	Pangramin Plus (ALK-Abello, Madrid, Spain)	Allergen adsorbed in aluminum hydroxide	2 years
Rondon <i>et al.</i> [4 [■]]	56	RDBBC	Placebo	<i>Phleum pratense</i>	Depigoid (LETI, S.L. Tres Cantos, Madrid, Spain)	Depigmented polymerized extract	2 years
Bozek <i>et al.</i> [5]	29	RDBBC	Placebo	<i>Betula verrucosa</i>	Puretal (HAL Allergy BV, Leiden, The Netherlands)	Allergoid adsorbed in aluminum hydroxide	2 years

AIT, allergen immunotherapy.

Since 2011, four different studies have provided evidence that SCIT is an effective and well tolerated treatment for LAR: one observational study of SCIT with a mixture of six grass pollens [3], and three doubled-blind placebo-controlled clinical trials (DBPCCT) of SCIT with *D. pteronyssinus* [2], *Phleum pratense* [4[■]] and *Betula verrucosa* pollen [5]. Table 2 shows the main characteristics and clinical results of these studies. Local allergic rhinitis is an example of precision medicine, where a correct early diagnosis enables the establishment of an etiologic treatment (AIT). Unfortunately, in clinical practice, LAR remains under-diagnosed [20].

The clinical effect of SCIT in LAR patients induces significant improvements in combined symptoms-medication scores, number of medication-free days, quality of life, and tolerance to higher allergen concentration in NAPT [2,3,4[■],5]. The clinical effect is evident as early as 6 months after SCIT initiation for grass mix, *Phleum* spp. and *D. pteronyssinus* progressing till the end of treatment in all studies [2,3,4[■]]. In the case of birch-SCIT the earliest clinical evaluation was made after 1 year. Moreover, SCIT effect over the number of medication free-days and nasal tolerance to allergen were not investigated [5]. *Phleum*-SCIT trial [4[■]] detected for the first time a clinical effect of SCIT on the conjunctival symptoms and asthma control of LAR patients, already apparent after 6 months of treatment.

Improvements in quality of life are especially relevant for long-term treatments like AIT [55]. Patients' perception is clearly important in the management of the disease and patient compliance [56]. The pollen-SCIT effect on quality of life in LAR individuals was explored by Rhino-conjunctivitis Quality of Life Questionnaires (RQLQ) in two clinical trials with different results [4[■],5]. Changes in

RQLQ score at least 0.5 are defined clinically important by Juniper [57,58]. The *Phleum*-SCIT clinical trial [4[■]] showed a short-term and sustained clinically important and statistically significant effect on the RQLQ perceived by LAR patients starting after 6 months of treatment. In birch-SCIT trial, a statistically significant but not clinically important reduction of RQLQ score was achieved possibly because of the small sample size [5].

All studies conducted until now have explored the clinical effect of SCIT in LAR, however, our knowledge about their immunological and potential long-term effects remains largely unstudied. Nevertheless, the data available suggest a similar immunological effect of AIT in patients with LAR and allergic rhinitis, with increase in serum levels of allergen-specific IgG4 and in the allergen concentration tolerated in nasal provocation throughout the treatment [2,3,4[■],5]. It is necessary to investigate the possible immunological mechanisms involved and the potential long-term effect of AIT in this disease.

After the excellent results obtained by SCIT in LAR, a phenotype of allergic rhinitis localized in the nasal mucosa, there is a need for exploring new types and routes of immunotherapy in further studies, as sublingual immunotherapy and local nasal immunotherapy.

CONCLUSION

In the last decade evidence in LAR is indeed growing. A significant number of articles regarding prevalence, evolution, diagnosis and treatment have been published from different geographical locations and target populations (adults, children and elderly patients). Local allergic rhinitis is a chronic

disease with a natural evolution towards worsening, and in which AIT has demonstrated to be clinically effective and well tolerated, and therefore, the treatment of choice for LAR. For that matter, LAR should be a differential diagnosis in rhinitis patients with negative basic allergological workup, regardless of their age, in order to offer the patient, the best treatment option.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the 'Instituto de Salud Carlos III' of the Ministry of Economy and Competitiveness (National Health Ministry FIS PI11/02619, FIS PI12/00900, FIS PI14/ 0864 and FIS PI17/01410; and by the European Regional Development Fund (ERDF): RiRAAF RD07/0064 and ARADyAL RD16/0006/000; Consejería de Salud PI-0346-2016 and PC-0098-2017. This work was also supported by the 'Rio Hortega' funding scheme of 'Instituto de Salud Carlos III' (CM17/00140)

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Rondon CCP, Eguluz-Gracia I, Plaza C, *et al.* Local allergic rhinitis is an independent rhinitis phenotype: the results of a 10-year follow-up study. *Allergy* 2018; 73:470–478.
- This prospective 10-year study shows that the LAR is a chronic condition tending to the clinical worsening and the association to conjunctivitis and bronchial symptoms. Moreover, the conversion rate to systemic atopy is comparable between LAR patients and healthy controls, implying that LAR is an independent rhinitis phenotype.
2. Rondon C, Campo P, Salas M, *et al.* Efficacy and safety of D. pteronyssinus immunotherapy in local allergic rhinitis: a double-blind placebo-controlled clinical trial. *Allergy* 2016; 71:1057–1061.
3. Rondon C, Blanca-Lopez N, Aranda A, *et al.* Local allergic rhinitis: allergen tolerance and immunologic changes after preseasonal immunotherapy with grass pollen. *J Allergy Clin Immunol* 2011; 127:1069–1071.
4. Rondon C, Blanca-Lopez N, Campo P, *et al.* Specific immunotherapy in local allergic rhinitis: a randomized, double-blind placebo-controlled trial with Phleum pratense subcutaneous allergen immunotherapy. *Allergy* 2018; 73:905–915.
- This study is the first DBPCCT of Phleum-SCIT in LAR, and shows that SCIT induces in the short-term a beneficial effect over LAR patients comparable with that of allergic rhinitis patients.
5. Bozek A, Kolodziejczyk K, Jarzab J. Efficacy and safety of birch pollen immunotherapy for local allergic rhinitis. *Ann Allergy Asthma Immunol* 2018; 120:53–58.
6. Rondon C, Romero JJ, Lopez S, *et al.* Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol* 2007; 119:899–905.
7. Lopez S, Rondon C, Torres MJ, *et al.* Immediate and dual response to nasal challenge with Dermatophagoides pteronyssinus in local allergic rhinitis. *Clin Exp Allergy* 2010; 40:1007–1014.
8. Rondon C, Canto G, Blanca M. Local allergic rhinitis: a new entity, characterization and further studies. *Curr Opin Allergy Clin Immunol* 2010; 10:1–7.

9. Rondon C, Bogas G, Barrionuevo E, *et al.* Nonallergic rhinitis and lower airway disease. *Allergy* 2017; 72:24–34.
10. Powe DG, Jagger C, Kleinjan A, *et al.* 'Entropy': localized mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy* 2003; 33:1374–1379.
11. Rondon C, Dona I, Lopez S, *et al.* Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response. *Allergy* 2008; 63:1352–1358.
12. Rondon C, Fernandez J, Lopez S, *et al.* Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis. *J Allergy Clin Immunol* 2009; 124:1005.e1–1011.e1.
13. Prieto del Prado A, Gracia IE, Gador B, *et al.* Analysis of clinical characteristics of a paediatric population with rhinitis. *J Allergy Clin Immunol* 2017; 139:AB156.
14. Lee KS, Yu J, Shim D, *et al.* Local immune responses in children and adults with allergic and nonallergic rhinitis. *PLoS One* 2016; 11: e0156979.
15. Ha EK, Na MS, Lee S, *et al.* Prevalence and clinical characteristics of local allergic rhinitis in children sensitized to house dust mites. *Int Arch Allergy Immunol* 2017; 174:183–189.
16. Bozek A, Ignasiak B, Kasperska-Zajac A, *et al.* Local allergic rhinitis in elderly patients. *Ann Allergy Asthma Immunol* 2015; 114:199–202.
17. Rondon C, Campo P, Zambonino MA, *et al.* Follow-up study in local allergic rhinitis shows a consistent entity not evolving to systemic allergic rhinitis. *J Allergy Clin Immunol* 2014; 133:1026–1031.
18. Rondon C, Campo P, Eguluz-Gracia I, *et al.* Local allergic rhinitis is an independent rhinitis phenotype: the results of a 10-year follow-up study. *Allergy* 2018; 73:470–478.
19. Rondon C, Campo P, Togias A, *et al.* Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol* 2012; 129: 1460–1467.
20. Hamizan AW, Rimmer J, Alvarado R, *et al.* Positive allergen reaction in allergic and nonallergic rhinitis: a systematic review. *Int forum Allergy Rhinol* 2017; 7:868–877.
21. Rondon C, Campo P, Blanca-Lopez N, *et al.* More research is needed for local allergic rhinitis. *Int Arch Allergy Immunol* 2015; 167:99–100.
22. Hellings PW, Klimek L, Cingi C, *et al.* Non-allergic rhinitis: position paper of the European Academy of Allergology and Clinical Immunology. *Allergy* 2017; 72:1657–1665.
23. Augé J, Vent J, Agache I, *et al.* EAACI Position paper on the standardization of nasal allergen challenges. *Allergy* 2018. [Epub ahead of print]
24. Campo P, Salas M, Blanca-Lopez N, Rondon C. Local allergic rhinitis. *Immunol Allergy Clin North Am* 2016; 36:321–332.
25. Rondon C, Campo P, Galindo L, *et al.* Prevalence and clinical relevance of local allergic rhinitis. *Allergy* 2012; 67:1282–1288.
26. Papadopoulos NG, Bernstein JA, Demoly P, *et al.* Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. *Allergy* 2015; 70:474–494.
27. Papadopoulos NG, Guibas GV. Rhinitis subtypes, endotypes, and definitions. *Immunol Allergy Clin North Am* 2016; 36:215–233.
28. Powe DG, Groot Kormelink T, Sisson M, *et al.* Evidence for the involvement of free light chain immunoglobulins in allergic and nonallergic rhinitis. *J Allergy Clin Immunol* 2010; 125:139.e1–145.e3.
29. Becker S, Rasp J, Eder K, *et al.* Nonallergic rhinitis with eosinophilia syndrome is not associated with local production of specific IgE in nasal mucosa. *Eur Arch Oto-rhino-laryngol* 2016; 273:1469–1475.
30. Huggins KG, Brostoff J. Letter: local IgE antibodies in allergic rhinitis. *Lancet* 1975; 2:618.
31. Blanca-Lopez N, Campo P, Salas M, *et al.* Seasonal local allergic rhinitis in areas with high concentrations of grass pollen. *J Investig Allergol Clin Immunol* 2016; 26:83–91.
32. Krajewska-Wojtyś A, Jarzab J, Gawlik R, Bozek A. Local allergic rhinitis to pollen is underdiagnosed in young patients. *Am J Rhinol Allergy* 2016; 30:198–201.
- Study performed in 121 Polish children aged 12–18 years, with confirmed NAR and seasonal symptoms. LAR to different pollens was confirmed in 60.3% of children, with a nonsignificant faster increase in nasal IgE compared with allergic rhinitis patients.
33. Jang TY, Kim YH. Nasal provocation test is useful for discriminating allergic, nonallergic, and local allergic rhinitis. *Am J Rhinol Allergy* 2015; 29: e100–e104.
34. Jung CG, Lee JH, Ban GY, *et al.* Prevalence and clinical characteristics of local allergic rhinitis to house dust mites. *Yonsei Med J* 2017; 58: 1047–1050.
35. Tao XY, Ng CL, Chen D, *et al.* Clinical characteristics and allergen sensitization patterns of patients with local allergic rhinitis in southern China. *Int Arch Allergy Immunol* 2018; 175:107–113.
36. Fuiano N, Fusilli S, Incorvaia C. A role for measurement of nasal IgE antibodies in diagnosis of Alternaria-induced rhinitis in children. *Allergol Immunopathol (Madr)* 2012; 40:71–74.
37. Zicari AM, Occasi F, Di Fraia M, *et al.* Local allergic rhinitis in children: novel diagnostic features and potential biomarkers. *Am J Rhinol Allergy* 2016; 30:329–334.

38. Buntarickpornpan P, Veskitkul J, Pacharn P, *et al.* The prevalence and clinical characteristics of local allergic rhinitis in Thai children. *J Allergy Clin Immunol* 2005; 135:AB282.
39. Duman H, Bostanci I, Ozmen S, Dogru M. The relevance of nasal provocation testing in children with nonallergic rhinitis. *Int Arch Allergy Immunol* 2016; 170:115–121.
40. Dordal MT, Lluch-Bernal M, Sanchez MC, *et al.*, SEAIC Rhinoconjunctivitis Committee. Allergen-specific nasal provocation testing: review by the rhinoconjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. *J Investig Allergol Clin Immunol* 2011; 21:1–12.
41. Rondon C, Campo P, Herrera R, *et al.* Nasal allergen provocation test with multiple aeroallergens detects polysensitization in local allergic rhinitis. *J Allergy Clin Immunol* 2011; 128:1192–1197.
42. Campo P, Rondon C, Gould HJ, *et al.* Local IgE in nonallergic rhinitis. *Clin Exp Allergy* 2015; 45:872–881.
43. Castelli S, Arasi S, Pawankar R, Matricardi PM. Collection of nasal secretions and tears and their use in allergology. *Curr Opin Allergy Clin Immunol* 2018; 18:1–9.
44. Campo P, Del Carmen Plaza-Seron M, Eguiluz-Gracia I, *et al.* Direct intranasal application of the solid phase of ImmunoCAP(R) increases nasal specific immunoglobulin E detection in local allergic rhinitis patients. *Int Forum Allergy Rhinol* 2018; 8:15–19.
45. Gomez E, Campo P, Rondon C, *et al.* Role of the basophil activation test in the diagnosis of local allergic rhinitis. *J Allergy Clin Immunol* 2013; 132: 975.e1–976.e5.
46. Campo P, Villalba M, Barrionuevo E, *et al.* Immunologic responses to the major allergen of *Olea europaea* in local and systemic allergic rhinitis subjects. *Clin Exp Allergy* 2015; 45:1703–1712.
47. Ok A, Enbom H, Eriksson NE, *et al.* Seasonal nonallergic rhinitis (SNAR)—a new disease entity? A clinical and immunological comparison between SNAR, seasonal allergic rhinitis and persistent nonallergic rhinitis. *Rhinology* 2005; 43:86–92.
48. Sennekamp J, Joest I, Filipiak-Pittroff B, *et al.* Local allergic nasal reactions convert to classic systemic allergic reactions: a long-term follow-up. *Int Arch Allergy Immunol* 2015; 166:154–160.
49. Bousquet J, Van Cauwenberge P, Khaltaev N, *et al.* Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108(5 Suppl): S147–S334.
50. Brozek JL, Bousquet J, Baena-Cagnani CE, *et al.* Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; 126:466–476.
51. Canonica GW, Bousquet J, Mullol J, *et al.* A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007; 62(Suppl 85):17–25.
52. Muraro A, Clark A, Beyer K, *et al.* The management of the allergic child at school: EAACI/GA2LEN Task Force on the allergic child at school. *Allergy* 2010; 65:681–689.
53. Dykewicz MS, Hamilos DL. Rhinitis and sinusitis. *J Allergy Clin Immunol* 2010; 125(2 Suppl 2):S103–S115.
54. James LK, Shamji MH, Walker SM, *et al.* Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol* 2011; 127:509.e1–516.e5.
55. Horn A, Zeuner H, Wolf H, Schnitker J. Health-related quality of life during routine treatment with the SQ-standardised grass allergy immunotherapy tablet: a non-interventional observational study. *Clin drug Investig* 2016; 36:453–462.
56. Bousquet J, Khaltaev N, Cruz AA, *et al.*, World Health Organization; GA(2)-LEN; AllerGen. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63(Suppl 86):8–160.
57. Juniper EF. Quality of life questionnaires: does statistically significant = clinically important? *J Allergy Clin Immunol* 1998; 102:16–17.
58. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996; 98: 843–845.