



Allergen Immunotherapy for Local Respiratory Allergy

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Abstract

Purpose of Review Local respiratory allergy (LRA) is an eosinophilic phenotype of chronic airway disease. Three entities have been described within the LRA spectrum: local allergic rhinitis (LAR) and local allergic asthma (LAA) in non-atopic patients, and dual allergic rhinitis (DAR) in atopic patients (coexistence of LAR and allergic rhinitis). In this article, we aim to review the current evidence on the therapeutic options for LRA.

Recent Findings No controlled study has assessed the effect of standard therapy (oral antihistamines, intranasal or inhaled corticosteroids, bronchodilators) in LRA subjects. Three randomized clinical trials and one observational study demonstrated that allergen immunotherapy (AIT) is able to control nasal and ocular symptoms, decrease the need for rescue medication, and improve quality of life in LAR individuals.

Summary Nasal or inhaled steroids can be expected to improve eosinophilic inflammation in LRA patients but cannot change the natural course of the disease. Moreover, the long-term and disease-modifying effects of AIT in LRA subjects need to be investigated.

Keywords Allergen immunotherapy · Dual allergic rhinitis · Endophenotypes · Local allergic asthma · Local allergic rhinitis · Local respiratory allergy

Introduction

Chronic rhinitis is an inflammatory disease of the nasal mucosa affecting > 30% of the Western population [1•]. The condition is responsible for a significant burden on the health systems in terms of both direct and indirect costs [1•]. Moreover, chronic rhinitis is associated with other inflammatory diseases of the respiratory mucosa, further amplifying its impact [2]. Nevertheless, the condition has been historically trivialized, and only in recent years, it has gained significant attention from physicians and researchers.

Chronic rhinitis has been classically divided into the allergic rhinitis (AR) and the non-allergic rhinitis (NAR) phenotypes [1•, 3]. AR patients are defined by the positivity of skin prick test (SPT) and/or serum allergen-specific (s)IgE [4].

Conversely, the negativity of both classical markers of atopy identifies NAR individuals [5•]. Nevertheless, several evidences indicate the existence of a new allergic phenotype of rhinitis in non-atopic patients who display nasal-specific reactivity to aeroallergens. This phenotype has been termed local allergic rhinitis (LAR) [6], and the diagnosis requires the implementation of the nasal allergen challenge (NAC) in the clinical algorithms for rhinitis [7••]. To complicate further the field, recent evidence suggests that nasal reactivity to aeroallergens with and without positive SPT can coexist in the same patient [8••].

The endotype guides treatment options in rhinitis [1•]. Allergic rhinitis and other eosinophilic endotypes usually respond to standard therapy (antihistamines and corticosteroids) [9]. Moreover, allergic forms of rhinitis, regardless of the atopic state, can benefit from a specific etiological treatment such as allergen immunotherapy (AIT) [10, 11••]. In this chapter, we will review the treatment options for local respiratory allergy with emphasis on AIT.

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Phenotypes of Local Respiratory Allergy

The definition of AR requires the positivity of at least one of the two classical markers of atopy (SPT and serum sIgE) in a

patient with a clinical history suggestive of allergy [4]. The consistency between clinical history (symptoms pattern) and atopy tests is crucial to establish the diagnosis of AR, as a significant proportion of healthy subjects also displays positive tests (they are atopic but not allergic) [12]. In cases with discrepancies between the results of IgE-sensitization tests and symptoms pattern, a NAC could help establish the clinical relevance of IgE-sensitization [7•]. By definition, AR patients test positive to the NAC, and NAR individuals display negative results [13].

Interestingly, up to one-fourth of non-atopic rhinitis patients with negative SPT and serum sIgE also display positive NAC responses, thus fulfilling criteria for LAR diagnosis [6, 14]. This fact further demonstrates that atopy and allergy reflect different phenomena. Importantly, a NAC is required to discriminate between LAR and NAR individuals [15]. Several features can help identify candidate subjects for a NAC among non-atopic rhinitis patients. As compared with NAR, LAR individuals are more frequently non-smoker women with family history of atopy and an earlier rhinitis onset [6]. As compared with LAR, AR individuals suffer from more severe rhinitis symptoms and react to lower concentrations of aeroallergens in the NAC [16, 17]. Similar to AR, house dust mites (HDM) and grass pollen are the most frequent allergens involved in the perennial and seasonal cases of LAR, respectively [18, 19•]. Nevertheless, nasal reactivity to *Alternaria alternata* is more often related to LAR than to AR cases, whereas *Olea europaea* and animal epithelia are more frequently involved in AR than in LAR cases [18, 19•].

Other common situation in the clinical practice is to find rhinitis patients with positive SPT to seasonal allergens only but suffering from perennial symptoms with seasonal exacerbation. This scenario was classically explained by the cooperation of allergic and non-allergic mechanisms in the same rhinitis patient (mixed rhinitis, MR) [20]. Nevertheless, recent evidence suggests that a significant proportion of these subjects display positive NAC responses to both seasonal and perennial allergens [8•], implying that “local” and “systemic” sensitization to aeroallergens can coexist in the same individual. This new allergic phenotype has been termed dual allergic rhinitis (DAR). Interestingly, DAR and AR individuals react to similar concentrations of seasonal and perennial allergens in the nasal challenge, but AR patients display higher concentrations of serum sIgE against seasonal allergens [8•]. As compared with MR individuals, DAR patients are younger and their nasal symptoms start more frequently with a seasonal pattern with further progression to perennial symptoms [8•]. This observation might be useful to identify candidate individuals for a NAC, among atopic rhinitis patients with discrepancies between clinical symptom pattern and IgE-sensitization tests.

Endotyping Local Respiratory Allergy

Specific nasal reactivity to aeroallergens is associated to eosinophilic inflammation, regardless of the atopic status for the corresponding allergen [21, 22]. Upon a positive NAC, allergic patients (AR, LAR, MR, and DAR) experience increases of eosinophil cationic protein (ECP) in the nasal secretions [8•, 16]. In allergic individuals, nasal ECP increases progressively during 24 h following a positive NAC [17, 23]. Conversely, a negative NAC does not induce increases of nasal ECP, even in atopic rhinitis patients [8•]. A positive NAC in AR and LAR subjects also induces an increase of nasal tryptase, peaking 15 min after allergen administration and rapidly returning to baseline values [17, 21]. Overall, these observations suggest that nasal reactivity to aeroallergens is associated with the classical phases of allergic inflammation (early and late), regardless of the atopic status [23, 24].

The involvement of sIgE in local respiratory allergy has been more controversial, especially due to the relatively small proportion of patients (20–40%) with detectable sIgE in the nasal secretions. Moreover, when detected, nasal sIgE was consistently very low [16, 17, 25]. Nevertheless, the pooled analysis of LAR individuals demonstrated that nasal sIgE significantly increased during 24 h following a positive NAC, although not every patient tested positive in at least one determination [17, 23]. In any case, in our opinion, it is not surprising that many LAR patients (negative for both SPT and serum sIgE by definition) do not have detectable sIgE in the nasal secretions, as this biological fluid drains in the lymphoid vessels, which in turn drains in the blood [21]. Of note, a recent article identified that the prevalence and concentration of sIgE in nasal secretions and serum are highly interlinked [26]. On the other hand, the presence of IgE in mucosal biopsies of atopic and non-atopic rhinitis patients has been demonstrated [27]. Interestingly, a recent article using Merocel© sponges detected nasal sIgE in 91% of LAR individuals [28]. Merocel© sponges grow inside the nostril to perfectly adapt to the anatomy, and upon removal, they scratch a significant amount of mucosal cells.

On the other hand, 50–66% of patients with local respiratory allergy due to HDM, *Olea europaea*, or *Alternaria alternata* (either LAR or DAR) display positive basophil activation test (BAT) responses [8•, 29–31]. Wortmannin experiments confirmed that the activation of peripheral basophils in these patients is mediated by sIgE [29]. These findings indicate that most patients with local respiratory allergy are actually sensitized to the allergens they test positive to in the nasal challenge, yet their sIgE is not bound to skin mast cells, but to peripheral basophils. To explain this observation, we hypothesize that similar to AR [32, 33], in DAR and LAR individuals, sIgE against aeroallergens is mostly produced at the mucosal level, following sequential class switch

recombination of IgG₁+ B cells [34]. After sensitizing nasal resident effector cells, sIgE would traffic to the blood stream through the lymphoid vessels to sensitize circulating basophils in first place [21]. After saturating FcεRI on peripheral basophils, sIgE would sensitize resident mast cells in the different tissues, including skin mast cells [24]. Only after the saturation of the whole receptor system, sIgE would be found at the free status in serum and other biological fluids [21]. The extremely high affinity of IgE ($K_d: 10^{-10}$ M) for FcεRI explains this binding sequence to the receptors expressed in the different tissues [35] and ultimately accounts for the outcome of each biomarker (NAC, BAT, SPT, serum/nasal sIgE) in every rhinitis phenotype [15].

Epidemiology Characteristics

Over the years, evidence about local respiratory allergy is growing, with an increasing number of reports from different ethnic backgrounds and countries, affecting individuals from all ages [16, 18, 36–48] (Table 1). The prevalence of LAR among non-atopic patients with rhinitis is estimated to be 50–75% [16, 17, 23, 38], although the range is wider among any rhinitis patients according to published reports (0–100%) [16, 18, 36–49]. Recent studies coming from Asian countries report a lower LAR prevalence (<20%) compared with European studies [40, 41, 43, 47, 49, 50], with the highest prevalence reported in Mediterranean areas [51] and Poland [52]. Prevalence of LAR in elder population has only been studied in Poland with an observed prevalence of 21% [42].

Recent publications have proportioned valuable information about LAR prevalence. A systematic review including 3400 patients and healthy controls reports a 24.7% probability of a positive NAC in non-atopic rhinitis patients [14]. Another analysis including 648 non-atopic rhinitis patients reported a 10.2% proportion of nasal sIgE, increasing up to 19.8% in those patients with a history suggestive of allergy [53].

Publications in pediatric populations are less abundant, although the prevalence seems similar to that reported for adults (0–67%), observing a lower prevalence in Asian countries compared with Mediterranean areas [45, 48, 54–57]. A recent publication from Greece reported a 29.2% prevalence of LAR among non-atopic children [58]. Similar to atopic respiratory allergy, poly-sensitization has been also described in local respiratory allergy [18, 19•, 59].

Natural Evolution Without Immunotherapy

Local respiratory allergy often starts during childhood and constitutes a differentiated rhinitis phenotype not evolving to systemic atopy over time [19•, 60]. The knowledge on the natural evolution of LAR was achieved through a 10-year

follow-up study performed in a large cohort of 194 patients and 130 healthy volunteers [19•]. The results showed that the conversion rate to systemic atopy is similar between LAR patients and the general population (9.7% vs. 7.8%, $p = 0.623$) [19•, 60].

This follow-up study also demonstrated that local respiratory allergy naturally evolves to the aggravation and the association of comorbidities such as conjunctivitis and asthma [19•, 60]. The proportion of LAR individuals with asthma progressed from 18.8 to 30.7% ($p = 0.009$), and conjunctivitis from 52.3 to 61.9% during the 10-year period [19•]. The clinical worsening was evidenced by the increase of severe rhinitis from 18.8 to 42.0% ($p < 0.001$), along with an impairment in the quality of life [19•]. The proportion of patients requiring emergency assistance increased from 17.6 to 42.6% ($p < 0.001$), with a decrease in lung function (94.1 to 89.1%, $p = 0.001$) [19•]. It has been shown that the clinical worsening occurred during the first 5 years of disease in most cases [60], with a slower progression in the subsequent 5 years [19•].

The nature of the asthmatic symptoms usually associated with LAR individuals has been recently investigated in patients with persistent LAR due to HDM [61•]. This study demonstrated a positive bronchial allergen challenge in 28.8% of LAR patients with asthmatic symptoms, with a significant increase of sputum eosinophils, monocytes, and ECP. These data support the existence of a bronchial counterpart of LAR (local allergic asthma, LAA) in non-atopic asthma patients [61•]. Moreover, a Japanese study investigated the existence of an ocular counterpart of LAR (local allergic conjunctivitis) in non-atopic patients with conjunctivitis by detecting total IgE in tears [62]. However, the specificity of IgE in tears was not investigated nor conjunctival allergen challenges were performed.

Diagnostic Approach

The first level on LAR diagnosis includes a detailed clinical history and a nasal exploration with nasal endoscopy, preferably, or otherwise with anterior rhinoscopy to rule out chronic rhinosinusitis or anatomical disorders [15, 63].

The next step involves evaluating the response of the target organ to the allergen challenge in those patients with clinical history suggestive of allergy and negative SPT and serum sIgE. The NAC is the gold standard for LAR diagnosis, since it has the optimal sensitivity and specificity [6, 15, 64]. A recent publication demonstrates that it is a very safe and reproducible technique [65•], although time-consuming and requiring technical and human resources. Importantly, it is possible to perform NAC with multiple allergens, thus shortening the diagnostic time by reducing the number of visits [59].

Table 1 Prevalence of local allergic rhinitis in adult population

Author	Year	Country	Study groups	Allergens	Positive NAC response <i>n</i> (%)
Carney et al. [36]	2002	UK	21 IR (perennial)	HDM, epithelia, grass	13/21 (61.8%) (total result with all allergens)
Wedback et al. [37]	2005	Sweden	15 IR (seasonal)	Birch, Timothy	7/15 (46.7%) (total result with all allergens)
Rondon et al. [16]	2007	Spain	50 IR (perennial)	HDM	27/50 (54%)
Rondon et al. [38]	2008	Spain	32 IR (seasonal)	Grass, olive	21/32 (65.6%) (total result with all allergens)
Fuiano et al. [54]	2012	Italy	36 NAR (perennial)	Alternaria	23/36 (64%)
Rondon et al. [17]	2012	Spain	158 IR (seas/perennial)	HDM Alternaria, pollen, epithelia	110/158 (69.6) (total result with all allergens)
Cheng KJ et al. [40]	2013	China	147 IR (perennial)	HDM	12/147 (8.1%)
Chang et al. [41]	2014	Korea	62 IR (perennial)	HDM	22/62 (35.5%)
Bozek et al. [42]	2015	Poland	131 IR (perennial)	HDM, pollens, molds, cat	46/131 (35.5%) (total result with all allergens)
Jang TY et al. [43]	2015	Korea	110 IR (perennial)	HDM	12/110 (10.9%)
Refsat et al. [44]	2015	Egypt	40 IR (perennial)	HDM	25/40 (62.5%)
Blanca-Lopez et al. [45]	2016	Spain	52 NAR (seasonal)	Phleum	28/52 (53.8%)
Badran et al. [46]	2016	Egypt	273 NAR	HDM/pollen	231/273 (84.6%) (total result with all allergens)
Duman et al. [55]	2016	Turkey	28 NAR (seas/perennial)	DP, DF, grass mix	7/28 (25%) (total result with all allergens)
Shin et al. [47]	2017	Korea	81 NAR (perennial)	HDM	6/81 (7.4%)
Krajewska-Wojtys et al. [48]	2017	Poland	84 NAR (perennial)	HDM Alternaria/cat	21/84 (21%) (total result with all allergens)
Ha EK et al. [57]	2017	Korea	64 NAR (perennial)	DP	5/64 (7.8%)
Tao XY et al. [49]	2018	China	79 NAR (seas/perennial)	Pollen/HDM	15/79 (18.9%) local IgE, no NAC (total result with all allergens)
Meng Y et al. [28]	2019	China	73 NAR (seasonal)	HDM	12/73 (16.4%) NAC plus local IgE (total result with all allergens)
Duarte-Ferreira et al. [30]	2019	Portugal	20 NAR (perennial)	HDM	17/20 (85%)
Tsilochristou et al. [58]	2019	Greece	24 NAR (seas/perennial)	Phleum, Olea, Alternaria, DP	7/24 (29%) (total result with all allergens)
Ishida M et al. [50]	2020	Japan	50 NAR (seas/perennial)	HDM/JCP	5/21 (23.8%) HDM 2/24 (14.3%) JCP NAC plus local IgE

DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; HDM, house dust mites; IR, idiopathic rhinitis; JCP, Japanese cedar pollen; NAC, nasal allergen challenge; NAR, non-allergic rhinitis

In a proportion of LAR individuals, sIgE in the nasal secretions is found, but showing a lower sensitivity compared with NAC [16, 23, 25, 30]. Therefore, nasal sIgE should be regarded as a research tool that cannot be recommended for daily practice [66, 67].

The BAT is another promising tool for LAR diagnosis, with a sensitivity of 50–66% for HDM and pollens, and with a high specificity (> 90%), as shown in different studies [8•, 29–31]. Moreover, unlike nasal sIgE, the BAT does not require a previous NAC to increase the sensitivity [8•]. However, the BAT should be still considered a research tool and the cost-effectiveness needs to be evaluated before general recommendations for routine diagnosis (Fig. 1).

Precision Medicine

Precision medicine is considered the way forward in optimal patient care and includes the combination of 4 *P* concepts: personalized care, prevention of disease, prediction of success

of treatment, and participation of the patients in the treatment plan. To implement precision medicine, a shift in the clinical approach—from phenotyping to endotyping—is needed [68]. The identification of the underlying disease mechanism is the first step in the way to achieve the control. The detection of reliable and easy-to-measure biomarkers is crucial for the implementation of precision medicine [69]. This fact is especially true in local respiratory disease, a chronic inflammatory condition commonly misdiagnosed as non-allergic.

The NAC is a very useful in vivo biomarker allowing for the recognition of allergic triggers of rhinitis, the differentiation between atopy and allergy, and the monitoring of the response to pharmacologic and biologic treatments [7•]. Therefore, precision medicine-based approaches in nasal pathology should consider the performance of a NAC in selected rhinitis individuals (e.g., those with a clinical history suggestive of allergy despite negative SPT/serum sIgE) [70]. The NAC is the gold standard to discriminate LAR and DAR patients from NAR and MR individuals, respectively [7•,

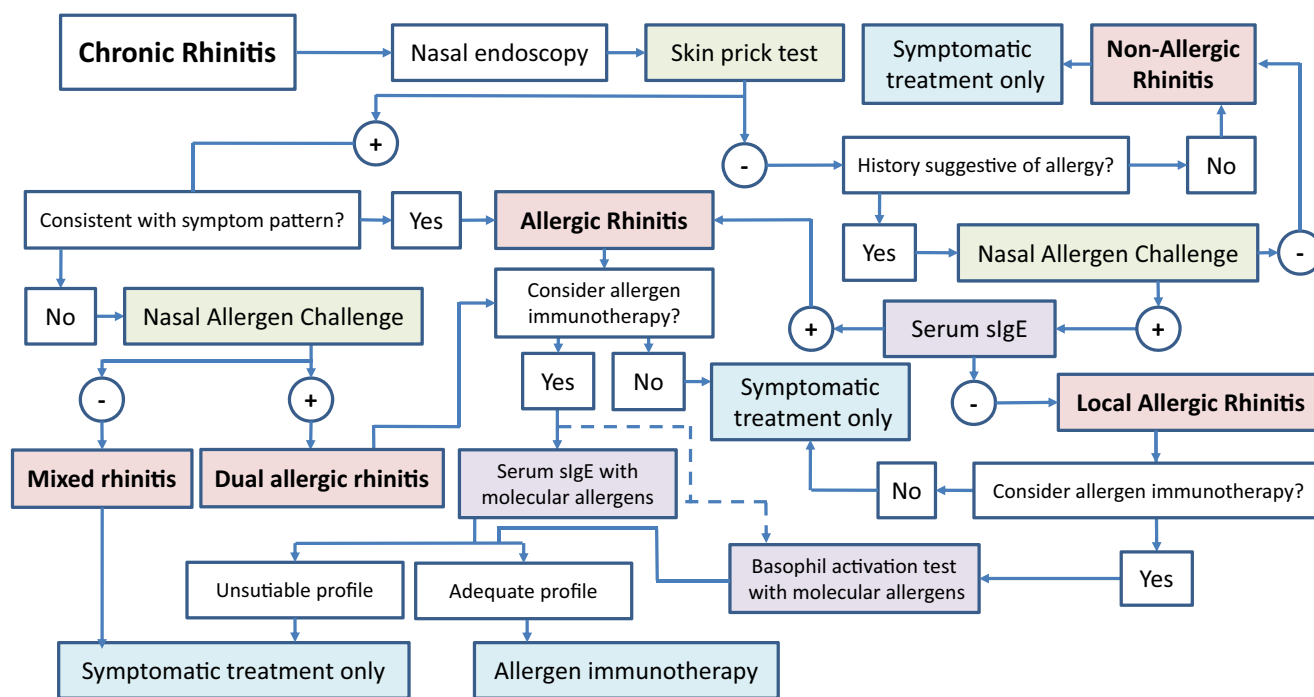


Fig. 1 Diagnostic and therapeutic algorithm for chronic non-infectious rhinitis. The green color indicates in vivo diagnostic tests; the purple color indicates in vitro diagnostic tests; the red color indicates phenotypes of chronic rhinitis (diagnosis); the blue color indicates therapeutic options;

the dotted line and arrowhead indicate that the test may be considered in addition to serum sIgE with molecular agents in the case of dual allergic rhinitis. sIgE, allergen-specific IgE

8••]. Indeed, the complexity of the rhinitis syndrome progressively demands the implementation of reliable diagnostic tests, beyond the classical markers of systemic atopy [69]. Only the performance of additional tests like the NAC or the BAT allows the differentiation of the distinct rhinitis phenotypes and ultimately prevents misdiagnosis [8••].

In this regard, the diagnosis of LAR helps to predict the success of symptomatic treatment for eosinophilic phenotypes [9, 38, 69] and of etiologic treatment like AIT for allergic phenotypes [11••, 71, 72••, 73••]. Therefore, the NAC would permit not only the recognition of LAR and DAR individuals but also the initiation of specific therapies with disease-modifying potential.

Therapeutic Options

In AR patients, ARIA guidelines, based on the GRADE system, recommend intranasal corticosteroids either alone or in combination with oral/nasal antihistamines [74]. However, currently, there are no controlled studies evaluating the effect of these drugs in local respiratory allergy.

Because LAR and DAR are eosinophilic phenotypes, it is reasonable to expect that patients will benefit from the treatment with nasal steroids and antihistamines. Therefore, first-line therapy for LAR and DAR individuals should be also nasal corticosteroids with/without antihistamines [2]. Despite

the lack of controlled studies, the clinical impression is that patients with local respiratory allergy usually show a similar response to these drugs than that seen in atopic respiratory allergy individuals [16, 19, 60].

Besides pharmacotherapy, most individuals with local respiratory allergy receive health education and are trained in allergen avoidance measures. Nevertheless, allergen avoidance is not always possible. Moreover, the aforementioned pharmacological treatment does not prevent the progression of the disease and asthma onset as illustrated in the follow-up studies [19, 60].

In patients with AR who do not achieve control with pharmacological treatment, AIT is indicated. Several reports demonstrate that AIT has a similar beneficial effect in LAR individuals [11••, 71, 72••, 73••], which will be thoroughly discussed in the next section.

Allergen Immunotherapy Studies

Respiratory allergy is a chronic inflammatory disease usually starting in childhood and tending to persist throughout life up to the elder period [75]. Local respiratory allergy presents a natural evolution to severity and difficulty to achieve control despite treatment with several symptomatic drugs [19••, 75]. Thus, local respiratory allergy has been recently proposed as a

potential factor explaining the lack of control in patients with upper airway inflammatory conditions [76].

AIT is an etiologic and cost-effective treatment for allergic respiratory disease that does not only control multi-morbidity (rhinitis, asthma, and conjunctivitis) but also induce a long-lasting beneficial effect and modifies the natural course of the disease. AIT modifies Th2-biased response inducing immune-tolerance to the allergen, which explains the maintenance of the clinical effect after treatment discontinuation (long-term effect) [75, 77–79].

The pathophysiological similarities between AR and LAR prompted investigators to question whether AIT could have a similar clinical and immunological effects in LAR, as demonstrated for AR. In the present review, we will analyze the main results of the four published studies (Table 2), emphasizing their design, allergens extracts, administration route and protocol, clinical and immunological outcomes, similarities, differences, limitations, and research needs for the future.

Four subcutaneous immunotherapy (SCIT) studies have been published in LAR adult patients to date, demonstrating that AIT is a clinically effective and safe treatment for the condition [11•, 71, 72•, 73•]. The published works comprise one open observational study [71] and three randomized double-blind placebo-controlled clinical trials (RCT) [11•, 72•, 73•]. Three of them investigated pollen AIT (mixture of grass [71], *Phleum pratense* [73•], and *Betula verrucosa* [72•]) using preseasonal and perennial administration protocols, and one of them investigated HDM AIT (*Dermatophagoides pteronyssinus*, DP) [11•]. Other administration routes such as sublingual, intranasal, epicutaneous, transcutaneous, intradermal, or intralymphatic have not been evaluated yet in patients with local respiratory allergy.

AIT with seasonal allergens may be administrated with preseasonal or perennial protocols. Preseasonal protocols consist of a periodical administration of immunotherapy only before the pollen season. In this modality, the patient undergoes an induction phase every year before the pollen season. In perennial protocol, patients undergo an induction phase only once during the first year of AIT, continuing with the maintenance phase until the end of the treatment [80].

From Observational to Randomized Controlled Trials

The first study with SCIT for LAR was published in 2011 [71]. It was an open observational study of 6 months of preseasonal grass SCIT including 20 Spanish patients with seasonal persistent moderate-to-severe LAR due to grass pollen. Ten patients were treated with preseasonal grass SCIT and rescue medication during the pollen season, and ten received only rescue medication. The AIT branch was given a mix of six grass species (*Dactylis*, *Festuca*, *Lolium*, *Phleum*, *Poa*, and *Secale*) titrated in mass unit (Pangramin Plus® Grass Mix 1000 STU/mL, ALK-Abelló, Madrid, Spain) [71]. In this

study, 6 months of preseasonal grass SCIT, induced a significant improvement of symptom and medication scores, number of medication-free days, and rhinitis severity. A 100% reduction of severe rhinitis and a 57% reduction of moderate rhinitis cases were observed. In addition, AIT increased the nasal tolerance to grass as measured by the NAC, with 3/10 patients (30%) in the AIT branch testing negative in the NAC after the treatment period. Serum allergen-specific IgG4 (sIgG4) also increased progressively and became significant after 12 months [71].

Randomized Clinical Trials

In 2016, a RCT of 2 years of perennial treatment with DP SCIT vs placebo in 36 Spanish patients with perennial persistent moderate-to-severe LAR was published [11•]. Patients were randomized to receive either subcutaneous Pangramin Plus® *Dermatophagoides pteronyssinus* 1000 STU/mL (ALK-Abelló S.A, Madrid, Spain) or placebo. The maintenance dose was 0.8 mL every 4 weeks. The Der p1 and Der p2 content were 3 µg/mL and 1.5 µg/mL respectively [11•]. In this trial, the clinical effect of SCIT was closely monitored, at baseline and after 1, 3, 6, 12, 18, and 24 months of treatment. The results revealed an early and maintained clinical beneficial effect of DP SCIT on symptoms, medication, and allergen tolerance outcomes, starting from the sixth month of therapy and progressively increasing to the end of the study. This improvement was apparent in combined symptom and medication scores (CSMS), individual symptoms and medication scores, number of medication-free days, and allergen concentration tolerated in the NAC [11•]. At the end of the study, 67% of patients tolerated a concentration of Der p1 ≥ 10 times higher than that before SCIT initiation, and half of them tested negative in the NAC [11•]. Moreover, patients treated with DP SCIT displayed progressively increasing serum DP-sIgG4 from the beginning of the study period, showing significant differences from the first year of AIT [11•].

After this first SCIT trial, two controlled studies of pollen SCIT were conducted, one with *Betula verrucosa* (Betula SCIT) and one with *Phleum pratense* (Phleum SCIT):

The RCT of perennial *Betula* SCIT included 28 LAR Polish patients who were randomized to receive either subcutaneous Purethal® Birch 20,000 Allergy Unit Milliequivalent (AUM)/mL (*Betula verrucosa*; HAL Allergy BV) or placebo for 2 years [72•]. The maintenance dose was 0.5 mL every month. One milliliter of Purethal contains 500 µg of modified birch pollen allergens. The Bet v 1 content was 52 µg/mL. The results of this RCT showed an early and maintained clinical effect in the CSMS and improvement on quality of life after 1 and 2 years of AIT [72•]. Interestingly, the seasonal increase of nasal sIgE was blunted from the first pollen season of the study in the active group, but not in the placebo group [72•].

Table 2 Main characteristics of allergen immunotherapy studies conducted in LAR

Publication	Phase of study and study design	Inclusion and exclusion criteria	Allergen extract	AIT schedule	No. of patients	Allergen dose and concentration	Monitorization time points	Primary outcome results	Secondary outcome results
Rondon et al. [71]	Phase: not applicable open observational	Inclusion criteria: age: 18–60 years, rhinitis during grass pollen season, positive NAC and/or NsIgE and negative SPT and serum sIgE. Exclusion criteria: positive NAC/NsIgE to overlapping allergens, previous AIT, CRSw/sNP, immunologic disease, pregnancy.	Grass pollen mix Pangramin Plus © ALK	6 months preseasonal	20	0.8 mL/month 1000 STU/mL	Basal 1, 3, 6, and 12 months	NAC ↑, sIgG4 ↑	RCSS ↑, MFD ↑, rhinitis severity ↑, NAC ↑, sIgG4 ↑
Rondon et al. [11••]	Phase II RDBPC active vs placebo	Inclusion criteria: age: 18–55 years, persistent--perennial rhinitis, positive NAC and/or NsIgE and negative SPT and serum sIgE. Exclusion criteria: previous AIT, CRSw/sNP, severe cardiologic or immunologic disease, severe atopic dermatitis, FEV1 < 70%, uncontrolled asthma, beta-blocker treatment, pregnancy.	<i>Dermatophagoides pteronyssinus</i> Pangramin Plus© ALK	24 months perennial	36	0.8 mL/month 1000 STU/mL 3 mcg Der p1 1.5 mcg Der p2	Basal 1, 3, 6, 12, 18, and 24 months	CSMS ↑, RCSS ↑, MS ↑, MFD ↑	NAC ↑, IgG4 ↑
Rondon, et al. [73••]	Phase II RDBPC active vs placebo	Inclusion criteria: age: 18–55 years, rhinitis during grass pollen season, Positive NAC and/or NsIgE, and negative SPT and serum sIgE. Exclusion criteria: positive NAC/NsIgE+ to overlapping allergens, previous AIT, CRSw/sNP,	<i>Phleum pratense</i> Depigoid© Laborat. Leti SL	24 months preseasonal 1st, perennial 2nd year	56	0.5 mL/month 1000 DPP/mL35 mcg Phl p 5	Basal 1, 3, 6, 12, 18, and 24 months	CSMS ↑	BSS ↑, CSS ↑, NSS ↑, MS ↑, MFD ↑, rhinitis severity ↑, asthma control ↑, RQLQ ↑, NAC ↑, IgG4 ↑

Table 2 (continued)

Publication	Phase of study and study design	Inclusion and exclusion criteria	Allergen extract	AIT schedule	No. of patients	Allergen dose and concentration	Monitorization time points	Primary outcome results	Secondary outcome results
Bozek, et al. [72••]	Unknown phase RDBPC active vs placebo	severe cardiologic or immunologic disease, severe atopic dermatitis, FEV1 < 70%, uncontrolled asthma, beta-blocker treatment, pregnancy. Inclusion criteria: rhinitis during birch pollen season, positive NAC, and negative SPT and serum sIgE. Exclusion criteria: asthma, non-allergic rhinitis, severe or nonstable diseases	<i>Betula verrucosa</i> Purethal© HAL allergy SLU	24 months perennial	29	0.5 mL/month 20,000 AUM/mL 52 mcg Bet v 1	Basal 6,12,18, and 24 months	CSMS ↑	RQLQ ↑, NAC ↑, sIgG4 ↑

BSS, bronchial symptoms score; CRSw/sNP, chronic rhinosinusitis with or without nasal polyps; CSMS, combined symptom medication score; CSS, conjunctival symptoms score; MFD, medication-free days; MS, medication score; NAC, nasal allergen challenge; *NsIgE*, nasal-specific IgE; NSS, nasal symptoms score; RCSS, rhinoconjunctivitis symptom score; RDBPC, randomized, double-blind, placebo-controlled; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; sIgG4/IgG/IgE, serum allergen-specific IgG4/IgG/IgE.

↑ Statistically significant improvement in active group

Most recently, a larger RCT of 2 years of *Phleum* SCIT vs placebo confirmed the early and maintained clinical effect of AIT on nasal, ocular, and bronchial symptoms; health-related quality of life; and the concentration of allergen tolerated in the NAC [73••].

In this RCT, patients were treated with a polymerized depigmented allergen extract: Depigoid© *Phleum pretense* 1000 DPP/mL (LETI, S.L. Tres Cantos, Madrid, Spain). The study included 56 LAR individuals from two different centers in Spain and had a 2-year duration [73••]. In the first year, patients were randomized to receive either 6 months of preseasonal *Phleum* SCIT (group A) or placebo (group B), followed by 6 months of wash-up period including the first pollen season (PS1). During the second year, both groups received 12 months of perennial *Phleum* SCIT including the second pollen season (PS2). The study design, as a parallel group trial with two arms during the first year (active vs placebo) and one active arm during the second year, provided several advantages. First of all, it permitted multiple comparisons: inter-group comparison of active vs placebo during the first year (group A vs group B) and intra-group comparison of active (group B second year) vs placebo (group B first year) in

which each subject was his own control. The design also allowed for the evaluation of the effect of cumulative dosage on the clinical and immunologic outcomes. This analysis was possible, making inter-group comparison during the PS2 (12 vs 6 months of SCIT) and at the end of the study (18 vs 12 months of SCIT) [73••].

In this RCT [73••], as in *Betula* SCIT study [72••], health-related quality of life was also evaluated using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). This is a helpful tool to assess patients' self-perceived benefit and the cost-effectiveness of therapeutic interventions [81]. Improvements in RQLQ are especially relevant for long-term therapies like AIT [82]. For the first time, the RCT demonstrated the short-term and sustained effect of SCIT on quality of life, as perceived by LAR patients during the PS1 and PS2. This clinically relevant improvement was apparent in overall RQLQ score and also for the seven individual domains [73••].

Moreover, *Phleum* SCIT also induced a significant and progressive increase of serum sIgG4 levels and of the nasal tolerance to the allergen from the sixth month of treatment. At the end of the study, 83% of patients treated with ≥ 6 months

of SCIT tolerated a concentration of *Phleum pratense* > 50 times higher than that tolerated at baseline, and 56% of individuals tested negative in the NAC [73•]. The progressive increase in serum sIgG4 against *Phleum pratense* and Phl p 1-5 confirmed sIgG4 as a useful response biomarker to AIT in LAR, and evidenced the relevance of Phl p1-5, the major allergen of *Phleum pratense* in atopic respiratory allergy, as the trigger of allergic symptoms in LAR patients as well.

Conclusions

Overall, the results obtained by SCIT studies conducted in local respiratory allergy patients evidence the ability of AIT to control the symptoms and increase the allergen tolerance while the therapy is being administered. Although the long-term effect of AIT in local respiratory allergy remains uninvestigated, it is tempting to speculate that similar to atopic respiratory allergy [10], the clinical benefits persist after therapy discontinuation.

Moreover, AIT is a safe treatment option for LAR patients, as only few moderate-to-mild local reactions occurred with the administration of both active and placebo doses [11•, 71, 72•, 73•]. Nevertheless, more studies with larger sample sizes are warranted to confirm these results.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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