Allergen Immunotherapy effectiveness in specific nasal reactivity of children with Local Allergic Rhinitis

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Acronyms
AIT – Allergen immunotherapy
SCIT - Subcutaneous allergen immunotherapy
LAR – Local allergic rhinitis
Dp - *Dermatophagoides pteronyssinus*
NAC - Nasal allergen challenge
PNIF - Peak nasal inspiratory flow
DAR - Dual allergic rhinitis
NAR – Non allergic rhinitis
NARES – Nonallergic rhinitis with eosinophilia syndrome

Abstract
Background:
Allergen immunotherapy (AIT) is the only disease-modifying treatment in allergy. Its efficacy has been demonstrated in the treatment of Local Allergic Rhinitis (LAR) in adults. This study intends to evaluate the effectiveness of AIT in specific nasal reactivity of paediatric patients with LAR.
Methods:
Patients diagnosed with LAR to *Dermatophagoides pteronyssinus* (Dp) were submitted to subcutaneous AIT (SCIT) (depigmented-polymerized Dp allergen extracts) for 3 years. Nasal allergen challenge (NACs) with Dp extract were performed before and 3 years after AIT. NAC response was assessed with peak nasal inspiratory flow (PNIF) and symptom score of Lebel. NACs were considered positive when there was a flow decrease of ≥ 20% in PNIF and a score of symptoms ≥ 3 points. Demographic data and NAC results were analysed.
Results:
We included 32 paediatric patients (mean age 9.9±3.08 years, 18 female) and 10 adult patients, (mean age 30.4±12.2 years, 7 female). The symptom score obtained at the 1st minute, 5th minute, 15th minute and 30th minute in response to NAC, were reduced after AIT. The nasal inspiratory flow decrease induced by NAC was also reduced after AIT. This reduction in nasal reactivity was observed in paediatric and in adult patients, both with statistical significance.
Conclusions:
AIT induced a decrease in Dp-nasal specific reactivity in children with LAR. This decline of nasal response to allergen exposure, after AIT treatment, emphasis the interest of this therapeutic approach in LAR, even in paediatric patients.

Impact statement
To date, allergen immunotherapy (AIT) effectiveness has been demonstrated mainly in LAR adult patients. In paediatric patients, this is the first study that evaluated the SCIT effectiveness in LAR

treatment. These data enrich the knowledge of LAR natural history and its treatment, namely in paediatric population.

Key words: Allergen immunotherapy, Local allergic rhinitis, Nasal allergen challenge, paediatric rhinitis

Introduction

Allergen immunotherapy (AIT) is effective in the treatment of allergic rhinitis (AR) and it is recommended in adults and children (1-3). Recently data suggested considering different AR phenotypes: AR itself, LAR and DAR (4,5). LAR is characterized by nasal symptoms, with perennial or seasonal evolution, in the absence of atopy (negative skin tests and serum IgE), not fitting into the classic dichotomy of AR versus non-allergic rhinitis (NAR). NAC is the gold standard for LAR and DAR diagnosis (6-9). The identification of T2 inflammation endotype, positive response to nasal allergen challenge (NAC) and association with other allergic comorbidities, support the existence of this nosological entity and its inclusion in the classification of rhinitis (10-14). The recognition of this entity, in paediatric age, highlights the need to clarify the pathophysiology and evolution of LAR, in order to introduce early therapeutic strategies to prevent the negative impact of the disease (15, 16). AIT is the only disease-modifying treatment in allergic diseases and its effectiveness in treating LAR has been reported (17-19). The efficacy of subcutaneous AIT in the treatment of LAR in adults was demonstrated in two systematic reviews and meta-analyses (20, 21). There was only one observational study that described the effectiveness of sublingual AIT in pediatric population (22).

This study aims to evaluate the effectiveness of AIT in reducing specific nasal reactivity in children with LAR.

Material and Methods

Study design

Retrospective study. Paediatric patients diagnosed with *Dermatophagoides pteronyssinus* (Dp)-induced LAR were included. They underwent AIT with depigmented and polymerized extracts of Dp (Leti, Spain), subcutaneously, for 3 years. Effectiveness was assessed by specific nasal reactivity, comparing the NAC response before and 3 years after AIT. Demographic data (gender and age) and clinical data (age of onset of rhinitis symptoms, rhinitis severity classification according to ARIA, atopic comorbidities) were analysed, and compared to adult patients with Dp-induced LAR (control group). NAC response were analyzed before and after AIT with Dp extracts, both in paediatric and adult patients. The specific nasal response of pediatric patients was compared with the specific nasal response of adult patients with Dp-induced LAR.

Dp-induced LAR Diagnosis

Patients with symptoms of chronic, perennial rhinitis, with exacerbations triggered by house dust exposure and absence of atopy (negative skin prick tests to a battery of common aeroallergen and negative perennial aeroallergen-specific IgE) were included. ENT morbidities that cause nasal obstruction and can mimic or worsen rhinitis were excluded (23,24). The diagnosis of LAR was defined by a positive response to nasal Dp extract challenge (25, 26).

Nasal Allergen Challenge (NAC)

Patients were submitted to NAC according to EAACI recommendations (27). NAC was performed after medical therapy period washout. A pump-aerosol spray was used to administer the Dp extracts (100 HEP, Leti, Spain). The response to NAC was assessed by symptom score (Lebel score) and by objective nasal patency measurement (peak nasal inspiratory flow, PNIF). It was assessed before and at 1st, 5th, 15th and 30th minutes after NAC.
The NAC response was considered positive if the Lebel score symptom was equal or greater than 3 and if the PNIF decrease was equal or greater than 20%.

Statistical analysis
Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. All data was analyzed anonymously. Frequency distribution was obtained for the different qualitative variables. For the continuous data, mean and standard deviation were calculated. The normality of the distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Variables with normal distribution were compared with Student's t-test. Continuous variables that did not have a normal distribution were compared using the non-parametric Wilcoxon test. Statistical significance was defined as $p<0.05$.

Results:
32 paediatric patients (older than 5 years) were included. They had an average age of de 9.9± 3.08 years old. Eighteen were female.
The symptoms began at 4.12±1.5 years old. All patients had moderate persistent rhinitis, according to ARIA criteria (6). None had conjunctivitis or asthma.
The control group included 10 adult patients, with an average age of 30.4±12.2 years old. Seven were female. Symptoms began at 21±10.04 years. One patient had conjunctivitis. None had asthma.
The demographic and clinical data are presented in Table I. Table II presents the responses to NAC in paediatric and in adults, before and 3 years after AIT.

Discussion
AIT is the only therapy with a disease-modifying effect that persists beyond the duration of treatment (17,18,28). To date, AIT effectiveness has been demonstrated mainly in adult patients with LAR (19). Two systematic revision and meta-analysis demonstrated the efficacy of subcutaneous AIT (SCIT) in LAR treatment in adult patients (20,21). In paediatric patients, only one observational study evaluated the sublingual AIT effectiveness in LAR treatment (22).
Our data showed that Dp-specific nasal reactivity was decreased after AIT, in both paediatric and adult LAR patients.
This decrease in nasal reactivity after AIT was assessed by NAC and it corroborates the effectiveness of AIT in the treatment of LAR, as described in the literature (19-21).
Concerning Dp—AIT in LAR treatment, it was evaluated in two studies in adults (SCIT) and in children (SLIT). In both studies, the efficacy was documented by symptom score and response to NAC (22,29). Indeed, NAC is the gold standard tool to diagnose LAR and the positive response has been considered an *in vivo* biomarker of LAR (25). It distinguishes LAR from non-allergic rhinitis (NAR), as it allows to identify the relevant allergens implicated (27,30).

In our study, both LAR diagnosis and monitoring of AIT response were supported by NAC response (symptom score and nasal patency assessed by PNIF) (27,30,31).

It has been argued that NAC is a difficult tool to be implemented in children, considering their alleged lower cooperation. However, in our experience, this is a safe and well tolerated diagnostic tool, in children as well in adolescents (32). It has been suggested that nasal cytology could be a faster method to assess NAC response. However, it also has limitations namely the need of a (not always) accessible laboratory support. Additionally, it does not distinguish LAR from NARES (33).

The response to NAC after AIT was similar in paediatric and adult patients. This supports that AIT should be considered a therapeutic option in paediatric patients with LAR, as it has been considered in adult patients (14,20,25,34). In fact, as in AR, early LAR diagnosis and treatment is crucial to control the negative impact in quality of life and to ensure the prevention of progression to more severe forms of disease and/or asthma (1,6,7,17,18).

The evaluation of NAC response 3 years after the LAR diagnosis, in a group of patients not submitted to AIT, and its comparison to paediatric and adults with LAR submitted to AIT, could be relevant to corroborate the effectiveness of AIT in LAR patients. It also could help to clarify the LAR evolution in paediatric patient and natural history of nasal allergy, namely AR, LAR and DAR. Indeed, the "entopy" concept, as well as LAR description and its relevance are recent in clinical practice. Several studies have been conducted to clarify the epidemiology, the diagnosis and the treatment of this disease (4, 34-39). It has been argued that LAR is not an initial phase of AR, but an AR phenotype with an underestimated prevalence, namely in children (13,26,40). It should be considered a distinct nosologic entity (41, 42). As well as AR, LAR is characterized by specific nasal reactivity documented by positive response to NAC and T2 inflammatory mediators (7, 11, 43). It also presents a progressive worsening of symptoms and progression to other allergic morbidities, such as conjunctivitis and asthma (41,42).

The diagnostic algorithm is well defined, both in adults and children (25, 26, 34). Our data emphasizes the importance of performing NAC before assuming the NAR diagnosis, to avoid depriving these patients of access to AIT.

Although some authors argue that local specific IgE is not relevant and there is no disease progression in patients with LAR, the scarce studies carried out in children suggest that the pathophysiology, clinical evolution, diagnostic methodology and therapeutic approach are similar in children and in adults (16,33,40).

More studies are needed to optimize the knowledge about nasal allergy, namely the concept of LAR in children, adolescents, and adults in order to define etiopathogenic approaches and specific treatment algorithms, to achieve control of LAR.

Likewise, the long-term effectiveness of AIT in LAR should be studied. To date, there is no published study that addresses this topic but AIT is crucial to promote the reduction of nasal reactivity and the acquisition of tolerance to allergens (19-21).

Limitation of study

This retrospective, real-world study did not include the evaluation of NAC response 3 years after the LAR diagnosis, in a group of patients not submitted to AIT.

Conclusion

Our data showed decreased allergen-specific response to NAC after Dp-AIT in children and adolescents with Dp-induced LAR.

This supports the AIT effectiveness in LAR treatment. It also emphasizes the relevance of AIT as a treatment approach in LAR, both in children and adolescents, as reported for adults in the literature. As far as our knowledge, this is the first study concerning SCIT in the treatment of LAR in paediatric patients.

Our data supports previous publications, that AIT is a therapeutic option to be considered in LAR evidence-based consensus treatment (46).

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Contributions:

GL: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing; Supervision

BT: Formal analysis, Writing review & editing

IF: Investigation, Methodology

FT: Investigation, Methodology

ATB: Writing review & editing

Conflict of interests:

No conflict of interest.

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Table I – Demographical and clinical characteristic, in both paediatric and adult patients with Dp-LAR

	Paediatric patients	Adult patients
n	32	10
M/F	14/18	3/7
Age (years, mean±SD)	9.9± 3.08	30.4±12.2
Age of onset of rhinitis symptoms (years, mean±SD)	4.12±1.5	21±10.04
Rhinitis severity (according to ARIA classification)	moderate persistent rhinitis – 100%	moderate persistent rhinitis – 100%
Asthma	Ø	Ø
Conjuntivitis	Ø	1/10

Table II – Response to NAC, before and 3 years after AIT, in patients with Dp-LAR

	Paediatric patients			Adult patients (control group)		
Lebel score (mean±SD)	Before AIT (T0)	After AIT (T3)	p-value	Before AIT (T0)	After AIT (T3)	p-value
1st minute after NAC	1.8±1.1	2.7±0.45	<0.0001	3.7±1.7	1.9±1.1	<0.0001
5th minute after NAC	3.8±2.6	1.03±0.86	<0.0001	6.2±3.5	0.77±0.66	<0.0001
15th minute after NAC	5.8±3.6	0	<0.0001	4.0±2.0	0	<0.0001
30th minute after NAC	6.5±2.2	0	<0.0001	5.1±1.7	0	<0.0001
PNIF decrease (%) after NAC	36.4±11.7	7.9±5.8	<0.0001	35.5±7.0	7.5±6.7	<0.0001