

Nasal reactivity evaluation in children with allergic rhinitis receiving grass pollen sublingual immunotherapy

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ABSTRACT

Background: The European Academy of Allergy and Clinical Immunology guidelines, strongly recommended allergen immunotherapy (AIT) as an effective treatment to achieve long-term clinical benefits and to modify the natural history of allergic diseases. Sublingual immunotherapy (SLIT) offers the possibility of home administration, which improves patient comfort and compliance.

Objective: The primary outcome of this study was to assess the change in nasal reactivity after grass-pollen AIT treatment.

Methods: This was a monocentric, prospective, observational study conducted in Rome from September 2016 to June 2018, in the Pediatric Department of Policlinico Umberto I. We enrolled children, ages between 6 and 12 years, with persistent allergic rhinitis (AR), sensitized to grass pollen. At the first visit (V0, September 2016), one group received the first dose of oral immunotherapy for grass-pollen spray buccal and the other group continued only standard therapy. All the patients had nasal specific immunoglobulin I (IgE) assay (Phl p1, Phl p5), active anterior rhinomanometry with a nasal provocation test (NPT), and spirometry. The patients attended two follow-up visits, in May 2017 (V1) and May 2018 (V2), with the same examinations as at V0.

Results: During the treatment, we observed, in the treated group, a significant increase in the mean nasal flow compared with untreated children ($p < 0.001$). In the AIT group, we found an improvement of nasal function and only 21.05% of all the children in the active group with a positive NPT result at V2. In the control group, we found, at V2, a worsening of nasal function, with 89.47% of the children with a positive NPT result. Furthermore, we found a significant reduction of nasal specific IgE levels at the end of the observation period in the treated group.

Conclusion: Analysis of our data provided evidence for a clinical effect of SLIT in inducing clinical changes and allergen tolerance in children with AR.

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Allergic rhinitis (AR) is a common disease in childhood, characterized by nasal discharge, itching, sneezing, and congestion. Typical incidence reports are between 10% and 30% of children and adults in the developed nations.¹ AR represents an emerging public health problem because it can become chronic and lead to a reduction of quality of life.² In children, AR is often associated with asthma and, if not under control, it may contribute to the worsening of asthma symptoms.³ AR may also affect sleep quality of children, with a consequent reduction in cognitive function and school performance.⁴ Clinical symptoms of AR seem to be related to the levels of serum specific immunoglobulin E (sIgE),

a marker of T helper type 2 systemic inflammation.⁵ However, when systemic atopy markers are negative, the presence of sIgE in nasal lavage and/or a positive specific nasal provocation test (NPT) makes the diagnosis of local AR (LAR), a type of rhinitis characterized by local entopy.⁶

An Italian survey⁷ in patients with AR about their satisfaction with pharmacologic treatment pointed out the importance of the adherence to the ARIA (Allergic Rhinitis and its Impact on Asthma)⁸ guidelines and recommended the allergen immunotherapy (AIT) in children with severe AR and not responding to drug therapy.⁷ Also, the European Academy of Allergy and Clinical Immunology guidelines⁹ recommend AIT as an effective treatment to achieve long-term clinical benefits and to modify the natural history of allergy. In the treatment of AR, after many years of subcutaneous immunotherapy, the sublingual immunotherapy (SLIT) has achieved more and more importance, mostly for the possibility of home administration and improving patient compliance.¹⁰ Immunotherapy has a long-lasting action on allergologic symptoms and a preventive effect on the onset of new sensitizations.¹¹ Anterior active rhinomanometry (AAR) enables, in

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patients with AR, the evaluation of nasal obstruction, expressed as the resistance to the airflow. AAR can be used to perform the nasal provocation test (NPT).¹² The primary outcome of this study was to evaluate, in children with AR affected by grass-pollen allergy, changes in nasal-specific reactivity after AIT. As secondary outcomes, we evaluated the immunologic modifications in nasal mucosa, such as the eosinophil count, sIgE in nasal lavage, and improvement in the quality of life and rhinitis symptoms.

METHODS

This was a monocentric, prospective, observational study conducted in Rome from September 2016 to June 2018, in the Pediatric Department of Policlinico Umberto I. The study was approved by the medical ethics review board of Sapienza University of Rome, Policlinico Umberto I. Patients' parents or guardians signed a written consent form. L. Schiavi and G. Brindisi contributed equally as first authors.

Study Population

We consecutively enrolled children ages between 6 and 12 years, with persistent AR, monosensitized to grass pollen. The diagnosis of AR was confirmed by pediatricians trained in allergic diseases (LS, GB, VDV, GDC), according to ARIA guidelines.⁸ All the patients recruited were on local therapy with nasal corticosteroids on request as needed. Exclusion criteria were the presence of chronic diseases, including uncontrolled asthma.

Study Design

The parents or guardians signed informed consent, and physicians (LS, GB, VDV) collected anamnestic information from the participants. At the first visit (V0), which took place in September 2016 in the peak of the grass-pollen season, SLIT treatment was proposed to all the children. Some of them (AIT group) accepted SLIT treatment and received the first dose of AIT for grass-pollen Sulgen (Roxall, Italy) (1 puff buccal spray: Phl p1/p5, 4.3/4.4 $\mu\text{g}/\text{mL}$) in addition to standard therapy with nasal corticosteroids (beclomethasone dipropionate, 100 $\mu\text{g}/\text{day}$) as needed. Those who did not accept SLIT (control group), continued only standard therapy with nasal corticosteroids as needed. All the patients had the following: nasal sIgE for Phl and Phl p5, nasal eosinophil assay, spirometry, and AAR with NPT.

The nasal symptoms score (NSS)¹⁴ was used to assess the severity of symptoms and the pediatric rhinoconjunctivitis quality of life questionnaire (PRQLQ)¹⁵ for the evaluation of children's quality of life. The AIT group performed SLIT (2 puffs per day on the oral mucosa), every year for 2 years beginning from V0. The

patients attended two follow-up visits in the peak of the pollen season, in May 2017 (V1) and May 2018 (V2), and the same examinations of V0 were performed. No adverse events or anaphylaxis were recorded during the AIT.

AAR and NPT

AAR studies the nasal function through the measurement of nasal airflow and resistance to the air passage.¹⁶ In our study, it was performed by using a Rinopocket ED200 (Euroclinic, Rome, Italy) rhinomanometer. During NPT, the first AAR was performed to determine baseline values of children's nasal airflow and resistance at a pressure of 150 Pa. The values obtained were compared with the height-dependent pediatric values, as reported in the literature.¹² Nasal obstruction was classified into five groups: very severe, if the mean airflow values are lower than 44% of predicted; severe, if values are between 44% and 54%; moderate, if values are between 55% and 65%; mild, if values are between 66% and 76%; and absent, if values are $> 76\%$.¹² We excluded unspecific hyperreactivity by nasal administration of lactose Allerkin test (Lofarma s.p.a, Milano, Italy). Then, we administered 80 UA of the grass-pollen extract Allerkin test into each nostril; 30 minutes after the insufflation of this extract, another AAR was performed. The NPT was considered positive if there was an increase in nasal resistance $> 50\%$ of the baseline value, at least in one nostril.

Nasal sIgE

Each patient underwent a nasal lavage with 10 mL of saline solution by following the method of Naclerio *et al.*¹⁷ Nasal lavage was performed before the NPT. To concentrate samples, 1.5 mL of nasal lavage was reduced to 50% of the initial volume by using refrigerated Savant SpeedVac Concentrators (Thermo Scientific, Waltham, MA). The samples were stored at -80°C until the final analysis. Nasal sIgE for Phl p1 and Phl p5 were determined by using ImmunoCAP Fluorescence Enzyme Immuno Assay (Phadia AB). The cutoff value was 0.35 UA/mL.

Nasal Cytology

For all children, a smear was prepared with material from the superficial layer of the inferior turbinate's central portion of both nostrils by using a curette (Rhino-Pro Curette, Arlington Scientific Inc., Springville, Utah).¹⁸ Subsequently, the smear was fixed, subjected to a May Grunwald-Giemsa staining technique, and then analyzed with a $\times 1000$ magnification optical microscope by evaluating 50 microscopic fields.

Table 1 Population features at the enrollment visit (V0)

	Allergen Immunotherapy Group	Control Group
No. patients	19	19
Age, mean $\pm$ SD, y	9.16 $\pm$ 2.7	8.47 $\pm$ 1.65
mNF, mean $\pm$ SD, %	52.37 $\pm$ 12.29	51.58 $\pm$ 13.23
Positive NPT result, no. (%)	14 (73.68)	14 (73.68%)
FEV ₁ , mean $\pm$ SD, %	99.87 $\pm$ 12.59	102.53 $\pm$ 12.95
Nasal IgE, mean $\pm$ SD, UA/mL		29.22 $\pm$ 20.07
Phleum p1, mean $\pm$ SD	26.10 $\pm$ 19.29	32.60 $\pm$ 23.56
Phleum p5, mean $\pm$ SD	32.55 $\pm$ 23.72	
NSS, mean $\pm$ SD	9.68 $\pm$ 1.60	10.32 $\pm$ 1.70
PRQLQ score, mean $\pm$ SD	78.84 $\pm$ 15.64	81.47 $\pm$ 14.23
Nasal eosinophils, mean $\pm$ SD	15.16 $\pm$ 10.29	12.74 $\pm$ 8.63

SD = Standard deviation; mNF = Mean nasal flow; NPT = nasal provocation test; FEV₁ = forced expiratory volume in the first second; IgE = immunoglobulin E; NSS = nasal symptom score; PRQLQ = pediatric rhinoconjunctivitis quality of life questionnaire.

Spirometry

Spirometry was performed with a Cosmed spirometer (Cosmed, Rome, Italy), according to American Thoracic Society/European Respiratory Society standards.¹⁸ Values are expressed as a percentage of predicted normal values adjusted for height, sex, and ethnicity.

NSS

The NSS is a written, four-item questionnaire, addressed to the parents of the children. The questionnaire assesses child rhinitis clinical symptoms (nasal obstruction, rhinorrhea, itching, and sneezing) in the previous 2 weeks. The answer to each item has a score that ranges from 0 to 3 (0, absent; 1, weak; 2, moderate; 3, severe). The sum of the scores provides a total index (maximum, 12), which indicates the severity of rhinitis.¹⁴

PRQLQ

The PRQLQ is a written disease-specific questionnaire that includes 23 items about five aspects: nasal symptoms, eye symptoms, practical problems, other symptoms, and daily activity limitation. It was administered to the children by a trained physician in the outpatient setting, and children were asked to score their experiences; for each item, a score from 0 (not altered) to 6 (extremely altered) was attributed. The overall score (maximum, 138) is obtained from the sum of all the items and indicates the quality of life of the pediatric patient with rhinitis.¹⁵

Statistical Analysis

Continuous variables are reported as mean $\pm$ standard deviation (SD) unless otherwise indicated. The crossover study data were analyzed for the assessment of treatment and period effects, by performing a split-

plot analysis of variance (ANOVA), with 1, as between-subject factors (treatment sequence), and 2, as within-subject factors (period 1 versus 2; pre- versus posttreatment). The full model was considered, which allowed for the assessment of all main effects and interactions. Pairwise comparisons were corrected by the Bonferroni correction factor; the results of paired differences were replicated and confirmed by appropriate nonparametric tests (Wilcoxon test). Bivariate analysis was performed with the Spearman linear regression test. A value of $p < 0.05$ was considered statistically significant. All analyses were carried out with SPSS 18.0 software for Windows (SPSS, Chicago, IL). We computed the minimum sample size with respect to a two-tailed, one-sample Student *t*-test, when considering, based on data from a previous pilot study (data not shown), that at least 36 patients are required to have a 90% chance of detecting, as significant at the 5% level, a nasal flow of 60% in the control group and 80% in the experimental group.

RESULTS

Patients

We enrolled 40 consecutive children (23 boys), 20 of whom were included in the AIT group, with a mean $\pm$ SD age of 9.16 $\pm$ 2.27 years, and the other 20 were included in the control group, with a mean $\pm$ SD age of 8.47 $\pm$ 1.65 years. One child in each group left the study voluntarily after V0 (5% of drop out); 38 children completed the study. All the children enrolled had forced expiratory volume in the first second of expiration of $>80\%$ of the predicted value. The mean $\pm$ SD nasal flow (mNF) was homogeneous between the two groups (AIT group, 52.37 $\pm$ 12.29 cm³/sec; control group: 51.58 $\pm$ 13.23 cm³/sec) as well as the nasal reactivity to grass

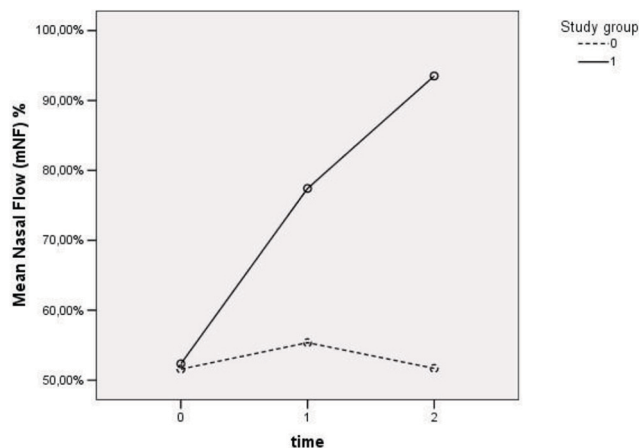


Figure 1. Modification of the mean nasal flow (mNF) at different time points in the allergen immunotherapy (AIT) group and the control group.

pollen with a positive NPT (AIT group, 73.68%; control group, 73.68%). There was not a significant difference in the basal values of nasal sIgE, nasal eosinophils, forced expiratory volume in the first second of expiration, NSS, and PRQLQ between the two groups (Table 1).

Nasal Function

A significant difference for treatments (AIT treatments versus standard therapy) is found in nasal function ($p < 0.001$) (Fig. 1) from the ANOVA performed on crossover study data. During the treatment, we observed, in the AIT group, a significant increase in the mNF compared with controls. In detail, at V2, the AIT group had a mean $\pm$ SD mNF of 93.50 ± 6.17 cm³/sec, whereas the control group had 51.68 ± 13.66 cm³/sec ($p < 0.001$). Furthermore, in the AIT group, we found an improvement of nasal function, finding that only 21.05% of all the children in the active group still presented a positive NPT result at V2. In the control group, we found, at V2, a worsening of nasal function, with 89.47% of the children with a positive NPT result.

Nasal sIgE

Our results showed a significant reduction of nasal sIgE levels in the AIT group at the end of the observation period from the ANOVA performed on crossover study data. In detail, at V2, the children in the AIT group had mean $\pm$ SD Phl p1 and Phl p5 levels of 8.04 ± 9.35 UA/mL and 12.85 ± 12.41 UA/mL, respectively, whereas the control group had mean $\pm$ SD Phl p1 and Phl p5 levels of 39.15 ± 29.33 UA/mL and 37.38 ± 28.42 UA/mL, respectively ($p < 0.001$) (Fig. 2).

Nasal Cytology

A significant difference between groups (AIT treatment versus standard therapy) was found in the nasal eosinophilic count from the ANOVA performed on

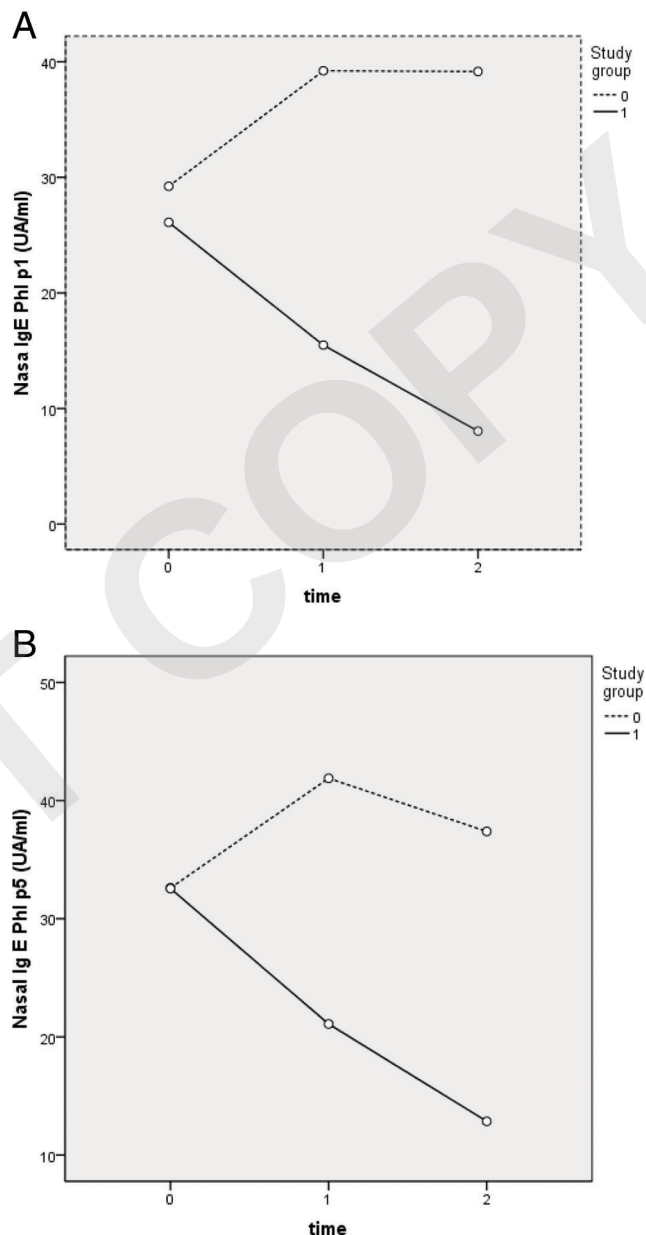


Figure 2. Variation of nasal immunoglobulin (IgE) levels at different time points in the allergen immunotherapy (AIT) group and the control group. (A) Phl p1. (B) Phl p5.

crossover study data. In fact, at the end of the observation period, the children in the AIT group had a significant reduction ($p < 0.001$) (Fig. 3) of the nasal eosinophil numbers (1.00 ± 0.94) compared with the control group (17.00 ± 8.91). In the other cell populations, we did not find significant changes between the AIT group and the control group during the observation period.

NSS and PRQLQ

A significant difference is also found by comparison of NSS and PRQLQ between the AIT group and the control group ($p < 0.001$) (Fig. 1a) from the ANOVA

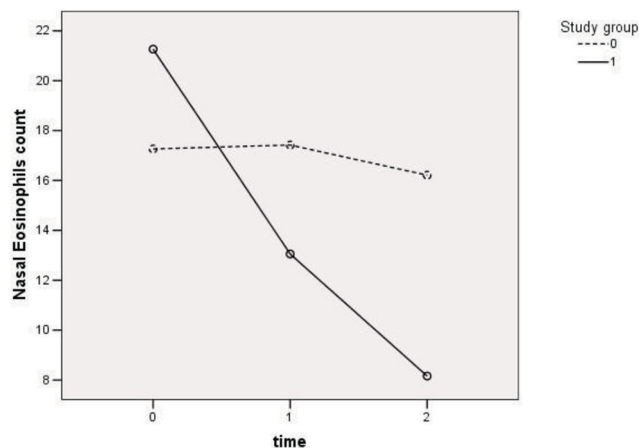


Figure 3. Modification of the nasal eosinophils count at different time points in the allergen immunotherapy (AIT) group and the control group.

performed on crossover study data. In detail, at V2, the NSS data showed, in the AIT group, a significant reduction of the total score (2.89 ± 1.85) in respect to controls (9.58 ± 1.98), which indicated an improvement of nasal symptoms in the former. The mean $\pm$ SD PRQLQ score of AIT group was 22.26 ± 1.98 , whereas the mean $\pm$ SD score of the control group was 79.42 ± 8.85 , with an enhancement of quality of life in the treated group.

DISCUSSION

The primary outcome of our study was to assess the changes in nasal reactivity in our patients on grass-pollen AIT treatment. The secondary outcome was to evaluate the changes in nasal eosinophil counts, nasal sIgE, quality of life, and rhinitis symptoms in these patients. The analysis of our data indicated that, at the end of the observation period, the children in the AIT group had a significant increase of mNF with AAR and a significant reduction of nasal reactivity after NPT when compared with the children who performed only standard therapy. So far, only a few studies evaluated children with AR nasal reactivity and SLIT effect by using objective parameters (AAR and NPT). Ciprandi *et al.*,²⁰ showed that SLIT is able to improve nasal obstruction and positively affect the response to the decongestion test in adults sensitized to dust mite, with persistent AR. Another study concluded that both subcutaneous immunotherapy and SLIT decrease the nasal reactivity at NPT and lead to a clinical improvement in children.²¹

Furthermore, in analyzing our data, we observed, in the active group, a significant decrease of nasal sIgE levels and eosinophils induced by AIT treatment, which suggested an effect of inhibition in local IgE production. This could mean a reduction of local allergic inflammation, although further studies are needed to confirm

these results. Several previous studies had evidence of the effect of AIT in inducing immunologic changes and allergen tolerance in patients with LAR.^{22,23} Bozek *et al.*²⁴ showed the efficacy of AIT in reducing nasal IgE production in adult patients with LAR. Moreover, Rondón *et al.*²⁵ highlighted that nasal sIgE detection is highly specific and could be useful in monitoring response to AIT in children with AR.

When considering the clinical evaluation of our children, we found, at V2, an improvement in clinical symptoms and quality of life in the AIT group, demonstrated by a reduction in NSS and PRQLQ scores. In the control group, these scores remained unchanged. Also, Lin *et al.*²⁶ observed, in their study, significant differences in nasal symptoms and quality of life in adults and children during AIT treatment. In a recent study on a Japanese pediatric population, Okamoto *et al.*²⁷ demonstrated that AIT significantly improved clinical symptoms of house dust mite induced perennial AR.

To our knowledge, this was the first study that evaluated, overall, children undergoing grass pollen AIT by using functional (AAR), inflammatory (nasal sIgE and eosinophil count), and clinical (NSS and PRQLQ) parameters. The major limitations were the small number of participants, all recruited in a single outpatient setting, and the time of observation of only 2 years.

CONCLUSION

We observed in children with AR and sensitized to grass pollen after AIT, the improvement of inflammation markers and objective nasal parameters. Because of these results, we suggest to also confirm AIT efficacy by using this noninvasive and high specific approach.

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