

Small airways in children with allergic rhinoconjunctivitis: the potential role of a multicomponent nutraceutical

Salvatore Leonardi¹, Giuseppe Parisi¹, Maria Papale¹, Anna Maria Zicari², Roberta Olcese³, Amelia Licari⁴, Gianluigi Marseglia⁴, Giorgio Ciprandi⁵

¹Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy University; ²Pediatrics Department, Umberto I Hospital, Roma, Sapienza University, Roma, Italy; ³Allergy Center, Istituto Giannina Gaslini, Genoa, Italy; ⁴Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; ⁵Allergy Clinic, Villa Montallegro, Genoa, Italy

Summary. Allergic rhinitis and asthma are closely linked. A progression from rhinitis to overt asthma is common. FEF_{25-75} is a spirometry parameter that could reflect small airways patency and could reliably predict early bronchial involvement in allergic rhinitis patients. MEF_{50} very strongly correlates with FEF_{25-75} . The aim of this study was to evaluate possible spirometry change in two groups of children suffering from AR over time. The first group took a course of a nutraceutical (Lertal®) before the observation (active group, AG); a second one was considered as control (control group, CG). The children were visited at baseline, at the end of the nutraceutical course, and after 1 year. FEV_1 , FVC, and MEF_{50} were the primary outcomes. After one year, children in AG had significantly higher MEF_{50} than CG children ($p=0.009$). In conclusion, the present study showed that a course with a multicomponent nutraceutical could prevent the MEF_{50} decline in children with allergic rhinoconjunctivitis. (www.actabiomedica.it)

Key words: allergic rhinitis, children, spirometry, asthma, MEF_{50} , nutraceutical

Introduction

Allergic rhinitis (AR) is a relevant risk factor for the development of asthma in children and is an important trigger factor for exacerbations in patients with asthma (1). Moreover, AR and asthma are closely associated both from a pathophysiological and a clinical point of view (2). AR frequently may precede asthma inasmuch as it has been proposed the term “asthma march” to define the progression from AR towards asthma (3). In this regard, a functional link has been described between nasal airflow and bronchial airflow (4,5). Alike, there is a close association between allergic inflammation and nasal obstruction (6,7). These concepts support the unbreakable relationship between the upper and lower airways, in health as well as in disease. Although upper and lower airways diseases share the same pathophysiological features, their man-

agement and treatment are commonly applied in an undesirable and independent manner, counteracting the concept of unified airways observed several years ago (8).

The increase of allergic rhinitis (AR) comorbidity in patients with asthma is consistent with the increase of asthma comorbidity in subjects with AR (8). AR is one of the most frequently reported asthma comorbid conditions (9). Moreover, AR appears to be a negative early-life predictive factor for an accelerated decline in lung function. Interestingly, a persistent, severe and protracted history of AR is associated both with a major airway dysfunction and with a severe asthma phenotype (6). In this regard, small airways are early impaired in AR patients and a pathological value of the forced expiratory flow between the 25% and 75% of the vital capacity (FEF_{25-75}), such as $<65\%$ of predicted, could be a reliable marker of subclinical asthma (11).

Actually, FEF_{25-75} has been considered also a surrogate marker to investigate small airways (12).

Taking account these concepts, lung function testing should be performed in patients with AR to early detect bronchial impairment. The gold standard parameter to define bronchial obstruction in asthma is the forced expiratory volume in one second (FEV_1), even though it may be normal during symptom-free periods (13). In this situation, FEF_{25-75} could be fruitfully considered (14). FEF_{25-75} correlates very well with another spirometry parameter: the maximal mid expiratory flow rate at 50% of vital capacity (MEF_{50}) as elegantly demonstrated (15). Equally, MEF_{50} provided a diagnostic and prognostic utility in clinical practice (16).

Notably, it has been reported that the progression from AR to asthma could be prevented by appropriate treatments, including allergen immunotherapy (17). In this regard, Lertal® is an oral food supplement, containing: *Perilla frutescens* 80 mg (as dry extract), Quercetin 150 mg, and Vitamin D₃ 5 mcg (200 IU). It exerts anti-allergic and anti-inflammatory activity that may be fruitful in reducing and preventing AR exacerbation as recently evidenced by a randomized controlled study (18,19).

On the basis of this background, the current study aimed at evaluating the carry-over effect of a Lertal® course (lasting 2-4 months) on lung function testing, mainly concerning MEF_{50} , in children with AR in one year.

Materials and Methods

Globally, 53 patients with allergic rhinitis were evaluated retrospectively.

Allergic rhinitis was diagnosed according to validated criteria, such as on the consistency between history and sensitization (1). These children belonged to a cohort included in a randomized, polycentric, double-blinded, parallel-group, placebo-controlled trial held in two phases (18,19).

Inclusion criteria were: age range 6-12 years, AR diagnosis, sensitization to house dust mites or pollens, Total Symptoms Score (TSS) ≥ 15 and at least 1 for nasal congestion, written informed consent of patients and of parents or legal guardians. Exclusion

criteria were: uncontrolled asthma, secondary rhinitis to other causes, concomitant acute or chronic rhinosinusitis, nasal polyps, current use of topical or systemic corticosteroids, antihistamines, antileukotrienes, inadequate washout of them, nasal anatomic defect, respiratory infections in the last 2 weeks, participation in other clinical studies in the last month, documented hypersensitivity to the study product or its excipients, and trip planned outside of the study area.

After 2-week run-in period, eligible patients were randomly (1:1 ratio) treated with Lertal® double-layer tablets (1 tab/day for 4 weeks) plus standard therapy or Lertal® placebo tablets (1 tab/day for 4 weeks) plus standard therapy: phase I. As Lertal® was considered as add-on treatment, the standard therapy was continuous antihistaminic treatment. Systemic or intranasal corticosteroids, leukotriene antagonists, and sodium cromoglicate were prohibited during the study.

The phase II was an open-label, parallel-group, extension study in which patients treated with study product in Period I continued treatment with Lertal® tablets, whereas patients initially treated with placebo received no further treatment. After the 4-week active treatment period, children treated with Lertal® plus standard therapy continued to take Lertal® tablets (1 tab/day for 4-12 weeks) alone (such as without antihistamines), whereas children treated with Placebo suspended any treatment. The current treatment lasted 4 weeks in children with pollen allergy, whereas 12 weeks in children with perennial allergy.

The duration of Lertal® treatment lasted 8 (in children with pollen allergy) or 16 weeks (in children with mite allergy) overall.

At the end of the trial, some children were observed for one year. During this one, children were treated with antihistamines on demand.

The children were visited at the enrolment, at the end of the trial, and after one year, a spirometry was performed during each visit. Three main parameters were evaluated: FEV_1 , FVC, and MEF_{50} . They were considered as percentage of predicted according with International guidelines (20).

Continuous data were summarized by means of common descriptive statistics: mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data were presented by

absolute and relative frequencies (n and %) or contingency tables.

Demographics characteristics (i.e. age, sex and type of allergy) were summarized overall and by treatment by means of summary descriptive statistics.

FEV₁, FVC, and MEF₅₀ values were summarized overall and by treatment by medians of summary descriptive statistics considering the overall population. Spirometry parameters were graphically represented by means of box plots by treatment in the overall population considering the medians and the interquartile range (IQR).

The between-group analyses were performed considering the overall population by means of t-test for independent samples or analogous non-parametric test (i.e. Wilcoxon rank-sum test in case of non-normal distribution of data assessed by Saphiro Wilk test).

Results

The demographic characteristics of the children are reported in Table 1. The mean age was 9.42 ± 1.97 years. There were 35 males. Thirty-three children had pollen allergy and 20 had mite allergy.

There was no significant difference between groups at baseline.

Table 1. Demographic characteristics of the subjects. Data are express as absolute numbers, mean, and standard deviation

	Active Group	Control Group	Total
Number of subjects	28	25	53
Age (years)	9.46 ± 2.05	9.36 ± 1.91	9.42 ± 1.97
Males	20	15	35
Females	8	10	18
Pollen Allergy	19	14	33
Mite Allergy	9	11	20

FEV₁

The median value was 94 (IQR 90-97.5) in the active group and 93 (IQR 89-95) in the control group at the enrolment. The median value was 95 (IQR 92-97) in the active group and 94 (IQR 93-96) in the control group at the end of the trial. The median value was 96 (IQR 94-99) in the active group and 93 (IQR 88-95) in the control group at on year (Figure 1).

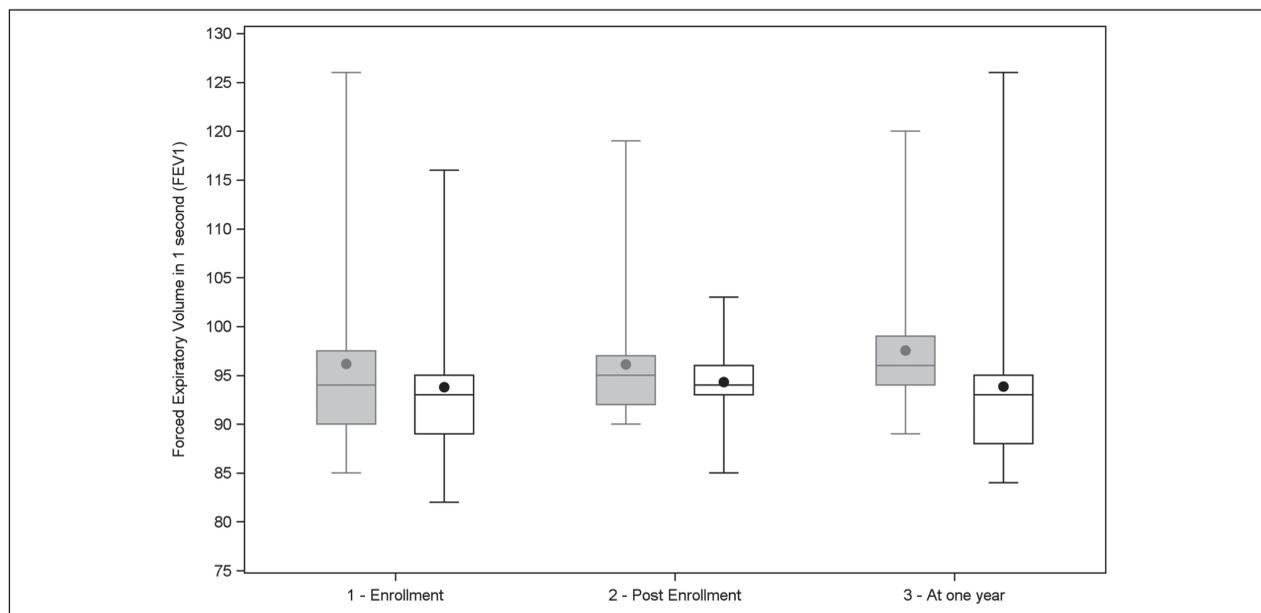


Figure 1. Box-plot of the FEV₁ values (expressed as % of predicted) in active group (grey) and control group (white) at the enrolment, at the end of the trial, and at one year. Data are expressed as medians, IQR, and minimum and maximum values

FVC

The median value was 94 (IQR 92-97.5) in the active group and 95 (IQR 90-97) in the control group at the enrolment. The median value was 96 (IQR 93-99) in the active group and 96 (IQR 92-98) in the control group at the end of the trial. The median value was 96.5 (IQR 93.5-99) in the active group and 94 (IQR 91-97) in the control group at on year (Figure 2).

MEF₅₀

The median value was 85 (IQR 83-88) in the active group and 85 (IQR 83-87) in the control group at the enrolment. The median value was 87 (IQR 85-88.5) in the active group and 87 (IQR 85-89) in the control group at the end of the trial. The median value was 88.5 (IQR 85.5-90.5) in the active group and 84 (IQR 82-87) in the control group at on year (Figure 3).

The intergroup analysis showed that there was no significant difference between group at any time about FEV₁ and FVC.

There was significant difference between groups at one year for MEF₅₀ (p=0.009).

These outcomes were confirmed after stratification for pollen or mite allergy (data not shown).

Discussion

FEF₂₅₋₇₅, as well as MEF₅₀, deserves an adequate and careful consideration in patients with asthma and/or allergic rhinitis as well as in the general population because low values can add fruitful information about asthma, rhinitis, and allergy in the common practice.

Many attempts were tried to prevent the progression from allergic rhinitis toward asthma, including pharmacological and immunological treatments.

Nutraceuticals are a wide class of compounds that consists of herbal medicine, probiotics, and vitamins. Many of these components exert clinically relevant effects and the literature reports evidence of beneficial properties (21).

The current study demonstrated that a course of a multicomponent nutraceutical, i.e. Lertal®, lasting 8 or 16 weeks, exerted a carry-over effect on MEF₅₀ within one year. MEF₅₀ is a spirometry parameter that substantially corresponds to the most popular FEF₂₅₋₇₅ as ery strongly correlates with it (15).

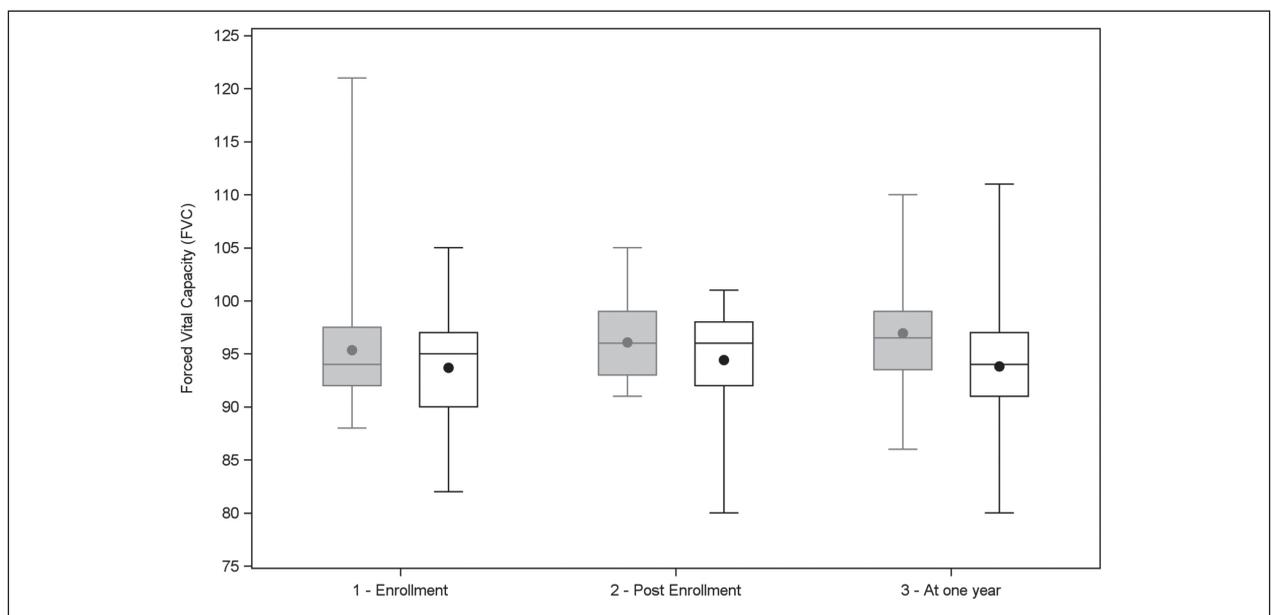


Figure 2. Box-plot of the FVC values (expressed as % of predicted) in active group (grey) and control group (white) at the enrolment, at the end of the trial, and at one year. Data are expressed as medians, IQR, and minimum and maximum values

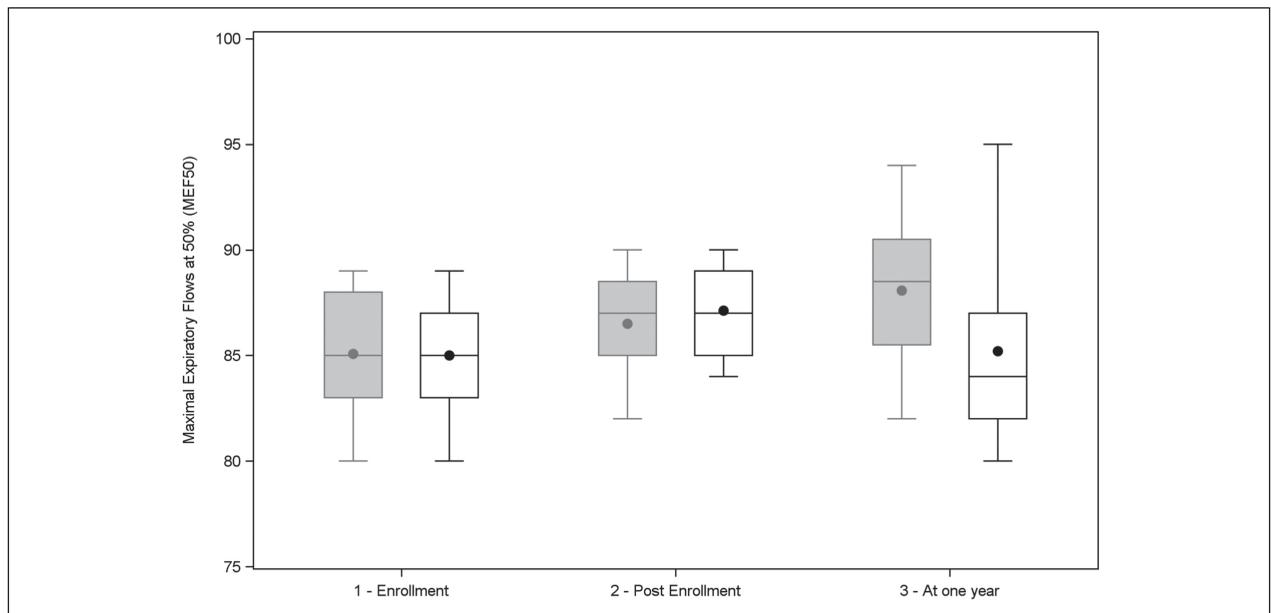


Figure 3. Box-plot of the MEF_{50} values (expressed as % of predicted) in active group (grey) and control group (white) at the enrollment, at the end of the trial, and at one year. Data are expressed as medians, IQR, and minimum and maximum values

Even though the difference between the groups (active and control) was slight and not clinically relevant, such as about 5%, the relevance of this finding lies in the over time change. In other words, the control group showed a trend to the reduction of MEF_{50} , whereas the children who took Lertal® exhibited an increase of MEF_{50} within one year. This outcome could mean a potential preventive effect towards the possible asthma onset in patients with allergic rhinitis. FEF_{25-75} , and consistently MEF_{50} , has been reported the most sensitive marker able to detect the progression from rhinitis to asthma as reported in some studies (22-24).

These outcomes could depend on the immunomodulatory property of the 3 components of the nutraceutical as recently described (9,10).

On the other hand, this study had some limitations including the open design and the lack of the proofs concerning a real prevention of asthma onset.

In conclusion, the present study showed that a course with a multicomponent nutraceutical could prevent the MEF_{50} decline in children with allergic rhinoconjunctivitis.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and Allergen). *Allergy* 2008;63(Suppl. 86):8-160
2. Deliu M, Belgrave D, Simpson A, Murray CS, Kerry G, Custovic A. Impact of rhinitis on asthma severity in school-age children. *Allergy*. 2014 Jun 24. doi: 10.1111/all.12467
3. Ciprandi G, Signori A, Tosca MA, Cirillo I. Spirometric abnormalities in patients with allergic rhinitis: indicator of an asthma march? *Amer J Rhinol Allergy* 2011;32:22-8
4. Ciprandi G, Caimmi D, Miraglia del Giudice M, La Rosa M, Salpietro C, Marseglia GL. Recent developments in united airways disease. *Allergy Asthma Immunol Res* 2012;4:171-7
5. Ciprandi G, Cirillo I. The lower airway pathology of Rhinitis. Update Review *J Allergy Clin Immunol* 2006; 118:1105-1109
6. Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Nasal obstruction in patients with seasonal allergic rhinitis: relationships between allergic inflammation and nasal airflow. *Int Arch Allergy Immunol* 2004;134:34-40

7. Ciprandi G, Marseglia GL, Klersy C, Tosca MA. Relationships between allergic inflammation and nasal airflow in children with persistent allergic rhinitis due to mite sensitization. *Allergy* 2005;60:957-60
8. Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950-958
9. Tay TR, Hew M. Comorbid “treatable traits” in difficult asthma: Current evidence and clinical evaluation. *Allergy*. 2018;73(7):1369-1382
10. Montella S, Baraldi E, Cazzato S, et al. Severe asthma features in children: a case-control online survey. *Ital J Pediatr*. 2016;42:9
11. Marseglia GL, Cirillo I, Vizzaccaro A, Klersy C, Tosca MA, La Rosa M, Ciprandi G. Role of FEF25-75 as early marker of small airways impairment in subjects with allergic rhinitis *Allergy Asthma Proc* 2007;28:74-8
12. Lipworth B. Targeting the small airways asthma phenotype: if we can reach it, should we treat it? *Ann Allergy Asthma Immunol* 2013;110:233-9
13. Simon MR, Chinchilli VM, Phillips BR, et al. Forced expiratory flow between 25% and 75% of vital capacity and FEV₁/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV₁ values. *J Allergy Clin Immunol* 2010;126:527-34.
14. Siroux V, Boudier A, Dolgopoff M, et al. Forced midexpiratory flow between 25% and 75% of forced vital capacity is associated with long-term persistence of asthma and poor asthma outcomes. *J Allergy Clin Immunol* 2016;137:1709-16
15. Bar-Yishay E, Amirav I, Goldberg S. Comparison of maximal midexpiratory flow rate and forced expiratory flow at 50% of vital capacity in children. *Chest*.2003;123:731-5
16. Guder G, Brenner S, Stork S, et al. Diagnostic and prognostic utility of mid-expiratory flow rate in older community-dwelling persons with respiratory symptoms, but without chronic obstructive pulmonary disease. *BMC Pulmonary Med* 2015;15:83
17. Valovirta E, Petersen TH, Piotrowska T, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol*. 2018;141:529-538.e13
18. Marseglia GL, Licari A, Ciprandi G. A polycentric, randomized, double blind, parallel-group, placebo-controlled study on Lertal®, a multicomponent nutraceutical, as add-on treatment in children with allergic rhinoconjunctivitis: Phase I during active treatment. *J Biol Reg* 2019;33:617-622
19. Marseglia GL, Licari A, Leonardi S, et al. A polycentric, randomized, parallel-group, study on Lertal®, a multicomponent nutraceutical, as preventive treatment in children with allergic rhinoconjunctivitis: Phase II. *Ital J Ped* 2019;45:84
20. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948-68
21. Mainardi T, Kapoor S, Bielory L. Complementary and alternative medicine: Herbs, phytochemicals and vitamins and their immunologic effects. *J Allergy Clin Immunol* 2009;123:283-94
22. Ciprandi G, Cirillo I, Signori A. Impact of allergic rhinitis on bronchi: an 8 year follow up study. *Am J Rhinol Allergy* 2011;25:72-6
23. Cirillo I, Gallo F, Ciprandi G. Impaired spirometry may predict bronchial hyper-responsiveness. *JACI in practice* 2018;6:2127-9
24. Ciprandi G, Silvestri M, Pistorio A, Tosca MA, Cirillo I. Clustering analysis in outpatients with allergic rhinitis in clinical practice. *Allergy* 2019 ;74:607-10

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Correspondence:

Giorgio Ciprandi

Via P. Boselli 5,

16146, Genoa, Italy

E-mail: gio.cip@libero.it