

Respiratory infections in allergic children: the preventive role of a multicomponent nutraceutical

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Summary. Allergic children with respiratory infections (RI) are a demanding challenge for the paediatrician. Antibiotic prescription represents a critical problem, mainly concerning the growing issue of resistance. To prevent RI would be therefore a goal in clinical practice. In this regard, modulation of immune system may have a critical role. The aim of the present study was to measure the number of respiratory infections and the use of antibiotics in two groups of children suffering from allergic rhinoconjunctivitis. 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 and after 1 year. The number of RI and of antibiotic courses was the primary outcomes. Children in AG reported a significant reduced number of RI and of antibiotic course in comparison with CG ($p=0.01$ and 0.002 respectively). In conclusion, the current study showed that a course with a multicomponent nutraceutical could reduce the number of respiratory infections and consequently the use of antibiotics in children with allergic rhinoconjunctivitis. (www.actabiomedica.it)

Key words: respiratory infection, antibiotics, allergic rhinoconjunctivitis, children, nutraceutical

Introduction

Allergic children with respiratory infections (RI), mainly if recurrent, are a relevant problem for the paediatrician in clinical practice. RI have a relevant impact on pharmaco-economy and are a burden for both the family and the society. In addition, antibiotic overuse/abuse represents the primary cause for the occurrence of antibiotic resistance: a demanding challenge for the future (1).

Many factors may be involved in promoting and/or causing frequent RI, including age, early attending at nursery school, air and home pollution, passive tobacco smoking, low socio-economic level, and allergy (2). In particular, allergy plays a crucial role in promoting the RI recurrence as the immune response is typically impaired in allergic subjects. In fact, allergic sub-

jects present a defect of the type 1 immune response that is appointed to fight infections by anti-infective cytokines, namely IFN- γ (3,4). Moreover, allergic subjects have the minimal persistent inflammation, that is associated with increased epithelial ICAM-1 expression, such as the main rhinovirus receptor (5). Viral infections are predominant, but bacterial superinfections may frequently appear. Consequently, there is an overuse/misuse of antibiotics that in turn induces antibiotic resistance (6,7).

RI treatment is commonly based on symptomatic drugs (e.g. acetaminophen) and antibiotics administration, but frequently without precise indication and so empirically prescribed. Consequently, prevention of RI is at present a demanding issue in clinical practice. Many medications have been proposed, including bacterial derivatives and probiotics

Bacterial derivatives, including probiotics, are frequently used in clinical practice (8). However, appropriately curing allergy by medications or specific immunotherapy could also reduce the impact of RI (9,10). Therefore, to correctly treat allergic rhinoconjunctivitis could prevent RI. 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). These components exert anti-allergic and anti-inflammatory activity that could be fruitful in preventing AR exacerbation as recently evidenced by a randomized controlled study (11,12).

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 the prevention of RI and the associated antibiotic use 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 (13). These children belonged to a cohort included in a randomized, polycentric, double-blinded, parallel-group, placebo-controlled trial held in two phases (10,11).

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 only with antihistamines on demand. The number of RI episodes and the number of antibiotics courses were recorded in a diary.

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.

Number of RI and antibiotic courses was summarized overall and by treatment by medians of summary descriptive statistics considering the overall population. Number of RI and antibiotic courses was 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.

The median number of RI was 2.0 (IQR 1-2) in the active group and 3.0 (IQR 2-4) in the control group. The difference was statistically significant: $p=0.01$ (Figure 1).

The median number of antibiotic courses was 1.0 (IQR 0-1) in the active group and 2.0 (IQR 1-3) in the control group. The difference was statistically significant: $p=0.002$ (Figure 2).

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

Discussion

Respiratory infections, mainly if recurrent, constitute a burdensome task in clinical practice. RI account for the first reason of antibiotic prescription (14). Moreover, RI in childhood cause frequent school absence and consequently parents' work days loss. Therefore, preventing RI could represent a compelling challenge in clinical practice (15).

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

	Active Group	Control Group	Total
Number of subjects	32	31	63
Age (years)	9.22 ± 2.06	9.58 ± 1.93	9.4 ± 1.99
Males	23	18	41
Females	9	13	22
Pollen Allergy	20	16	36
Mite Allergy	12	15	27

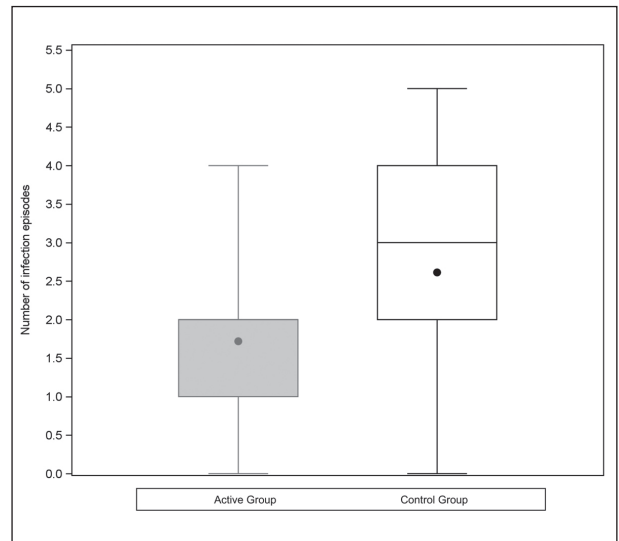


Figure 1. Box-plot of the number of respiratory infections in active group (grey) and control group (white). Data are expressed as medians, IQR, and minimum and maximum values

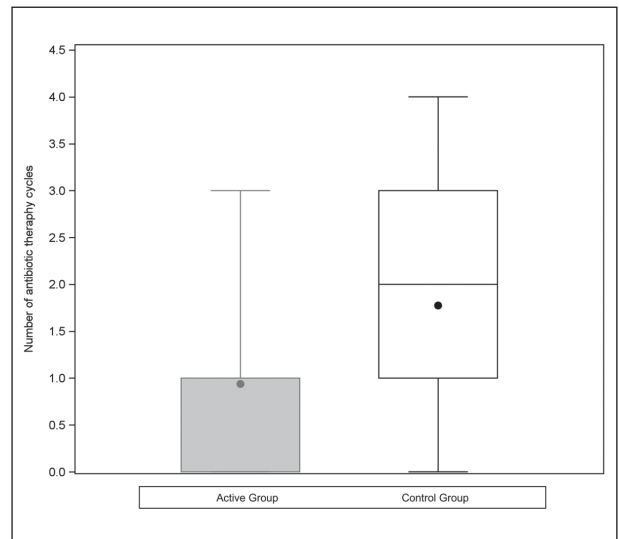


Figure 2. Box-plot of the number of courses of antibiotic therapy in active group (grey) and control group (white). Data are expressed as medians, IQR, and minimum and maximum values

The immune system fights RI involving the innate and the adaptive response by both umoral and cellular signalling. Actually, immune system responds to pathogens through very complex and complicated mechanisms (16). An effective response results from a balance between aggressive and reparative processes finely modulated by regulatory pathways.

On the basis of this background, we tested the hypothesis that a multicomponent nutraceutical (Lertal®), able to prevent allergic rhinoconjunctivitis exacerbations, could also prevent RI.

This study demonstrated that allergic children treated with a multicomponent nutraceutical had less RI and used significantly less antibiotics than control children. This finding may suggest that the nutraceutical exerted a preventive effect on RI. In particular, the outcomes of this study confirmed the findings observed both during the phase I and phase II of the reference trial. This fact provided the evidence that a course of Lertal®, lasting 8 or 16 weeks, exerted a carry-over effect within one year.

This result could be explained by the anti-inflammatory, immune-modulatory, and anti-allergic properties of the 3 components of the nutraceutical. In particular, Vitamin D₃ is essential for the normal function of the immune system and may exert a role in both prevention and potential treatment of AR, restoring physiological T regulatory activity and exerting also anti-inflammatory activity (17,19). The dry seed extract of *Perilla frutescens* contains rosmarinic acid and other flavonoids, such as luteolin, apigenin and chrysoeriol, and has shown *in vivo* and *in vitro* potential anti-allergic activity (20,21). Quercetin tends to stabilize cell membranes and block degranulation of mast cells and basophils, inhibiting the release of pro-inflammatory mediators and cytokines implicated in allergic inflammation (22,23).

This study has some limitations including the open design and the lack of the assessment of the cause of RI and the symptom severity. However, the patients were well selected and followed as the study was an extension of a randomized controlled trial.

In conclusion, the current study showed that a course with a multicomponent nutraceutical could reduce the number of respiratory infections and consequently the use of antibiotics 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

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