Acta Biomed 2020; Vol. 91, N. 2: 356-359 DOI: 10.23750/abm.v91i2.9719

Lertal®, a multicomponent nutraceutical, could reduce the use of antihistamines in children with allergic rhinoconjunctivitis

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Summary. Antihistamines are the cornerstone treatment of allergic rhinitis (AR). To quantify the antihistaminic consume is particularly relevant in clinical practice, since a remarkable use is usually associated with severe symptoms. The aim of the study was to measure the use of antihistamines in two groups of children suffering from AR. 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). Both groups took antihistamines on demand. The children were visited at baseline and after 1 year. The number of days of antihistaminic use was the primary outcome. Children in AG had a significant reduced number of antihistamines use in comparison with CG (p=0.008). In conclusion, the current study showed that a course with a multicomponent nutraceutical could reduce the use of symptomatic antihistamines in children with allergic rhinoconjunctivitis. (www.actabiomedica.it)

Key words: allergic rhinitis, antihistamines, children, medication use, nutraceutical

Introduction

Allergic rhinitis (AR) is characterized by typical symptoms, including itching, sneezing, watery rhinorrhea, and congestion (1). All of them are sustained by histamine release from activated mast cells. Mast cell activation occurs every time that the allergic patient exposes him/herself to the causal allergen (2). Therefore, antihistamines are commonly prescribed in the management of AR as first-line choice (3). In addition, they are widely used because of quickly relieving allergic symptoms: usually within an hour.

The quantification of their consumption may be particularly relevant in clinical practice, because a remarkable use is usually associated with severe symptoms (4). In addition, symptomatic use of antihistamines is a useful parameter for evaluating the effectiveness of specific treatments (5,6).

On the other hand, AR is caused by a type2 inflammation, mainly concerning an eosinophilic infiltrate of the nasal mucosa (7). Therefore, to dampen allergic inflammation represents a milestone in AR management (8). However, more aggressive pharmacological treatments, namely corticosteroids, are requested to control allergic inflammation. As pharmacological treatments might be harmful, a growing interest has been addressed to nutraceuticals. In this regard, Lertal® is an oral food supplement, containing: *Perilla frutescens* 80 mg (as dry extract), Quercetin 150 mg, and Vitamin D_3 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 (9,10).

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 antihistamines use in children with AR in one year.

Materials and Methods

Globally, 63 patients with allergic rhinitis were evaluated retrospectively.

Allergic rhinitis was diagnosed according to validated criteria, such as on the consistency between history and sensitization (11).

These children belonged to a cohort included in a randomized, polycentric, double-blinded, parallel-group, placebo-controlled trial held in two phases (9,10).

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 use of antihistamines was recorded in a diary and was reported as number of days of antihistamine therapy.

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 days of antihistamine therapy was summarized overall and by treatment by medians of summary descriptive statistics considering the overall population. Number of days of antihistamine therapy 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 9.4 $\pm$ 1.99 years. There were 41 males. Thirty-six children had pollen allergy and 27 had mite allergy.

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	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

At baseline, there was no significant difference between groups.

The median number of days of antihistamine therapy was 15 (IQR 10-21) in the active group and 30 (IQR 15-45) in the control group. The difference was statistically significant: p=0.008.

Figure 1 reports the box-plot in the two groups.

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

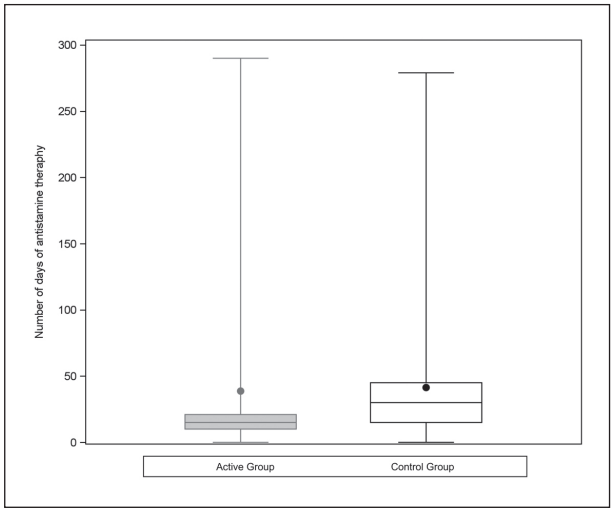

Figure 1. Box-plot of the number of days of antihistamine therapy in active group (grey) and control group (white). Data are expressed as medians, IQR, and minimum and maximum values

Discussion

Antihistamine therapy is usually prescribed in patients suffering from allergic rhinitis as is effective and quickly relief symptoms. The widespread use of antihistamines depends also on their anti-allergic activity (12-15). The quantity of antihistamine use has been considered a reliable parameter to evaluate the severity of allergic rhinitis (1,4).

The current study showed that children, treated with a multicomponent nutraceutical, used significantly less antihistamines than control children. This finding means that the nutraceutical exerted a preventive effect on allergic rhinitis exacerbations. 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, could exert 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 D_3 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 (16-18). 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 (19,20). 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 (21,22).

This study has some limitations including the open design and the lack of the assessment of 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 use of symptomatic antihistamines 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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Received: 28 March 2020
Accepted: 28 April 2020
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