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 rhinorhoea, 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 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 (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 ± 1.99 years. There were 41 males. Thirty-six children had pollen allergy and 27 had mite allergy.
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).

**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     |

**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 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 (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.

References

1. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. Int Forum Allergy Rhinol. 2018;8:108-352
2. Méndez-Enríquez E, Hallgren J. Mast Cells and Their Progenitors in Allergic Asthma. Front Immunol. 2019;10:821
3. Wallace DV, Dykewicz MS, Oppenheimer J, Portnoy JM, Lang DM. Pharmacologic Treatment of Seasonal Allergic Rhinitis: Synopsis of Guidance From the 2017 Joint Task Force on Practice Parameters. Ann Intern Med. 2017;167:876-881
4. Ciprandi G, La Mantia I. VAS for assessing the perception of antihistamines use in allergic rhinitis. Acta Biomed. 2019;90(7-S):41-44
5. Didier A, Wahn U, Horak F, Cox I. Five-grass-pollen sublingual immunotherapy tablet for the treatment of grass-pollen-induced allergic rhinoconjunctivitis: 5 years of experience. Expert Rev Clin Immunol. 2014;10:1309-24
6. Hafner D, Reich K, Matricardi PM, Meyer H, Kettner J, Narkus A. Perspective validation of Allergy-Control-Score: a novel symptom-medication score for clinical trials. Allergy 2011;66:629-36
7. Ciprandi G, Tosca MA, Marseglia GL, Klersy C. Relationships between allergic inflammation and nasal airflow in children with seasonal allergic rhinitis. Annals Allergy Asthma Immunol 2005;94:258-61
8. 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
9. 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
10. 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
11. Brožek 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
12. Ciprandi G, Cosentino C, Milanese M, Mondino C, Canonica GW. Fexofenadine reduces nasal congestion in perennial allergic rhinitis Allergy 2001;56:1068-1070
13. Ciprandi G, Pronzato C, Ricca V, Varese P, Giacco GS, Canonica G. Terfenadine exerts antiallergic activity reducing ICAM-1 expression on nasal epithelial cells in patients with pollen allergy. Clinical Experimental Allergy 1995;25:871-878
14. Ciprandi G, Buscaglia S, Catrullo A, et al. Azelastine eye drops reduce and prevent allergic conjunctival reaction and exert anti-allergic activity. Clinical Experimental Allergy 1997;27:182-91
15. Ciprandi G, Tosca MA, Passalacqua G, Canonica GW. Long-term cetirizine treatment reduces allergic symptoms and drug prescriptions in children with mite allergy. Annals of Allergy Asthma Immunol 2001;87:222-6
16. Yepes-Nunes JJ, Brozek JL, Fiocchi A, et al. Vitamin D supplementation in primary allergy prevention: systematic review of randomized and non-randomized studies. Allergy 2018;73:37-49
17. Kim YH, Kim KW, Kim MJ, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. Ped Allergy Immunol 2016;27:580-90
18. Aryan Z, Rezaei N, Camargo CA. Vitamin status, aeroallergen sensitization, and allergic rhinitis: a systematic review and meta-analysis. Int Rev Immunol 2017;36:41-53
19. Ju H, Qiu JF, Ma LJ, Hu YJ, Li P, Wan JB. Phytochemical and phytopharmacological review of Perilla frutescens L. (Labiatae), a traditional edible-medicinal herb in China. Food Chem Toxicol. 2017;108(Pt B):375-391
20. Igarashi M, Miyazaki Y. A review on bioactivities of Perilla: progress in research on the functions of Perilla as medicine and food. Evid Based Complement Alternative Med 2013;2013:925342.
21. Chirumbolo S. The role of Quercetin, Flavonols and Flavones in modulating inflammatory cell function. Inflamm Allergy Drug Targets 2010; 9(4):263-85.
22. Mlcek J, Jurikova T, Skrovankova S, Sochor J. Quercetin and its anti-allergic immune response. Molecules 2016;21,623