Balkan Med J 2015;32:352-8

In Vivo Anti-Inflammatory Effect of H1 Antihistamines in Allergic Rhinitis: A Randomized Clinical Trial

Corina I. Bocşan[1], Adriana I. Bujor[2], Nicolae Miron[2], Ştefan C. Vesa[1], Diana Deleanu[2], Anca D. Buzoianu[2]

[1]Department of Clinical Pharmacology, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj Napoca, Romania
[2]Department of Allergology, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj Napoca, Romania

Background: Allergic rhinitis is characterized by a chronic inflammation of nasal mucosa and represents a risk factor for asthma occurrence. H1 antihistamines reduce the symptoms of rhinitis, but some compounds may have anti-inflammatory properties.

Aims: We evaluated the plasma level of some cytokines in patients with persistent allergic rhinitis (PAR) and their evolution after a 4-week treatment with H1 antihistamines, as well as the risk of asthma after 1.5 years.

Study Design: Randomized clinical trial.

Methods: Eighty-five patients with PAR and 30 healthy volunteers were included in the study. The patients with PAR were randomly divided into 2 groups: 41 patients treated with 5 mg/day desloratadine and 44 patients under 5 mg/day levocetirizine for 4 weeks. The clinical and biological evaluations were performed before and after treatment and included rhinitis symptoms and total symptoms score, type of sensitization, and plasmatic levels of total IgE, IL-1β, IL-6, IL-8 and TNF-α.

Results: IL-8 and TNF-α were significantly increased in patients with PAR compared to healthy volunteers (5.85 vs 3.12, $p<0.001$ and 2.32 vs 1.06, $p<0.001$, respectively). Both H1 antihistamines reduce all symptoms of allergic rhinitis, including nasal congestion and the plasmatic level of IL-1β, IL-6, IL-8 and TNF-α, after 4 weeks of treatment. The reduction of cytokine levels was not influenced by patients' age, sex, duration or severity of rhinitis, or type of sensitization. Levocetirizine has a superior effect compared to desloratadine in reducing the rhinitis symptoms and cytokines' level. Twenty eight (32.9%) of the patients presented asthma symptoms after 1.5 years. The occurrence of asthma was influenced by house dust sensitization (OR-14.6; CI 95% 1.8-116.3; $p=0.01$), but baseline values of cytokines were not predictive factors for its appearance.

Conclusion: Levocetirizine and desloratadine as a prolonged therapy reduce plasmatic levels of some pro-inflammatory cytokines in patients with PAR. Levocetirizine has a better effect on decreasing the symptoms and plasmatic levels of IL-1β and IL-8. (ClinicalTrials.gov Identifier: NCT02507635)

Founding: POSDRU and University of Medicine and Pharmacy, Iuliu Haţieganu, Cluj Napoca.

Keywords: Cytokines, histamine H1 antagonists, allergic rhinitis

Allergic rhinitis is an IgE-mediated process that induces inflammation of the nasal mucosa (1,2). Clinically, it is characterized by symptoms like sneezing, rhinorrhea, nasal congestion and nasal itching, and ocular symptoms may sometimes appear, especially in allergic rhinitis due to pollen. Up to 30% of patients with severe persistent allergic rhinitis are at risk of developing asthma (3).

Allergic rhinitis is a consequence of a disruption of the Th1/Th2 balance, with a dominant Th2 response that occurs after allergen exposure (1,4). Allergic inflammation is a cascade of

Address for Correspondence: Dr. Ştefan C. Vesa, Department of Clinical Pharmacology, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj Napoca, Romania
Phone: +40740125980 e-mail: stefanvesa@gmail.com
Received: 11.10.2015 Accepted: 26.02.2015 • DOI: 10.5152/balkanmedj.2015.15884
Available at www.balkanmedicaljournal.org

Cite this article as:
Bocşan CI, Bujor AI, Miron N, Vesa ŞC, Deleanu D, Buzoianu AD. In vivo anti-inflammatory effect of H1 antihistamines in allergic rhinitis. Balkan Med J 2015;32:352-8.

processes that involve several cells and mediators. The mast cell is the major cell involved in the early stage of inflammation. Sequentially synthesized cytokines released from mast cells, together with eosinophil-specific ones, are responsible for chronic allergic inflammation (4).

TNF-α is the major cytokine, either synthesized or stored in mast cells (5). Mast cells also produce interleukins, such as IL-3, IL-4, IL-5, IL-6, IL-8, IL-1β, and IL-13 (5-7). All of these cytokines, together with the released histamine, are responsible for impaired vascular permeability and adhesion processes, proliferation and differentiation of activated B cells, stimulation of eosinophil growth and differentiation (8,9). Eosinophils are another major source of cytokines, especially in the late phase of allergic inflammation. They can synthesize and release IL-1β, TNF-α, IL-3, IL-4, IL-5, and IL-8 (5,10). However, the concentration of mediators released from eosinophils is lower compared to other cells involved in allergic inflammation (10).

Increased levels of IL-1β, TNF-α, IL-6 and IL-8 were observed in nasal lavage after allergen provocation tests or under natural exposure conditions, in both intermittent and persistent allergic rhinitis (11-15).

The main purpose of the treatment of persistent allergic rhinitis is to improve symptoms and patients' quality of life and prevent the development of asthma (1). Therapeutic strategies also target a reduction of pro-inflammatory mediators released from activated cells, including mast cells and epithelial cells. The presence of allergic inflammation in nasal mucosa may increase the risk of asthma occurrence, especially in patients with persistent allergic rhinitis (1). H1 antihistamines are widely recommended in all types of allergic rhinitis, regardless of symptom severity or persistence (1). They control all of the symptoms, but to a lesser extent nasal congestion (1, 16). New generation agents, such as levocetirizine and desloratadine, possess anti-inflammatory properties, reducing allergic inflammation (16,17).

The aim of the study was to determine the plasmatic profile of IL-1β, IL-6, IL-8 and TNF-α in patients with persistent allergic rhinitis and their evolution after 4 weeks of treatment with levocetirizine and desloratadine under natural exposure to allergens. We also investigated the possible predictive role of these cytokines in the occurrence of bronchial asthma after 1.5 years.

MATERIALS AND METHODS

Patients

Eighty-five patients with persistent allergic rhinitis, diagnosed according to international criteria (1), without any known history of atopy, were included in the study. The mean age was 29.91±9.92 years and the male to female ratio was 1.07. We also included 30 healthy subjects, mean age 28.92±8.91 years, with a male to female ratio of 1, as a control group.

The patients were evaluated in the Department of Allergology of the Regional Institute of Gastroenterology and Hepatology "Prof. Dr. Octavian Fodor", Cluj-Napoca, between February 2009 and November 2011. The study protocol was approved by the Ethics Committee of the Iuliu Haţieganu University of Medicine and Pharmacy and each patient signed the informed consent before the study began.

The exclusion criteria were as follows: the presence of asthma or nasal polyps, acute and chronic upper respiratory infections, administration of intranasal or systemic corticosteroids or H1 antihistamines in the past 30 days.

After baseline clinical and biological evaluation, patients were randomly divided into two subgroups using adaptive biased-coin randomization, with the 1st being treated with 5 mg/day levocetirizine and the 2nd with 5 mg/day desloratadine, for four weeks. At the end of the four weeks, the patients were similarly evaluated.

Clinical evaluation

The following demographic data were noted: age, gender, and area of origin (rural/urban). Patient history provided data regarding the presence and severity of AR symptoms: rhinorrhea, nasal congestion, sneezing, nasal and ocular itching, and the duration of disease. Each symptom was evaluated on a scale from 0 to 3 (0=absent, 1=mild, 2=moderate, and 3=severe), followed by calculation of the total symptoms score (TSS). A TSS <6 was considered indicative of mild rhinitis, while a TSS >6 was considered indicative of moderate or severe rhinitis (1).

The patients were clinically evaluated after 1.5 years to determine the possible onset of bronchial asthma. We evaluated the presence of asthma symptoms (cough, wheezing, and dyspnea) or asthma exacerbation, that need specific treatment in this period of time. We also performed spirometry to check pulmonary function at baseline and after a 1.5-year follow-up. The occurrence of asthma was taken into consideration if one of these criteria was present during the 1.5-year period.

Skin prick tests (SPT)

Allergy was diagnosed using SPT. The allergen panel included: house dust mites, mixed grass pollens, betulacee pollen, mixed weed pollens, and cat and dog fur. We used allergen extracts (Stallergens, France) and SPT was performed according to international guidelines (18) as well as the particularities of exposure to allergens in Romania.

TABLE 1. Patients' demographic data

Parameter		Des (n=41)	Lev (n=44)	p
Age*		32.6±13.1	27.3±6.5	p=0.01
Sex^	M	43.9% (18)	59.1% (26)	p=0.1
	F	56.1% (23)	40.9% (18)	
Environment^	Urban	80.5% (33)	86.4% (38)	p=0.5
	Rural	19.5% (8)	13.6% (6)	
Type of AR^	Mild	31.7% (13)	25% (11)	p=0.6
	Moderate severe	68.3% (28)	75% (33)	
Duration (months)‿		24 (6-60)	30 (7.5-48)	p=0.5
Sensitization^	Indoor	39% (16)	18.2% (8)	p=0.002
	Outdoor	4.9% (2)	34.1% (15)	
	Indoor + outdoor	56.1% (23)	47.7% (21)	

*: Data are expressed as mean±SD; ^: Data are expressed as (%, n); Data are expressed as‿(median; 25-75th percentile)
SD: standard deviation; n: number; AR: allergic rhinitis; Des: desloratadine; Lev: levocetirizine; M: male; F: female

TABLE 2. Patients' symptoms and total symptom score before and after treatment

Parameter		Des (n=41)	Lev (n=44)	p
TSS	baseline	9 (5-11)	8 (6-11.75)	p=0.4
	4 weeks	1 (0-4)	0.5 (0-3.75)	
Rhinorrhea	baseline	3 (2-3)	2 (1-3)	p=0.6
	4 weeks	0 (0-1)	0 (0-1)	
Nasal itching	baseline	2 (1-2)	2 (1-2.75)	p=0.9
	4 weeks	0 (0-1)	0 (0-1)	
Nasal congestion	baseline	2 (1-3)	2 (1-3)	p=0.05
	4 weeks	1 (0-2)	0.5 (0-2)	
Sneezing	baseline	2 (1-2)	2 (1-3)	p=0.2
	4 weeks	0 (0-0)	0 (0-0)	
Ocular itching	baseline	1 (0-2)	2 (0.25-2.75)	p=0.8
	4 weeks	0 (0-0)	0 (0-0)	

Data are expressed as‿(median; 25-75th percentile)
TSS: total symptoms score; Des: desloratadine; Lev: levocetirizine

Total plasma IgE

Total plasma IgE was determined using the electrochemiluminescence immunoassay method (ECLIA). The values were expressed as UI/mL, with a normal value <100 UI/mL (1).

Plasma cytokine levels

Plasma levels of IL-1β, IL-6, IL-8 and TNF-alpha were determined. The blood was sampled (5 ml without anticoagulant) at baseline and after 4 weeks of treatment. The blood samples were centrifuged in the 1st hour, followed by serum separation. The serum was stored at -80°C until determination.

Cytokine determinations were performed using the ELISA technique (R&D Systems, Minneapolis, USA). The samples and standard dilutions were assayed according to the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (Chicago, IL, USA). Data were labelled as nominal and continuous variables. Nominal variables were characterized as percentages. We tested the normal distribution of continuous variables using the Kolmogorov-Smirnov test. They were characterized as the mean and standard deviation (for normally distributed variables) or as the median and the 25th-75th percentiles (for non-normally distributed variables). We chose adequate statistical tests according to data distribution.

The Mann-Whitney test and Spearman's rho correlation coefficient were used for the univariate analysis of continuous variables. The Wilcoxon signed-rank test was applied to assess the differences in cytokine levels between baseline and four-week time points. The influence of different parameters on subsequent cytokine changes was studied using repeated measures analysis of variance (ANOVA), after base-10 logarithmic transformation of the non-normally distributed dependent variables. The Chi-square test was used for data analysis. The level of statistical significance was set at $p<0.05$.

RESULTS

The patients' clinical and demographic data are shown in Table 1.

Clinical evaluation

Moderate or severe persistent allergic rhinitis was present in 61 (71.8%) patients, also demonstrated by the median value of TSS, 9 (5-11). Among rhinitis symptoms, rhinorrhea was the most severe (2.1±0.9), being significantly higher in the desloratadine group (p=0.01), followed by nasal congestion. Ocular symptoms were more severe in the levocetirizine group (p=0.03) (Table 2).

TABLE 3. Baseline plasma level of cytokines in healthy volunteers and patients with allergic rhinitis

	Healthy volunteers (n=30)		Patients with PAR (n=85)	
Cytokine	Range	Median (25-75th percentile)	Range	Median (25-75th percentile)
IL-1β (pg/mL)	undetected-0.2	0.13 (0-0.25)	undetected-1.72	0.122 (0-0.29)
IL-6 (pg/mL)	0.44-9.96	1.57 (0.95-1.94)	0.37-8.62	1.28 (0.87-1.87)
IL-8 (pg/mL)	undetected-31.2	3.12 (2.35-7.94)	undetected-38.67	5.85 (3.22-10)
TNFα (pg/mL)	0.550- 2.816	1.06 (0.73-2)	0.58-7.37	2.32 (1.55-2.92)

PAR: persistent allergic rhinitis

TABLE 4. Patients' biological parameters before and after treatment

Parameter		Des (n=41)	Lev (n=44)	p
Total IgE	baseline	115 (44.5-280)	151.6 (50.8-287.5)	p=0.9
	4 weeks	75 (31.1-154.5)	79.5 (34.5-166)	
IL-1β	baseline	0.03 (0-0.29)	0.12 (0.02-0.26)	p=0.04
	4 weeks	0.005 (0.00-0.13)	0.03 (0-0.10)	
IL-6	baseline	1.4 (0.8-2.6)	1.2 (0.8-1.7)	p=0.8
	4 weeks	1.2 (0.5-1.8)	0.9 (0.6-1.1)	
IL-8	baseline	5.3 (3.1-9.4)	6.3 (3.3-11.1)	p=0.02
	4 weeks	4.6 (2.5-6.4)	3.8 (1.6-6.3)	
TNFα	baseline	2.1 (1.4-2.7)	2.4 (1.76-3.2)	p=0.8
	4 weeks	1.4 (1.1-1.7)	1.5 (1.08-2.4)	

Data are expressed as ⁀(median; 25-75th percentile)

Des: desloratadine; Lev: levocetirizine

The four-week H1-antihistamine treatment improved allergic rhinitis symptoms, demonstrated by a highly significant reduction of TSS (p<0.001), with no differences between groups (p=0.4). All of the symptoms, including ocular ones, were improved by levocetirizine and desloratadine, but nasal congestion was significantly improved in the levocetirizine group (p=0.05) compared to the desloratadine group.

Total IgE

The baseline plasma level of total IgE was increased, with no significant differences between the 2 groups (p=0.3). The level of total IgE was higher in patients with allergic rhinitis to pollen, with no significant differences compared to patients with other types of sensitization (p=0.8). The four-week evaluation revealed a significant decrease in IgE plasma level (p<0.001), especially in patients with allergic rhinitis to pollen (p=0.006). The reduction of total IgE was not influenced by the type of treatment, patient age, gender and area of origin, the duration or severity of allergic rhinitis (p>0.05).

Cytokines

The plasma levels of the cytokines investigated were significantly higher in patients with allergic rhinitis compared to healthy subjects for IL-8 (p<0.001) and TNFα (p<0.001) (Table 3).

There was a moderate positive correlation between the baseline values of IL-1β and IL-6 (r=0.339, p=0.001), IL-1β and TNFα (r=0.360, p=0.001), IL-6 and IL-8 (r=0.365, p=0.001), IL-6 and TNF-α (r=0.395, p<0.001), and IL-8 and TNF-α (r=0.369, p=0.001), and a weak one between IL-1β and IL-8 (r=0.230, p=0.03).

After the four-week treatment with H1 antihistamines, plasma levels of IL-1β (p<0.01), IL-6 (p<0.01), IL-8 (p<0.01) and TNF-α (p<0.01) decreased significantly compared to baseline values. The reduction in the investigated cytokines was not influenced by patient age, gender and area of origin, duration or severity of rhinitis, and type of sensitization, except for IL-8. IL-8 significantly decreased in patients with mild allergic rhinitis compared to its moderate-severe forms (p=0.01). The reduction of IL-8 and IL-1β was more pronounced in the levocetirizine group compared to the desloratadine group (Table 4).

Bronchial asthma

Twenty-eight patients (32.9%) presented bronchial asthma at the 1.5-year evaluation. The risk of bronchial asthma was independently influenced by sensitization to house dust mites (OR-14.6; CI 95% 1.8-116.3; p=0.01). The baseline levels of the cytokines investigated were not a predictive factor for the occurrence of bronchial asthma (p>0.05).

DISCUSSION

This study described the plasma profile of pro-inflammatory cytokines in patients with newly diagnosed allergic rhinitis. We evaluated the effects of two second generation H1 antihistamines, levocetirizine and desloratadine, showing that they improved symptoms and reduced the pro-inflammatory markers in allergic rhinitis.

Th2-specific cytokines were extensively evaluated in previous studies, especially IL-4 (8,13,17,19), which has a pivotal role in the stimulation of IgE synthesis (13), together with IL-6 and IL-1β (5,7,13). On the other hand, TNF-α has pleiotropic functions in allergic inflammation, meaning that it is an important mediator in both phases (5,20). IL-8 is the main neutrophil chemoattractant factor, released by activated mast

cells (17,20). Considering all of these observations, the evaluation of cytokine modulation by the pharmacologic treatment is a process that can reduce allergic inflammation.

Baseline plasma levels of total IgE were higher in patients with AR, regardless of its severity or the type of sensitization. This observation is similar to other data that prove the involvement of IgE and eosinophils in allergic inflammation (5,21). Total IgE is higher in patients with pollen allergy, because they were included in the study during the pollen season, when they have specific symptoms. It is well known that the level of IgE depends on allergen concentration (5). Prolonged treatment with H1 antihistamines reduced the plasma level of total IgE, with no differences between levocetirizine and desloratadine. The reduction of total IgE was also mentioned by Maiti et al. (22) in patients with seasonal allergic rhinitis treated with rupatadine or levocetirizine for 2 weeks. In this study, rupatadine had a better effect in reducing total IgE than levocetirizine, but in our study we did not investigate the effect of rupatadine. We compared the effects of levocetirizine and desloratadine on total IgE levels.

In our study, we observed high plasma levels of IL-8 and TNF-**α** in patients with allergic rhinitis compared to healthy subjects. There are studies showing that IL-1β, IL-6, IL-8 and TNF-**α** are increased in the nasal secretions of patients with allergic rhinitis after allergen provocation tests (11,12,14) or under natural conditions of exposure to allergens (13,20, 21). To the best of our knowledge, this is the first study to evaluate these cytokines in the serum of patients with allergic rhinitis, showing high levels of IL-8 and TNF-**α**. The observation could explain the chronic evolution of allergic rhinitis and the association of asthma (3). In their study, Ohkubo et al. (12) observed that migrating cells and epithelial cells are the main source for IL-6 and IL-8 production and their synthesis is stimulated by allergen exposure. In our study, the high plasma level of IL-8 could be a consequence of these migrating cells that release high quantities of IL-8, which can be detected in the plasma, not only in nasal secretion. We detected very low levels of IL-1β in patients with allergic rhinitis (25.88% of the patients had undetectable values). Only 22% of them had IL-1β plasma levels above the maximal value, detected in healthy subjects. IL-6 is an early released cytokine in allergic inflammation, immediately after allergen exposure (12). In our study, we determined IL-6 levels at presentation moments and the exposure to allergen was continuous. The obtained result is similar to that reported in the study carried out by Gröger et al. (21), who found normal levels of IL-6 in PAR patients. Probably, the persistence of allergic inflammation does not depend on IL-6.

The four-week treatment with levocetirizine and desloratadine significantly reduced allergic rhinitis symptoms, including nasal congestion. This was also mentioned in previous studies (16,19). Levocetirizine reduced nasal congestion to a greater extent than desloratadine, similar to other studies (17,19,23).

Second generation H1 antihistamines also have anti-inflammatory properties, together with their effects of blocking histamines (24, 25), demonstrated first in *in vitro* studies. But the promising *in vitro* effects were described for higher concentrations compared to the levels obtained after therapeutic doses and were not constantly demonstrated in *in vivo* studies.

Levocetirizine and desloratadine significantly decreased the plasma levels of IL-1β, IL-6, IL-8 and TNF-α after 4 weeks of treatment. The anti-inflammatory effect is significantly higher for levoetirizine, due to the more pronounced reduction of IL-1β and IL-8. This could be explained by the different pharmacokinetic and pharmacodynamic properties of levocetirizine and desloratadine. Levocetirizine has a lower volume of distribution and higher affinity for H1 receptors (24,25). The data obtained in the present study are similar to the results obtained by Ciprandi et al., who revealed that levocetirizine has a more pronounced anti-inflammatory effect than desloratadine in patients with seasonal allergic rhinitis, after 2 weeks of treatment (17). Deruaz et al. (23) showed that IL-4, IL-5, IL-8, eotaxine and ECP in nasal lavage are not reduced after a single administration of desloratadine or levocetirizine, but they considered their possible anti-inflammatory effect if they were administered for a longer period of time. In the present study, H1 antihistamines are administered continuously for 4 weeks and the results obtained could confirm the hypothesis raised by Deruaz et al. (23).

Our study is not consistent with other published data. In their study, Tworek et al. (26) found that desloratadine 5 mg/day did not reduce the plasma level of IL-4, IL-10, IL-18 and TGF-β in patients with allergic rhinitis to grass pollen after a 4-week treatment. Similarly, Reinartz et al. (27) mentioned the lack of desloratadine effect on inflammatory parameters after a 1-week treatment, but like Deruaz et al. (23), they raised the hypothesis that a prolonged treatment may have a greater influence on the level of pro-inflammatory cytokines. In our study, we investigated cytokines with stimulatory effect on the immune system, while the study of Tworek et al. (26) focused on other types of cytokines, so H1 antihistamines might have a different influence on cytokine patterns in patients with allergic rhinitis.

Approximately 30% of patients with severe allergic rhinitis develop bronchial asthma over time, supporting the theory that allergic rhinitis and asthma may be part of the same disease (1,3). Our findings support this theory, as 32.9% of the patients had asthma symptoms after 1.5 years. There is no clear data on the exact time of asthma occurrence in patients

with persistent allergic rhinitis, but our study revealed that this risk is correlated with allergic rhinitis duration and sensitization to house dust mites, similar to other studies (3,28,29). However, there is no correlation between baseline cytokine levels and the risk of asthma after 1.5 years. Moreover, there is no correlation between the type of H1 antihistamines used to treat allergic rhinitis and the risk of asthma occurrence. One published study suggests that VEGF and IL-5 can be important determinants of the development of asthma symptoms in allergic rhinitis patients (30), but we evaluated other cytokine patterns, so this could explain the discrepancies between the two studies.

Finally, the limitations of the study must be pointed out. The investigation of pro-inflammatory cytokines was not correlated with the adhesion molecules involved in the pathogenesis of allergic rhinitis. We included a small number of patients in the study, with different types of sensitization, to both outdoor and indoor allergens. We randomly divided patients into subgroups, taking into account the recommended H1 antihistamines. This could explain the differences between the levocetirizine and desloratadine subgroups regarding the type of sensitization, more patients sensitized to pollen being included in the levocetirizine subgroup. Further studies could investigate the effect of H1 antihistamines on the plasma levels of both cytokines and adhesion molecules and to differentiate the results according to the type of sensitization. The follow-up period for the occurrence of asthma was shorter than in other studies, but we had a limitation of time due to project duration.

In conclusion, patients with persistent allergic rhinitis have high plasma levels of TNF-α and IL-8. Levocetirizine and desloratadine improve allergic rhinitis symptoms, including nasal congestion. Prolonged levocetirizine and desloratadine therapy reduces the plasma levels of several pro-inflammatory cytokines. Levocetirizine has a better anti-inflammatory effect in decreasing the level of serum cytokines. Baseline levels of pro-inflammatory cytokines do not seem to predict the onset of asthma after the 1.5-year follow-up.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Iuliu Haţieganu University of Medicine and Pharmacy.

Informed Consent: Each patient signed the informed consent before the study began.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - C.I.B., A.D.B.; Design - C.I.B., A.D.B.; Supervision - C.I.B., D.D.; Resource - C.I.B., Ş.C.V.; Materials - C.I.B., A.I.B., D.D., N.M.; Data Collection &/or Processing - C.I.B., A.I.B., D.D.; Analysis &/or Interpretation - C.I.B., A.D.B., Ş.C.V.; Literature Search - C.I.B., A.D.B., Ş.C.V.; Writing - C.I.B., Ş.C.V., A.D.B.; Critical Reviews - Ş.C.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was partially funded by POSDRU grant no. 159/1.5/S/138776 grant with title "Model colaborativ instituţional pentru translarea cercetării ştiinţifice biomedicale în practica clinică-TRANSCENT" and by a research grant 27020/48/2011 of University of Medicine and Pharmacy, Iuliu Haţieganu, Cluj Napoca.

REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al; World Health Organization; GA(2)LEN; AllerGen. Allergic rhinitis and its impact on asthma. *Allergy* 2008;63(Suppl 86):8-160. [CrossRef]
2. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24:758-64. [CrossRef]
3. Leynaert B, Neukirch C, Kony S, Guénégou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004;113:86-93. [CrossRef]
4. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. *Allergy Asthma Immunol Res* 2010;2:65-76. [CrossRef]
5. Okayama Y, Kawakami T. Development, migration, and survival of mast cells. *Immunol Res* 2006;34:97-115. [CrossRef]
6. Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 2003;111(Suppl 2):S486-94. [CrossRef]
7. Amin K. The role of mast cells in allergic inflammation. *Respir Med* 2012;106:9-14. [CrossRef]
8. Bradding P, Roberts JA, Britten KM, Montefort S, Djukanovic R, Mueller R, et al. Interleukin-4, -5, and -6 and tumor necrosis factor-alpha in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. *Am J Respir Cell Mol Biol* 1994;10:471-80. [CrossRef]
9. Bradding P. The role of the mast cell in asthma: a reassessment. *Curr Opin Allergy Clin Immunol* 2003;3:45-50. [CrossRef]
10. Lee NA, Gelfand EW, Lee JJ. Pulmonary T cells and eosinophils: conspirators or independent triggers of allergic respiratory pathology? *J Allergy Clin Immunol* 2001;107:945-57. [CrossRef]
11. Wagenmann M, Schumacher L, Bachert C. The time course of the bilateral release of cytokines and mediators after unilateral nasal allergen challenge. *Allergy* 2005;60:1132-8. [CrossRef]
12. Ohkubo K, Ikeda M, Pawankar R, Gotoh M, Yagi T, Okuda M. Mechanisms of IL-6, IL-8, and GM-CSF release in nasal secretions of allergic patients after nasal challenge. *Rhinology* 1998;36:156-61.

13. Bachert C, van Kempen M, van Cauwenberge P. Regulation of proinflammatory cytokines in seasonal allergic rhinitis. *Int Arch Allergy Immunol* 1999;118:375-9. **[CrossRef]**
14. Benson M, Wennergren G, Fransson M, Cardell LO. Altered levels of the soluble IL-1, IL-4 and TNF receptors, as well as the IL-1 receptor antagonist, in intermittent allergic rhinitis. *Int Arch Allergy Immunol* 2004;134:227-32. **[CrossRef]**
15. Bachert C, Wagenmann M, Hauser U. Proinflammatory cytokines: measurement in nasal secretion and induction of adhesion receptor expression. *Int Arch Allergy Immunol* 1995;107:106-8. **[CrossRef]**
16. Bachert C. A review of the efficacy of desloratadine, fexofenadine, and levocetirizine in the treatment of nasal congestion in patients with allergic rhinitis. *Clin Ther* 2009;31:921-44. **[CrossRef]**
17. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokines pattern in patients with seasonal allergic rhinitis: a pilot study. *Clin Exp Allergy* 2004;34:958-64. **[CrossRef]**
18. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. *Clin Transl Allergy* 2013;3:3. **[CrossRef]**
19. Ciprandi G, Cirillo I, Vizzaccaro A, Civardi E, Barberi S, Allen M, et al. Desloratadine and Levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with perennial allergic rhinitis: a pilot study. *Int Immunopharmacol* 2005;5:1800-8. **[CrossRef]**
20. Gosset P, Tillie-Leblond I, Malaquin F, Durieu J, Wallaert B, Tonnel AB. Interleukin-8 secretion in patients with allergic rhinitis after an allergen challenge: interleukin-8 is not the main chemotactic factor present in nasal lavages. *Clin Exp Allergy* 1997;27:379-88. **[CrossRef]**
21. Gröger M, Klemens C, Wendt S, Becker S, Canis M, Havel M, et al. Mediators and cytokines in persistent allergic rhinitis and nonallergic rhinitis with eosinophilia syndrome. *Int Arch Allergy Immunol* 2012;159:171-8. **[CrossRef]**
22. Maiti R, Rahman J, Jaida J, Allala U, Palani A. Rupatadine and levocetirizine for seasonal allergic rhinitis: a comparative study of efficacy and safety. *Arch Otolaryngol Head Neck Surg* 2010;136:796-800. **[CrossRef]**
23. Deruaz C, Leimgruber A, Berney M, Pradervand E, Spertini F. Levocetirizine better protects than desloratadine in a nasal provocation with allergen. *J Allergy Clin Immunol* 2004;113:669-76. **[CrossRef]**
24. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002;32:489-98. **[CrossRef]**
25. Gillard M, Christophe B, Wels B, Peck M, Massingham R, Chatelain P. H1 antagonists: receptor affinity versus selectivity. *Inflamm Res* 2003;52(Suppl 1):S49-50. **[CrossRef]**
26. Tworek D, Bocheńska-Marciniak M, Kupczyk M, Górski P, Kuna P. The effect of 4 weeks treatment with desloratadine (5mg daily) on levels of interleukin (IL)-4, IL-10, IL-18 and TGF beta in patients suffering from seasonal allergic rhinitis. *Pulm Pharmacol Ther* 2007;20:244-9. **[CrossRef]**
27. Reinartz SM, Overbeek SE, Kleinjan A, van Drunen CM, Braunstahl GJ, Hoogsteden HC, et al. Desloratadine reduces systemic allergic inflammation following nasal provocation in allergic rhinitis and asthma patients. *Allergy* 2005;60:1301-7. **[CrossRef]**
28. Valero A, Justicia JL, Anton E, Dordal T, Fernández-Parra B, Lluch M, et al. Epidemiology of allergic rhinitis caused by grass pollen or house-dust mites in Spain. *Am J Rhinol Allergy* 2011;25:e123-8. **[CrossRef]**
29. Sala-Cunill A, Bartra J, Dalmau G, Tella R, Botey E, Raga E, et al; Comitè de Allergia. Prevalence of asthma and severity of allergic rhinitis comparing 2 perennial allergens: house dust mites and Parietaria judaica pollen. *J Investig Allergol Clin Immunol* 2013;23:145-51.
30. Sohn SW, Lee HS, Park HW, Chang YS, Kim YK, Cho SH, et al. Evaluation of cytokine mRNA in induced sputum from patients with allergic rhinitis: relationship to airway hyperresponsiveness. *Allergy* 2008;63:268-73. **[CrossRef]**