

The effect of H1-antihistamines on allergic inflammation in patients with allergic rhinitis

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Abstract. Introduction: Allergic rhinitis (AR) is the most frequent allergic disease and a risk factor for asthma occurrence. The relationship between AR and asthma is well known but not completely understood. This relationship could be explained by the presence of inflammatory cells from the upper airway in the lower one. The aim of this study is to evaluate the presence of minimal persistent inflammation in the lungs using fractional exhaled nitric oxide (FeNO) in patients with AR and correlate it with the severity of the disease. The second aim is to evaluate the effect of AH1 on this subclinical inflammation in AR patients. Material and method: The study included 79 patients with persistent allergic rhinitis. Clinical evaluation was done based on the presence and severity of AR symptoms and quality of life was measured using the visual analogue scale (VAS). Biological evaluation included the absolute eosinophil count. FeNO was measured using NIOXMINO®. After the initial evaluation, patients were randomly divided into two groups, 39 patients were treated with levocetirizine 5 mg/day and 40 patients received desloratadine 5 mg/day. Patient assessment was performed at baseline and after one month of treatment with H1-antihistamines. Results: Fifty-six patients (70.9%) had moderate-severe AR, with a total symptom score (TSS) of over 6. Sleep quality was impaired; VAS was negatively correlated with TSS ($R=-0.458$, $p=0.000$). Patients with AR had elevated levels of peripheral eosinophils (median value 5.11) and FeNO (median value 27). There was no correlation between basal level of eosinophils and basal FeNO ($R=0.052$, $p=0.648$). AH1 improved TSS (median values 8 vs. 0, $p<0.001$) and VAS (median values 4.6 vs. 9.8, $p<0.001$), reduced peripheral eosinophil (median values 5.11 vs. 4.10, $p<0.001$) and FeNO (median values 27 vs. 16, $p<0.001$) count after 1 month of treatment. Desloratadine was more efficient in the reduction of FeNO levels (38 vs. 14) compared to levocetirizine (23 vs. 17.5) ($p=0.05$). Conclusions: Patients with persistent AR have elevated peripheral eosinophil and FeNO levels. Levocetirizine and desloratadine improve symptoms and increase quality of life in patients with persistent AR. Levocetirizine and desloratadine as a continuous therapy determine a reduction of FeNO levels, limiting the progression of allergic inflammation to the lower airway.

Key Words: Allergic rhinitis, FeNO, H1-antihistamines, VAS

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Introduction

Allergic rhinitis (AR) is the most frequent allergic disease, which affects 20-30% of the world's population (Bousquet et al. 2008, Bousquet et al. 2010). AR and bronchial asthma are both clinical manifestations of atopy. The relationship between AR and asthma has become notorious for several years. Asthma and AR are now considered as two expression of the same pathological process, presented as „united airways disease” (Bousquet et al. 2003, Bousquet et al. 2010). Thus, these two diseases often coexist and therapeutic guidelines recommend performing a complete evaluation in patients with AR in order to diagnose the possible association with asthma. AR is now considered a risk factor for asthma development; approximately 30% of patients with persistent allergic rhinitis (PAR) may develop asthma in time (Leynaert et al. 2004).

Nowadays, a number of factors influence the severity and persistence of AR symptoms, which may increase the risk of developing asthma. These factors are related to changes in lifestyle and urbanization, increased air pollution, spending more time indoors, which implies a prolonged exposure to house dust

mites, exposure to a new type of allergens and chronic stress (Mösgeles & Klimek 2007).

Allergic inflammation is the key to understanding these diseases. The relationship between asthma and AR is not completely understood. This concept could be explained by the presence of inflammatory cells and mediators from the upper airway in the lower one, acting as triggering factors in bronchial inflammation (Canonica & Complati 2009). We found similar inflammatory cells in both asthma and rhinitis, such as eosinophils, mast cells, T lymphocytes and monocytes, and the same pro-inflammatory mediators (histamine, cytokines like IL-4, IL-5, IL-13, GM-CSF, eotaxine and adhesion molecules) (Bousquet et al. 2008, Bousquet et al. 2003, Leynaert et al. 2004). The amplitude of allergic inflammation is not necessarily identical in nasal and bronchial mucosa, but eosinophilic airway inflammation is present in the nasal mucosa of patients with asthma, even if they don't have nasal symptoms (Bousquet et al. 2008, Leynaert et al. 2004).

One of the non-invasive possibilities to evaluate lower airway inflammation is the measurement of fractional nitric oxide in

breath, which is a marker of eosinophilic airway inflammation (Barnes & Kharitonov 1996). The most important factors that influence FeNO levels are atopy, asthma and rhinitis as clinical expression of allergy (Majid & Kao 2010, Kim et al. 2016). FeNO levels are higher in atopic patients than in healthy subjects. FeNO measurement is used in differentiating asthma phenotypes (Haldar et al 2008) or diagnosing asthma and monitoring therapeutic responses (Verini et al. 2010). FeNO levels over 35 ppb indicate eosinophilic airway inflammation and subsequently asthma (Majid & Kao 2010), while levels between 25-35 ppb could indicate allergic inflammation. Many studies have shown increased FeNO levels in patients with AR (Kim et al. 2016), but further studies are needed to establish the role of FeNO as a predictive factor for asthma onset in these patients. Desloratadine and levocetirizine are second generation non-sedating H1-antihistamines (AH1) widely used in the treatment of AR. Their efficiency on symptom control has been proven in several studies. There is also evidence of the anti-inflammatory effect of second generation H1-antihistamines, determining a decrease in the levels of different cytokines and inflammatory cells (Leurs et al. 2002).

The aim of this study is to evaluate the existence of minimal persistent inflammation in the lungs using fractional exhaled nitric oxide (FeNO) in patients with PAR and correlate it with disease severity. We also aimed to assess the effect of AH1 on this subclinical inflammation in AR patients.

Material and method

Seventy-nine patients with persistent allergic rhinitis evaluated in the Allergy Department of "Prof. Dr. Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, between February 2009 and July 2011 were included in this study. Patients with acute or chronic respiratory infections, smokers, patients with nasal polyps or asthma, and patients under treatment with corticosteroids and H1-antihistamines in the last 30 days prior to presentation were excluded from the study. PAR was diagnosed according to international guidelines, based on patient history and skin prick test (SPT) (Bousquet et al. 2008). We used a common panel of inhaled allergens (Hal Allergy), including: house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), grass pollen, cereal pollen, tree mix 1 pollen (*Betula*, *Alnus*, *Corylus*), cat and dog dander, *Alternaria alternata*, weed pollen of *Artemisia vulgaris* and *Ambrosia artemisiifolia*.

Baseline clinical evaluation included medical history for demographic data: age, gender and the presence of AR symptoms: rhinorrhea, nasal and ocular itching, nasal congestion and sneezing. The severity of symptoms was evaluated using two distinct tools: the total symptom score (TSS) and the visual analogue scale (VAS). Patients self-assessed symptom severity on a scale from 0 to 3 (0 - absence, 1 - mild, 2 - moderate, 3 - severe). The symptom score was obtained for each patient by adding the score for every symptom. VAS is a quantitative method that can be used to evaluate AR severity and quality of life impairment. VAS represents a self-assessment test which evaluates patient sleep quality on a scale from 0 to 10 (0 - „I don't sleep" and 10 - „I sleep very well"). VAS values are expressed in cm.

Eosinophil (Eo) count in peripheral blood was performed manually on a slide and values were expressed as %. The normal value was considered to range between 2-4%.

The measurement of fractional exhaled nitric oxide (FeNO) was done according to the recommendations of the American Thoracic Society, using NIOXMINO® (Aerocrine, Sweden) (ATS/ERS recommendations 2005). Measurements were made in sitting position without prior spirometry. Patients inhaled air without nitric oxide through the mouth piece and exhaled constantly with a visual feedback on the screen. For pollen allergic patients measurements were done during the pollen season. Values were expressed in parts per billion (ppb).

Both clinical evaluation and FeNO measurement were performed at baseline and after 1 month of treatment with H1-antihistamines. Patients were randomly divided into two subgroups using adaptive biased-coin randomization. The first group (39 patients) was treated with levocetirizine 5 mg/day, and the second (40 patients) was treated with desloratadine 5 mg/day. The study protocol was approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, and each patient signed an informed consent before enrolling in the study.

Statistical analysis was performed using SPSS version 21 (Chicago, IL, USA). Data were labeled as nominal variables expressed as percentage and continuous variables. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Variables with normal distribution were expressed as mean and standard deviation, while variables that were not normally distributed were expressed as median and 25th-75th percentiles.

Statistic tests were chosen based on data distribution. Differences in parameters within groups were assessed using the Wilcoxon Signed Rank test and differences between groups with the Mann Whitney test. The influence of different parameters on cytokine changes in time was studied using the repeated measures analysis of variance (ANOVA). Spearman's rank correlation coefficient was employed to highlight different correlations between the studied parameters. P values <0.05 were considered statistically significant.

Results

Demographic data are presented in Table 1.

Fifty-six patients (70.9%) presented moderate-severe AR, with no differences between levocetirizine and desloratadine-treated subgroups ($p=0.465$). Disease severity was also demonstrated by a TSS value over 6 (8.51 ± 3.44), which indicates moderate-severe AR. The four-week treatment with either levocetirizine or desloratadine significantly improved AR symptoms and reduced TSS (Table 2). There were no significant differences between levocetirizine and desloratadine in what concerns the reduction in TSS (Table 4).

Quality of life measured using VAS was impaired at baseline (Table 2). There was a negative correlation between TSS and VAS during baseline evaluation ($R=-0.458$, $p=0.000$). VAS was significantly increased after 1 month (Table 2), with no significant differences between AH1 (Table 4). There were also no significant differences in VAS improvement related to AR severity ($p>0.05$) or polysensitization ($p>0.05$).

Table 1. Patients' demographic data

Parameter	Patients (n=79)	
Age (years)*	30.44±9.9	
Gender [^]	male	50.6% (40)
	female	49.4% (39)
Allergen sensitization [^]	Outdoor	21.5% (17)
	Indoor	26.6% (21)
	Indoor + outdoor	51.9% (41)
Severity [^]	Mild	29.1% (23)
	Moderate-severe	70.9% (56)

*Data are expressed as mean±SD; [^] Data are expressed as (% , n);

Table 2. Evolution of clinical parameters

Clinical parameter	baseline	4-weeks	p
Total symptom score	8 (5-11)	0 (0-4)	<0.001
VAS	4.60 (3.20-6)	9.8 (8.60-10)	<0.001

Data are expressed as \bar{x} (median; 25th-75th percentile), Significance p<0.05

Table 3. Evolution of Eo and FeNO

Parameter	baseline	4-weeks	p
Peripheral Eo	5.11(3-7.20)	4.10 (2.40-5.80)	<0.001
FeNO	27 (18-46)	16 (12-21)	<0.001

Data are expressed as \bar{x} (median; 25th-75th percentile), Significance p<0.05

Table 4. Evolution of clinical parameters, Eo and FeNO in Levocetirizine and Desloratadine groups, before and after the 4-week treatment

Parameter	Desloratadine (n=40)	Levocetirizine (n=39)	p	
TSS	baseline	9 (5-11)	8 (6-11.75)	0.571
	4 weeks	1 (0-4)	0 (0-3.75)	
VAS	baseline	5 (3.80-6)	4.25 (2.90-5.95)	0.166
	4 weeks	9.85 (8.50-10)	9.80 (8.65-10)	
Eo	baseline	5.00 (3.20-6.50)	5.20 (2.70-7.80)	0.235
	4 weeks	4.10 (2.60-5.80)	4 (2.35-6.35)	
FeNO	baseline	38 (19-49)	23 (16.25-43)	0.05
	4 weeks	14 (11-21)	17.5 (14-22.5)	

Data are expressed as \bar{x} (median; 25th-75th percentile), Significance p<0.05

Elevated eosinophil levels were observed in patients with AR, when compared to the normal values accepted in the present study. There was no correlation between baseline eosinophil levels and AR severity (5.21 vs. 5.17, p>0.05) or the type of sensitization (4.30 vs. 5.71 vs. 5.41, p>0.05). There was also no correlation between baseline eosinophil levels and baseline

FeNO levels (R=0.052, p=0.648). AH1 significantly reduced the percentage of eosinophils in peripheral blood after 1 month of therapy, with no differences between levocetirizine and desloratadine (Table 4).

FeNO levels were increased in patients with AR (Table 3) compared to the standardized cut-off value (20 ppb). Nine patients had borderline values between 25-35 ppb, while 31 patients had values over 35 ppb. There was no correlation between baseline FeNO levels and AR severity (R=0.132, p=0.246), TSS (R=0.131, p=0.249) or VAS (R=-0.007, p=0.951). FeNo levels were significantly reduced by the 4-week treatment with AH1, desloratadine being more effective than levocetirizine (Table 4).

Discussions

This study evaluated the presence of minimal persistent inflammation in upper and lower airways in patients with AR, using exhaled NO. We evaluated the effect of two types of second generation H1-antihistamines, levocetirizine and desloratadine, on symptom improvement and allergic inflammation.

AR is characterized by typical inflammation of nasal mucosa, secondary to allergen exposure, leading to specific symptoms (Bousquet et al. 2008) (rhinorrhea, nasal itching, nasal congestion and sneezing). In our study, symptom score (SS) was greater than 6 in more than half of the patients, showing moderate-severe AR. This observation is in accordance with other studies that noticed a prevalence of moderate-severe AR of over 70% (Bousquet et al. 2005, Samoliński et al. 2009) in patients who present themselves at an allergy clinic. According to ARIA classification (Bousquet et al. 2008, Bousquet et al. 2010), moderate-severe AR implies an impairment of daily activity and sleep. In our study, there was a negative correlation between VAS (which investigated sleep impairment) and TSS at baseline evaluation. This observation may support the use of VAS in AR evaluation as routine assessment. In everyday practice, the specialist prefers to only make use of symptom evaluation, without performing a clear investigation of quality of life, except in clinical trials. The VAS test is an easy assessment method in outpatient care, which only takes a few minutes, and it could be used in all patients while evaluating their medical history.

The clinical efficacy of H1-antihistamines was proved in many studies (Bousquet et al. 2008, Bousquet et al. 2010, Canonica & Complati 2009). After 1 month of treatment, H1-antihistamines improved symptoms and quality of life in patients with PAR, with no difference between desloratadine and levocetirizine. H1-antihistamines significantly reduced TSS, and increased values obtained in the VAS test demonstrated once again that H1-antihistamines could control AR symptoms. The results obtained in our study are in accordance with previous studies (Bousquet et al. 2010, Bachert 2009) observing a reduced symptom score in both intermittent and persistent forms (Bousquet et al. 2008, Bousquet et al. 2010, Bousquet et al. 2010) in adults and children (Bousquet et al. 2008, Lee et al. 2009, Maiti et al. 2010, Bousquet et al. 2010).

Exhaled nitric oxide is a well-known marker of eosinophilic lower airway inflammation. Eosinophil count revealed an increased percentage of peripheral eosinophils in patients with PAR in the present study. As eosinophils are the main cells involved in the late phase of allergic inflammation, we expected

to obtain increased levels because all the patients included in the study had PAR. There was no correlation between peripheral eosinophil count and AR severity, observation that was published in the pediatric population (Chen *et al.* 2006). The severity of AR was better correlated with eosinophil count in nasal mucosa (Chen *et al.* 2006), a different measurement compared to the present study.

IgE-mediated inflammation leads to an increase in exhaled nitric oxide. Previous studies showed that patients with AR due to pollen have increased FeNO levels during the pollen season, even if they don't have asthma symptoms or they only have mild ones (Mösgeles & Klimek 2007, Zhu *et al.* 2016). Other studies showed that patients with allergic rhinitis have increased FeNO and adenosine levels compared to healthy subjects, indicating the presence of a subclinical lower airway inflammation in patients with allergic rhinitis (Vass *et al.* 2006, Henriksen *et al.* 1999). In our study, we obtained elevated FeNO levels in 50.6% of the patients (median level 27 ppb). This may increase the risk of developing asthma in time due to the minimal persistent inflammation in the lower airway. If the previous study mentioned elevated FeNO levels in patients with AR due to pollen (Mösgeles & Klimek 2007), in the present one high FeNo levels were observed independently of the type of sensitization, similar to Zhu's study (Zhu *et al.* 2016). The present finding supports the use of FeNO in detecting the progression from AR towards asthma and in diagnosing bronchial hyper-reactivity, which supports the hypothesis that AR and asthma are 'one airway, one disease'. Early diagnosis of bronchial hyper-reactivity means early therapeutic intervention that could prevent this progression. Second generation H1-antihistamines also have an additional anti-inflammatory effect, independent from H1-blockade (Leurs *et al.* 2002). The effect of H1-antihistamines on subclinical lower airway inflammation in patients with AR was investigated in a few studies. *In vitro* studies showed that the activity of NO-synthases could be down-regulated by H1-antihistamines (Králová *et al.* 2009). Animal studies showed that histamines released by mast cell degranulation played an important role in the production of nitric oxide, increasing bronchial hyper-reactivity (Benedich Kahn *et al.* 2008). Based on this observation, H1-antihistamines might attenuate NO production in mast cells from the lung, subsequently reducing FeNO levels.

In vivo studies noticed that levocetirizine reduced FeNO levels after 3 months of treatment in children with AR due to house dust mites (Marcucci *et al.* 2011). In our study, we demonstrated the efficacy of both desloratadine and levocetirizine in reducing FeNO levels after 1 month of treatment in patients with PAR, regardless of the type of sensitization. The effect was more pronounced in patients treated with desloratadine. This observation could be explained by the differences in sensitization. The randomization was done according to the recommended treatment and more patients with house dust mite sensitization were under treatment with desloratadine. We may conclude that continuous treatment with H1-antihistamines may be more efficient in indoor allergen sensitization. The present findings argue that proper treatment with second generation H1-antihistamines might reduce allergic inflammation in both upper and lower airways. H1-antihistamines are not effective drugs in asthma, but a few studies investigated them as add-ons to leukotriene modifiers,

obtaining good results in what concerns the reduction of FeNO levels (Wilson 2002, Nelson 2003).

Several limitations of the study were considered. The sample size was limited in each group and we included patients with sensitization to both indoor and outdoor allergens. As we mentioned before, we randomly divided patients into two subgroups based on recommended H1-antihistamines and not on the type of sensitization. Thirdly, patient follow-up was not longer than 3 months, not long enough to notice if they develop asthma. Further studies are needed to confirm the role of FeNO in anticipating asthma occurrence in patients with AR. It would also be interesting to assess both FeNO levels and other serum inflammatory markers in patients with AR.

Conclusions

Patients with PAR have high peripheral eosinophil and FeNO levels. Levocetirizine and desloratadine improve symptoms and quality of life in patients with PAR. Continuous therapy with levocetirizine and desloratadine reduces FeNO levels, limiting the progression of allergic inflammation to the lower airway.

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