

Fexofenadine with either montelukast or a low-dose inhaled corticosteroid (fluticasone) in the treatment of patients with persistent allergic rhinitis and newly diagnosed asthma

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Submitted: 11 November 2009

Accepted: 5 December 2009

Arch Med Sci 2009; 5, 4: 564-569

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Abstract

Introduction: Asthma often coexists in patients with persistent allergic rhinitis. The aim of this study was to investigate the effects of treatment with a combination of antihistamine (fexofenadine) and either an antileukotriene agent (montelukast) or a low-dose inhaled corticosteroid (fluticasone) in patients with persistent allergic rhinitis and newly diagnosed asthma.

Material and methods: 40 patients with persistent allergic rhinitis and newly diagnosed asthma received fexofenadine (120 mg/day) with fluticasone (200 µg/day) for 6 weeks then fexofenadine (120 mg/day) with montelukast (10 mg/day) for another 6 weeks. Symptom scores, anterior rhinoscopy, spirometry and serum concentrations of soluble intercellular adhesion molecule 1 were evaluated before and after 6-week treatment periods.

Results: The sICAM-1 serum concentration before treatment was 243.4 ±20.7 ng/ml, after treatment 221 ±20.4 ng/ml in the fexofenadine-fluticasone group; and before treatment was 240.9 ±19.8 ng/ml, after treatment 218.3 ±17.6 ng/ml in the fexofenadine-montelukast group. The total symptom score before treatment was 8.15 ±1.37, after treatment 3.625 ±0.77 in the fexofenadine-fluticasone group; and before treatment was 8.275 ±1.38, after treatment 3.55 ±0.78 in the fexofenadine-montelukast group. The asthma symptom score before treatment was 7.1 ±0.8, after treatment 2.1 ±1.5 in the fexofenadine-fluticasone group; and before treatment was 6.9 ±2.3, after treatment 1.7 ±1.4 in the fexofenadine-montelukast group.

Conclusions: The combination of fexofenadine with either montelukast or a low-dose inhaled corticosteroid (fluticasone) equally reduces the serum sICAM-1 concentration and gives the same clinical effect in patients with persistent allergic rhinitis and newly diagnosed asthma.

Key words: intercellular adhesion molecule 1, persistent allergic rhinitis, asthma, montelukast, fluticasone.

Introduction

Epidemiological studies give strong evidence for an association between allergic rhinitis and asthma. The prevalence of allergic rhinitis in asthma is up to 80%, whereas asthma can affect 20 to 50% of rhinitic patients [1-5]. Allergic rhinitis is associated with the augmentation of non-specific bronchial hyperresponsiveness (BHR) [3, 4]. Regardless of the presence of BHR, allergic rhinitis usually precedes asthma and is a potential risk factor

for the development of asthma [6, 7]. Most research on this issue is based on the hypothesis that the association between allergic rhinitis and asthma is related to a common inflammatory background.

Intercellular adhesion molecule-1 (ICAM-1) plays a critical role in allergic rhinitis and asthma, participating in T-cell interactions, signal transduction, cell activation, proliferation and cytokine production [8]. Intercellular adhesion molecule-1 is involved in the initial stages of recruitment and migration of leukocytes from the circulation to the site of inflammation. The soluble form of ICAM-1 (sICAM-1) can activate eosinophils to secrete cationic proteins and, in accordance with our study, could be a useful inflammatory marker to determine clinical severity of asthma and allergic rhinitis [3].

The epidemiological and pathophysiological findings, common for allergic rhinitis and asthma, support the "one airway, one disease" hypothesis. Following that concept, targeting one site may improve the other one.

The aim of this study was to compare the effect of two different therapies on clinical outcomes and sICAM-1 concentration in serum in patients with persistent allergic rhinitis and newly diagnosed asthma.

Material and methods

Patients

Forty patients (28 women, 12 men; mean age 32.05 ±6.73) with at least a 2-year history of persistent allergic rhinitis, positive skin prick test to perennial allergens relevant for Central Europe (house dust mite, cat and dog), total nasal symptom score of at least 5 and asthma symptoms lasting less than 3 months were enrolled in the study. Allergic rhinitis was classified according to the Allergic Rhinitis and Its Impact on Asthma Guidelines [9], where persistent means that "symptoms are present more than 4 days a week and for more than 4 weeks" [9]. All patients had asthma symptoms (cough, wheezing, chest tightness, and shortness of breath) lasting no longer than 3 months preceding the study and all of them had positive results in the methacholine bronchial challenge test.

Patients could not be pregnant, be sensitized to seasonal allergens (grass, tree and weed pollen) or be current smokers. Furthermore, patients with severe illnesses (renal, hepatic or cardiovascular), respiratory tract infection during the 6-week period preceding the study, nasal septal deviation, nasal polyps, or acute or chronic rhinosinusitis were excluded. Leukotriene receptor antagonists, topical or systemic corticosteroids, allergen-specific immunotherapy, sleep medication, and other anti-allergic and anti-asthmatic treatment, except for

the study medication, were all prohibited. As a rescue medication patients could use the short acting β_2 agonist salbutamol (Ventolin, GlaxoSmithKline).

Study design

This prospective, cross-over study, performed outside the pollen season, consisted of two 6-week treatment periods and a 2-week wash-out period. On the first visit all subjects signed an informed consent form agreeing to participate in the study and medical history of asthma and allergic rhinitis was taken. After a two-week run-in period, the baseline symptom questionnaire was administered, physical examination, skin prick test, anterior rhinoscopy, and spirometry with dose-response methacholine challenge test were performed, and a blood sample was taken. Eligible subjects were assigned to the group receiving for 6 weeks fexofenadine (Telfast 120 mg, Aventis Pharma Ltd, West Malling, UK; 120 mg/day) with inhaled fluticasone propionate (Flixotide Disc 100 μ g, GlaxoSmithKline; 200 μ g/day = 2 puffs/day). After the 2-week wash-out period patients received for 6 weeks fexofenadine (Telfast, Aventis Pharma Ltd, West Malling, UK, 120 mg/day) with montelukast sodium (Singulair 10 mg, Merck & Co Inc, Whitehouse Station, NJ; 10 mg/day). After each 6-week treatment period, and after the wash-out period, symptom scores, study medication use, concomitant medication use and adverse events were evaluated, and physical examination, anterior rhinoscopy, spirometry and blood sampling were performed. The study was approved by the local ethical board.

Efficacy endpoints

The primary efficacy endpoints were serum sICAM-1 concentrations, total nasal symptom score, asthma symptom score, and anterior rhinoscopy score. The secondary efficacy endpoints were concomitant medication use and adverse events.

Total daytime nasal symptom score

Total daytime nasal symptom score was represented as the sum of the 4 individual scores (congestion, itching, sneezing, nasal discharge), each graded using a 4-point severity scale: 0 = none; 1 = mild (noticeable but not bothersome); 2 = moderate (noticeable and some of the time bothersome); and 3 = severe (bothersome most of the time/very bothersome some of the time); the maximum total nasal symptom score was 12.

Anterior rhinoscopy

Evaluation of nasal cavity, morphology and patency was performed using an optical method.

The chondrocostal structure was assessed with morphology of the nasal mucous membrane being described with respect to colour, oedema, redness and discharge using a 0-3 point scale (0 – no symptoms, 1 – mild, 2 – moderate, 3 – severe) and results were represented as the sum of the 4 individual scores; the maximum total nasal symptom score was 12.

Asthma symptom score

Patients with persistent asthma underwent spirometry and reported their wheeze/dyspnoea, cough, activity and sleep using a 4-point scale: wheeze/dyspnoea (0 – none, 1 – some, 2 – medium, 3 – severe); cough (0 – none, 1 – occasional, 2 – frequent, 3 – continuous); activity (0 – normal, 1 – can run a short distance or climb three flights of stairs, 2 – can walk only, 3 – missed school/work or stayed indoors); sleep (0 – fine, 1 – slept well, slight wheeze or cough, 2 – awake 2-3 times, wheeze and/or cough, 3 – bad night, awake all the time). Total daily asthma symptom score ranged from 0 to 12 [8].

Spirometry

Spirometry was performed on the randomization visit and on the last day of treatment periods with a computer-assisted spirometer (Lung Test 1000, MES Dymek, Dabrowski SA, Krakow, Poland) according to standardized guidelines [11]. Values were expressed as percentage of predicted values.

Serum sICAM-1 concentration

The serum concentration of sICAM-1 was examined by sandwich enzyme-linked immuno-sorbent assay (R & D System, Warsaw, Poland) according to the instructions of the manufacturer. Minimum detectable concentrations were 0.35 ng/ml.

Adverse events

Safety evaluations included treatment-induced adverse events and discontinuations because of adverse events. Adverse events were recorded by each subject in diary cards and the severity of adverse event was graded using a 10-point scale with 0 indicating none and 10 indicating very severe symptoms.

Statistical analysis

All data are presented as means \pm SEM. Normality of distributions were evaluated using the Shapiro-Wilk test. Parametric and nonparametric methods were used for statistical evaluation. Comparison between groups before and after treatment was performed with Student's *t*-test (parametric method) and the Mann-Whitney U test

(nonparametric method). $P < 0.05$ was regarded as statistically significant. Statistica 5.1 PL for Windows software (StatSoft Polska, Krakow, Poland) was used for analyses.

Results

Of 364 patients screened 43 were randomized and 40 (93%) completed the study; patient discontinuations were because of withdrawal of consent (2) and patient removal (1). Baseline patient characteristics including demographic, allergic rhinitis and asthma history are listed in Table I.

Total nasal symptom score

The total daily nasal symptom score was the highest at baseline, before treatment periods. Comparing the group treated with fexofenadine and fluticasone with the group treated with fexofenadine and montelukast, we found that both treatment options significantly improved total daily nasal symptom score but we did not find any statistically significant difference between them (Figure 1, Table II).

Table I. Patient baseline characteristics. Values are presented as mean \pm SEM

Number of subjects	40	
Ethnic origin	Caucasian (100%)	
Sex F : M	28 : 12	
Mean age	32.05 \pm 6.73	
Duration of persistent allergic rhinitis [years]	7.5 \pm 0.4	
Skin prick tests [wheal/flare mm]	Histamine	5.3 \pm 0.2/14.4 \pm 1.7
	Der p I	4.2 \pm 0.5/12.1 \pm 1.7
	Der p II	3.8 \pm 0.2/11.4 \pm 1.3

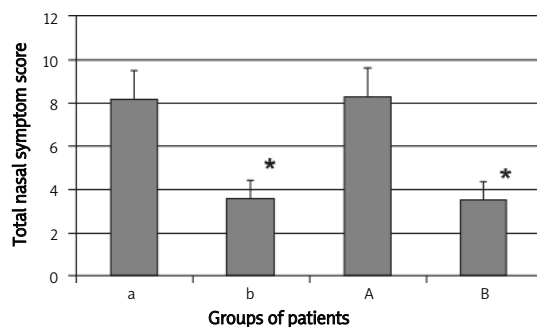


Figure 1. Mean total nasal symptom score in patients with persistent rhinitis and newly diagnosed asthma after 6 weeks of treatment with fexofenadine and fluticasone or with fexofenadine and montelukast a – group treated with fexofenadine and fluticasone before treatment, b – after treatment, A – group treated with fexofenadine and montelukast before treatment, B – after treatment, * $p < 0.001$. Error bars represent SEM

Table II. Results in patients with persistent allergic rhinitis and newly diagnosed asthma treated for 6 weeks either with combination of fexofenadine and fluticasone or with combination of fexofenadine and montelukast. Values are presented as mean ± SEM

	Fexofenadine + fluticasone		Fexofenadine + montelukast	
	Baseline	After treatment	Baseline	After treatment
Total nasal symptom score	8.15 ±1.37	3.62 ±0.77	8.27 ±1.38	3.55 ±0.78
Anterior rhinoscopy score	6.9 ±1.3	3.2 ±0.9	6.5 ±1.3	3.0 ±1.1
Asthma symptom score	7.1 ±0.8	2.1 ±1.5	6.9 ±2.3	1.7 ±1.4
Spirometry [l/s]	3.6 ±0.17	3.76 ±0.6	3.69 ±0.2	3.72 ±0.21
sICAM-1 [ng/ml]	243.4 ±20.7	221 ±20.4	240.9 ±19.8	218.3 ±17.6

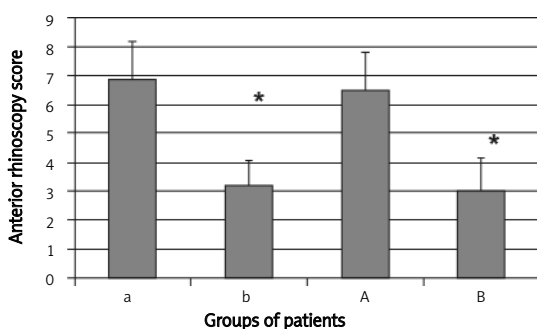


Figure 2. Anterior rhinoscopy score in patients with persistent rhinitis and newly diagnosed asthma after 6 weeks of treatment with fexofenadine and fluticasone or with fexofenadine and montelukast a – group treated with fexofenadine and fluticasone before treatment, b – after treatment, A – group treated with fexofenadine and montelukast before treatment, B – after treatment, **p* < 0.001. Error bars represent SEM

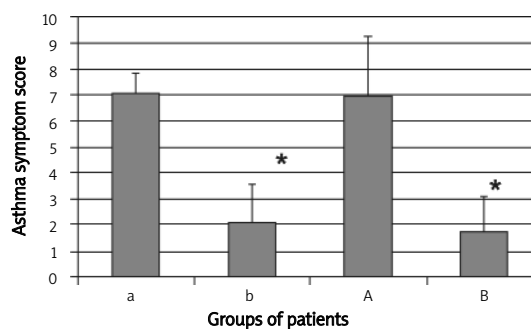


Figure 3. Mean asthma symptom score in patients with persistent rhinitis and newly diagnosed asthma after 6 weeks of treatment with fexofenadine and fluticasone or with fexofenadine and montelukast a – group treated with fexofenadine and fluticasone before treatment, b – after treatment, A – group treated with fexofenadine and montelukast before treatment, B – after treatment, **p* < 0.001. Error bars represent SEM

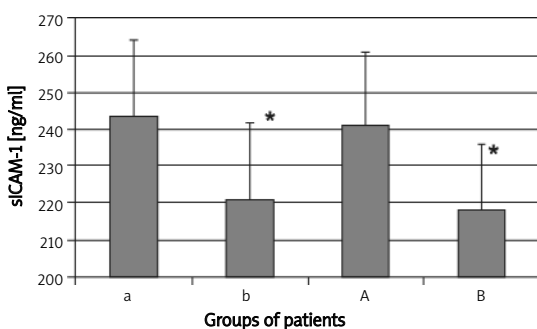


Figure 4. Mean serum soluble intercellular adhesion molecule 1 (sICAM-1) in patients with persistent rhinitis and newly diagnosed asthma after 6 weeks of treatment with fexofenadine and fluticasone or with fexofenadine and montelukast a – group treated with fexofenadine and fluticasone before treatment, b – after treatment, A – group treated with fexofenadine and montelukast before treatment, B – after treatment, **p* < 0.001. Error bars represent SEM

Anterior rhinoscopy

The combination therapy either with fexofenadine and fluticasone or fexofenadine and montelukast resulted in a significant improvement in the morphology of the nasal mucous membrane (colour, oedema, redness and discharge), providing significant improvement in total nasal symptom score assessed in anterior rhinoscopy. The rhinoscopic total nasal symptom scores were similar in both groups (Figure 2, Table II).

Asthma symptom score

Fexofenadine either with low-dose inhaled glucocorticosteroid (fluticasone) or with montelukast significantly reduced the asthma symptom score. There was no statistically significant difference between treatment options in mean change from baseline in ASS (Figure 3, Table II).

Spirometry

The mean FEV1 constituted about 90% of the predicted value at baseline and remained un-

changed in patients treated for 6 weeks either with the combination fexofenadine/fluticasone or with fexofenadine/montelukast (Table II).

Soluble form of intercellular adhesion molecule-1 concentration in serum

There was a significant decrease of sICAM-1 concentration in blood serum after fexofenadine/fluticasone or fexofenadine/montelukast treatment in comparison to sICAM-1 baseline levels. Furthermore, there was no significant difference between treatments (Figure 4, Table II).

Adverse events

There were no severe adverse events in the study. Patients reported adverse events such as headaches or cough of very low intensity, and the frequency of these events was comparable in both groups.

Concomitant medication use

The average use of a short acting β_2 agonist during the 6-week treatment period was 3.95 ± 0.35 in patients treated with a combination of fexofenadine with fluticasone and 4.01 ± 0.28 in patients treated with a combination of fexofenadine with montelukast. There were no significant differences in the rescue medication use between the active treatment groups.

Discussion

Among the group of patients with persistent allergic rhinitis and newly diagnosed asthma, who had never been treated with inhaled glucocorticosteroids and leukotriene receptor antagonists (LTRA), addition of the leukotriene receptor antagonist montelukast to fexofenadine produced the same improvement in serum ICAM-1 concentration, nasal symptom score, anterior rhinoscopic score and asthma symptom score as the low-dose glucocorticosteroid fluticasone added to fexofenadine.

Previous data have demonstrated that inhaled corticosteroids (beclomethasone or fluticasone) have overall greater efficacy than leukotriene receptor antagonists (montelukast or zafirlukast) in adults and children with persistent mild to moderate asthma. Although both montelukast and inhaled glucocorticosteroids significantly improved symptoms, symptom-free days, patients' quality of life [12], and pulmonary function [13, 14], as well as significantly reducing exhaled nitric oxide, blood eosinophil counts, serum cationic protein levels, serum ICAM-1, E-selectin, IL-4, IgE, and eosinophil cationic protein concentrations [14-21], greater improvements occurred with inhaled glucocorticoid than with montelukast [15]. Furthermore, Jayaram

[22] and Meltzer [23] revealed that even a low dose of inhaled fluticasone was more effective than montelukast in reducing symptoms, improving quality of life and maintaining an anti-inflammatory effect in asthmatics. Although Stelmach demonstrated that children with newly diagnosed asthma sensitized to house dust mites treated for 6 weeks either with inhaled budesonide or montelukast showed comparable significant improvement in clinical score and FEV1 [14], Dempsey [15] revealed no significant improvement in FEV1 in patients with mild persistent asthma treated with inhaled triamcinolone or montelukast.

Regardless of the results, all these studies were performed in patients with mild to moderate persistent asthma [13, 24], sometimes with concomitant allergic rhinitis and usually in patients who had been treated previously with inhaled glucocorticosteroids, LTRA and β_2 agonists. This is the first study evaluating patients exclusively with at least 2 years' history of persistent allergic rhinitis and newly diagnosed asthma with regard to patients' history of asthma symptoms and positive results in methacholine provocation tests. None of the eligible patients had been treated with inhaled anti-asthmatic agents and the majority of them had used only antihistamine or topical decongestants before the study. In the present study, contrary to previous studies, we revealed that the combination of fexofenadine either with montelukast or with a low-dose inhaled corticosteroid, fluticasone, gives the same clinical effect in patients with persistent allergic rhinitis and newly diagnosed asthma. The improvement in forced expiratory volume in one second was unnoticeable due to normal FEV1 values at baseline.

Fluticasone propionate as well as montelukast exerts a significant action on the early and late phase of allergic inflammation, also reducing the cellular influx during the late phase, likely due to the modulation of ICAM-1 expression. Both fluticasone [25] and montelukast [26, 27] may prevent airway inflammation by down-regulating the production and/or release of ICAM-1 from nasal and bronchial epithelial cells. Intracellular adhesion molecule 1 deficient mice developed impaired leucocyte trafficking to the lung, less lung inflammation and less airway hyperresponsiveness than healthy controls. In humans, the level of sICAM-1 is higher in asthmatic and rhinitic patients than in healthy subjects and decreases after treatment with inhaled glucocorticosteroid and montelukast [3, 25-27]. Reduction of sICAM-1 after the treatment may be related to the decreased allergic inflammation due to therapy. According to the results of our study, both low-dose inhaled fluticasone and montelukast added to fexofenadine similarly reduced the serum ICAM-1 concentration.

In conclusion, the results of this study indicate that montelukast reduced sICAM-1 concentration comparably to low-dose inhaled fluticasone in patients with persistent allergic rhinitis and newly diagnosed asthma.

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