ORIGINAL ARTICLE

Anti-inflammatory Properties of Montelukast, a Leukotriene Receptor Antagonist in Patients With Asthma and Nasal Polyposis

C Schäper,[1] O Noga,[2] B Koch,[1] R Ewert,[1] SB Felix,[1] S Gläser,[1] G Kunkel,[2] B Gustavus[2]

[1]Department of Internal Medicine B – Cardiology, Intensive Care, Pulmonary Medicine and Infectious Diseases, Greifswald, Germany
[2]Department of Pneumology and Infectious Diseases, Charité, University Medicine, Berlin, Germany

Abstract

Background: Leukotrienes, especially LTC4, are important inflammatory mediators in allergic and nonallergic inflammation of the entire airways. Of particular interest are numerous theories regarding the pathogenesis of aspirin intolerance with subsequent hyperproduction of leukotrienes and inhibition of cyclooxygenase.
Objective: To examine the influence of the cysteinyl-leukotriene receptor antagonist montelukast on clinical symptoms and inflammatory markers in nasal lavage fluid in patients with bronchial asthma and nasal polyps, and determine its dependency on aspirin sensitization.
Methods: Twenty-four patients (7 women, 17 men; median age, 55.5 years) with nasal polyps and controlled asthma (n=12 with aspirin intolerance) were treated with 10 mg montelukast once daily for 6 weeks in a blinded, placebo-controlled fashion. The placebo phase was randomly assigned 4 weeks before (n=12) or after treatment (n=12). Symptom score, rhinoendoscopy, rhinomanometry, smears for eosinophils, and nasal lavages for the determination of different mediators were performed.
Results: Compared to placebo, there were significant improvements in the nasal symptom score and airflow limitation as well as a reduction in the inflammatory mediators in nasal lavage fluid after treatment. Furthermore, reduced eosinophils in nasal smears and peripheral blood were observed 2 and 6 weeks after treatment.
Conclusion: Leukotriene 1 receptor blockade led to a significant decrease in eosinophil inflammation accompanied by a reduction in other mediators such as neurokinin A and substance P in the nasal lavage fluid of patients with nasal polyps and asthma, with or without aspirin intolerance.

Key words: Polyposis nasi. ASA intolerance. Leukotrienes. Eosinophils. ECP. Substance p. Neurokinin A. Montelukast. Nasal lavage.

Resumen

Antecedentes: Los leucotrienos, especialmente el LTC4, son mediadores inflamatorios importantes en la inflamación alérgica y no alérgica de todas las vías respiratorias. Son de especial interés las numerosas teorías relativas a la patogenia de la intolerancia al ácido acetilsalicílico, con la hiperproducción de leucotrienos y la inhibición de la ciclooxigenasa posteriores.
Objetivo: Estudiar la influencia de montelukast, un antagonista del receptor de cisteinil-leucotrienos, sobre los síntomas clínicos y los marcadores inflamatorios del líquido de lavado nasal en pacientes con asma bronquial y pólipos nasales, así como determinar su grado de dependencia de la sensibilización al ácido acetilsalicílico.
Métodos: Veinticuatro pacientes (7 mujeres, 17 hombres; mediana de edad: 55,5 años) con pólipos nasales y asma controlada (n = 12 con intolerancia al ácido acetilsalicílico) fueron tratados con 10 mg de montelukast una vez al día durante 6 semanas siguiendo un diseño ciego y controlado con placebo. La fase con placebo se asignó aleatoriamente 4 semanas antes (n = 12) o después del tratamiento (n = 12). Se llevaron a cabo la puntuación de los síntomas, rinoendoscopias, rinomanometrías, frotis para detectar eosinófilos y lavados nasales para determinar los diferentes mediadores.

Resultados: En comparación con placebo, se observaron mejoras significativas en la puntuación de los síntomas nasales y en la limitación del flujo aéreo, así como una reducción de los mediadores inflamatorios en el líquido de lavado nasal después del tratamiento. Asimismo, se observó una menor cantidad de eosinófilos en los frotis nasales y en la sangre periférica 2 y 6 semanas después del tratamiento.
Conclusión: La inhibición del receptor de leucotrienos de tipo 1 dio lugar a una disminución significativa de la inflamación mediada por eosinófilos acompañada de una reducción de otros mediadores como la neurocinina A y la sustancia P en el líquido de lavado nasal de pacientes con pólipos nasales y asma, con o sin intolerancia al ácido acetilsalicílico.

Palabras clave: Poliposis nasal, intolerancia al AAS, leucotrienos, eosinófilos, ECP, sustancia P, neurocinina A, montelukast, lavado nasal.

Introduction

Airway inflammation incorporates pathophysiological processes that lead to variant forms of airflow limitation and rhinitis, which occur frequently and impair quality of life [1,2]. In this context, leukotrienes (LTs) are important mediators of upper and lower airway inflammation [3,4], promoting inflammatory cell recruitment and the production of different cytokines and stimulating airway remodeling and mucus secretion [3].

Despite a great deal of scientific progress, the complex interplay of existing pathways in airway inflammation is not completely understood. This interplay includes concepts of neurogenic inflammation [5] that focus on inflammation caused by neuropeptides such as substance P and neurokinin A, the role of neurotrophins such as nerve growth factor or brain-derived neurotrophic factor in airway inflammation [6,7], and the interaction of these pathways with LTs. Polyposis nasi is a common disease with unknown etiology [8]. There is essentially no therapy available with long-term effects, and only corticosteroids are suitable and helpful as a long-term strategy. Several studies have demonstrated the antiinflammatory properties of corticosteroids, with decreases in eosinophils, eosinophil cationic protein (ECP), interleukin 5 (IL-5), vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 (ICAM-1) [9]. However, the local application of steroids is not sufficient in most cases, hence the need for oral corticosteroids. This therapy, however, is limited by the undesired actions of these drugs. In some patients with asthma, aspirin (acetylsalicylic acid, ASA) and all nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclooxygenase enzymes cox-1 and cox-2 trigger asthmatic attacks and naso-ocular reactions. This clinical syndrome is characterized by eosinophilic inflammation of nasal and bronchial tissue, often associated with nasal polyps, combined with an increased release of cysteinyl-LTs (CysLTs). LTC4 synthetase is markedly overexpressed in eosinophils and mast cells from bronchial biopsy specimens of most patients treated with ASA. Avoiding NSAIDs does not prevent the progression of inflammation, and corticosteroids continue to be the mainstay of therapy; however, anti-LT drugs are also indicated for the treatment of this underlying disease [10].

Nasal polyposis (NP) can also be described as a chronic inflammatory disease of the upper respiratory tract leading to the production of edematous polyps in the nasal cavities which are responsible for persistent nasal obstruction [11,12]. NP is a common disease that is normally treated by surgical intervention, and symptoms improve in more than 85% of cases [13]. The surgical removal of polyps, however, is often only a short-term solution since the recurrence rate of eosinophilic polyps is extremely high, especially in untreated ASA-sensitive patients [14]. The etiology of NP is not yet completely understood. Only corticosteroids are suitable as a long-term treatment strategy; they are helpful in 50% of patients, leading to decreased symptoms and lower recurrence rates. However, recurrence rates still range from 3% to 10%. NP is frequently combined with bronchial asthma (25%-30% of cases) or ASA intolerance [8,15,16].

The triad of ASA intolerance, bronchial asthma, and polyposis nasi (Sampter syndrome) is well-known in the literature [3]. LTs and prostaglandins are products of arachidonic acid metabolism, and are key mediators in acute and chronic inflammatory diseases of the airways [17,18]. In ASA-intolerant patients, the 5-lipoxygenase pathway is activated, most likely in mast cells, leading to the rapid production of LTs [19].

CysLTs mediate inflammatory and contractile processes through specific interaction with cell surface receptors belonging to the G protein-coupled receptor family. Pharmacological studies have identified 2 classes of CysLT receptors: CysLT1 receptors and CysLT2 receptors. While CysLTs can function as agonists for both types of receptors, CysLT1s are expressed in leukocytes, in the lung, and in airway smooth muscle [20].

LTC4 and D4 are 1000-fold more potent than histamine [21]. LT modifiers such as the CysLT1 receptor antagonist montelukast are a relatively new class of anti-inflammatory drugs, with increasing applications in areas such as asthma therapy [22].

Besides the mast cell, the eosinophil granulocyte is the key cell for acute allergic, late-phase and nonspecific chronic inflammation. Eosinophils are the main source of LTs [23].

The aim of this study was to examine the influence of the CysLT receptor antagonist montelukast on the clinical symptoms and markers of nasal lavage in neurogenic and eosinophil inflammation in patients with bronchial asthma and nasal polyps, and its dependency on ASA sensitization.

Materials and Methods

Study Design

This study had a single-blind, randomized, placebo-controlled, crossover design. Ten mg of montelukast was given once daily in the evening for 6 weeks. The placebo phase was 4 weeks either before (Group 1) or after (Group 2) montelukast treatment. The patients visited the clinic every 2 weeks. All visits were scheduled between 8 AM and 10 AM. Symptom scores and peak flow data for nasal and bronchial symptoms were documented on diary cards every morning and evening.

The nasal symptom scores were calculated as 2-week mean values. Nasal airway function and clinical examination were performed at baseline and after every 14 days of treatment. Short-acting $ß_2$-agonists were not used for at least 8 hours before lung function testing.

All participants gave informed consent and the study was approved by the local ethics committee.

Patients

Twenty-four patients (17 men), with a median age of 55.5 years (range, 32-66 years), were enrolled. They all had nasal polyps and mild to moderate asthma.

Six patients in each group (group 1 and 2) also had clinically documented ASA intolerance.

Asthma was diagnosed by history, physical examination, and lung function testing (Body-Lab II, Erich Jaeger, Würzburg, Germany), bronchial challenge with inhaled acetylcholine, and bronchial reversibility with inhaled salbutamol (0.2 mg).

Allergy with rhinitis or asthma was diagnosed by history. Sensitivity was confirmed by a skin prick test (SPT) for the most common inhalant allergens (house dust mites, animal allergens, and grass, tree, and herb pollen) performed at baseline. Additionally, specific serum immunoglobulin (Ig) E (CAP class, ≤1; Pharmacia CAP System) and total IgE (Pharmacia Diagnostics, Uppsala, Sweden) were measured.

All patients had previously undergone sinus surgery and had a long history of nasal polyposis.

Exclusion Criteria

Excluded from the study were pregnant and nursing women and patients who had used local anti-inflammatory or antiallergic drugs (eg, corticosteroids, antihistamines, or disodium cromoglycate) in the 3 weeks prior to enrolment, oral corticosteroids in the last 6 weeks, or polypectomy in the last 6 months. No patient was on immunotherapy. All the patients were nonsmokers, and none had any systemic disease.

Inhaled steroids (ICS) and bronchodilators were allowed, but the ICS dosage was kept stable during the trial and changes in short-acting $ß_2$-agonist consumption were documented.

Clinical Symptoms

Patients were instructed to record their nasal and pulmonary symptoms on diary cards daily throughout the trial period. The clinical score for the major nasal symptoms included obstruction, sneezing, itching, rhinorrhea, quality of smell, and pulmonary symptoms related to dyspnea, quality of sputum, and cough. Additionally, $ß_2$-agonist consumption was recorded. The severity of symptoms was graded on a 4-point scale based on the difficulty of tolerating the symptoms and interference with daily activities and sleeping. The number of sneezes within the last 12 hours was counted and transformed into a score, with 0, 0 sneezes; 1,1-4 sneezes; 2, 5-9 sneezes; and 3, ≥10 sneezes. The total nasal symptom score of 0 to 12 was calculated by adding these scores for each patient.

The rhinoscopic examination was performed by the same physician at baseline and after treatment to confirm nasal blockage, rhinorrhea, and irritation on a 4-point rating scale (0, absent; 1, mild; 2, moderate; and 3, severe). Within the study design rhinorrhea was estimated by signs of hypersecretion at the moment of examination, nasal blockage was judged by local congestion of the nasal mucous membranes, and irritation was defined as an increased local hyperemia of nasal mucous membranes.

Rhinomanometry

To analyze the degree of nasal airway obstruction, nasal peak inspiratory flow (cm^3/s) and nasal airway resistance (expressed in $Pa/[cm^3/s]$) were measured by anterior rhinomanometry (Rhinotest MP 500; Allergopharma Joachim Ganzer KG, Reinbeck, Germany) of each nostril, calculated at a pressure of 150 Pa, with merging of values from the left and right nostril. Repeated measurements were performed and the mean of 5 values was recorded provided the coefficient of variation was less than 5%.

Olfactometry

The quality of smell was tested with a modified olfactometric test containing different aromas. The test included odor discrimination and threshold for each nostril. The results achieved were merged to a 4-point score of 0, normal smell; 1, mild impaired smell; 2, moderate impaired smell; and 3, no smell.

Nasal Lavage Procedure

Nasal lavage (NAL) was performed by instilling 5 mL of sterile saline (preheated to 37°C) into each nasal cavity using a tube connected to a syringe inserted into the foam rubber-closed nostril. After 10 seconds, each fluid sample was collected by repeated aspiration from both nasal cavities and the surface of the inferior turbinate and placed in polypropylene tubes, which were immediately placed on ice. After centrifugation at 1000 g for 10 minutes at 4°C and removal of cellular elements, the supernatants were aliquoted for the different assays and stored at –80°C until analysis. The recovery of aspirated lavage fluid was 86±8%.

Assessment of Mediators

Assessment of nasal lavage and measurement of CysLTs, soluble ICAM-1 (sICAM-1), human serum albumin (HSA), and ECP were performed as described previously [24].

The peptides SP and NKA were measured with highly specific competitive commercial enzyme-linked immunosorbent

(ELISA) kits in 50 µL of lavage fluid in duplicate. SP (Cayman Chemical; Ann Arbor, Michigan, USA) was measured to pg/mL of lavage fluid (minimal detectable concentration, 7.8 pg/mL).

NKA (Peninsula Laboratories, INC. Belmont, California, USA) was similarly measured to ng/mL of lavage fluid (minimal detectable concentration, 0.06-0.08 ng/mL).

Nasal Cytology

Nasal smears were taken from the inferior turbinate following lavage using a cotton wool swab dampened with physiological saline. The sampled cells were transferred to glass slides by gentle rolling and air-dried overnight. Eosinophils stained by the May-Grünwald-Giemsa technique were counted from smears by the differentiation of 100 cells, and the results were expressed as a percentage of total cell count. All specimens were examined by the same microscopists and 2 investigators in a blinded fashion.

Blood Samples

Blood samples were taken for differential counts (of absolute eosinophil and leukocyte numbers) before and at the end of each study period.

Lung Function

Spirometry (Body-Lab II) was performed at baseline, after 2 and 6 weeks of treatment with montelukast, and after 4 weeks on placebo. Peak-flow measurements (mini-Wright; Clement Clarke, Harlow, UK) were measured twice daily in the morning (AM peak expiratory flow [PEF], 8 AM-10 AM) and evening (PMPEF, 6 PM-8 PM) in triplicate before medication, and the best effort was documented by the patients on their diary cards.

Statistical Analysis

Data are expressed as means±SEM or as median and range. Clinical scores and concentrations of cysLTs, ECP, substance P, neurokinin A, sICAM-1, histamine, and albumin in NAL fluids, and eosinophil counts were compared using the Wilcoxon signed-rank test (pretreatment/posttreatment), and treatment versus placebo was compared using the Mann-Whitney U test.

A value of $P<.05$ was considered significant. The variables from the patients' diary cards were calculated as 2-week averages of daily values during the treatment period, at baseline, and at the end of the placebo phase. Differences in sex, atopy and ASA intolerance were examined by the Fisher exact test. The Spearman correlation coefficient (r) was calculated to analyze possible correlations between pairs of parameters, with significance set at $P<.05$. Statistical tests were performed using SPSS/PC, version 16.0 (SPSS Inc. Chicago, USA).

Results

Clinical Data

All 24 patients completed both treatment periods, and no adverse effects were observed during the trial. Twelve patients (9 men) with a median age of 54.5 years (range, 32-65 years) were included in Group I; 4 of the patients had atopy. In Group II, there were also 12 patients (8 men); the median age was 57.5 years (range, 35-66 years) and 6 of the patients had atopy.

In each group, 6 patients had ASA intolerance. Group I started with a 4-week placebo phase and continued with 6 weeks of montelukast treatment while group II started with treatment and continued with placebo.

Nasal Symptoms

The overall nasal symptom scores during treatment with montelukast showed a significant reduction in all areas ($P<.05$). The improvement started in the first 2 weeks and remained significant throughout the active treatment phase compared to the placebo phase.

During montelukast treatment, the mean scores decreased from 1.8 to 0.6 for nasal blockage, from 1.5 to 0.6 for rhinorrhea, and from 0.6 to 0.25 for itching. In a similar manner, the quality of smell improved from 2.0 to 0.3 and the total symptom score improved from 5.9 to 1.75 ($P<.001$). No significant changes in symptoms were observed during the placebo period.

Rhinoscopical Findings

There was a significant reduction in edema, hypersecretion, blockage, and total symptom score under treatment, as measured by mean scores at baseline and after 6 weeks of treatment (Figure 1).

Rhinomanometry

Nasal airway flow increased significantly ($P<.01$) during montelukast treatment compared to placebo (Figure 2).

Mediator Levels in NAL Fluid

Mean NAL fluid concentrations of SP, NKA, cysLTs, ECP, and albumin decreased significantly compared to baseline levels during treatment with montelukast, whereas no such changes were observed during the placebo period (Table 1). The baseline values of both groups showed no significant differences; there were also no differences between either of the 2 treatment groups or either of the 2 placebo groups (data not shown).

Eosinophils

Significant reductions in eosinophils in nasal smears and peripheral differential blood were seen during the treatment phase after 2 and 6 weeks (Figure 3) ($P<.01$), whereas these values remained unchanged during the placebo phase.

Lung Function

The improvement in lung function was maintained over the 6-week period, as shown by spirometry recorded at the clinic visits and by daily peak flow recordings at home (Table 2). At the end of the 6 weeks of treatment, there was a trend (not significant) of a 5% increase in forced expiratory volume in the first second (FEV_1) (mean increase, 0.2 L).

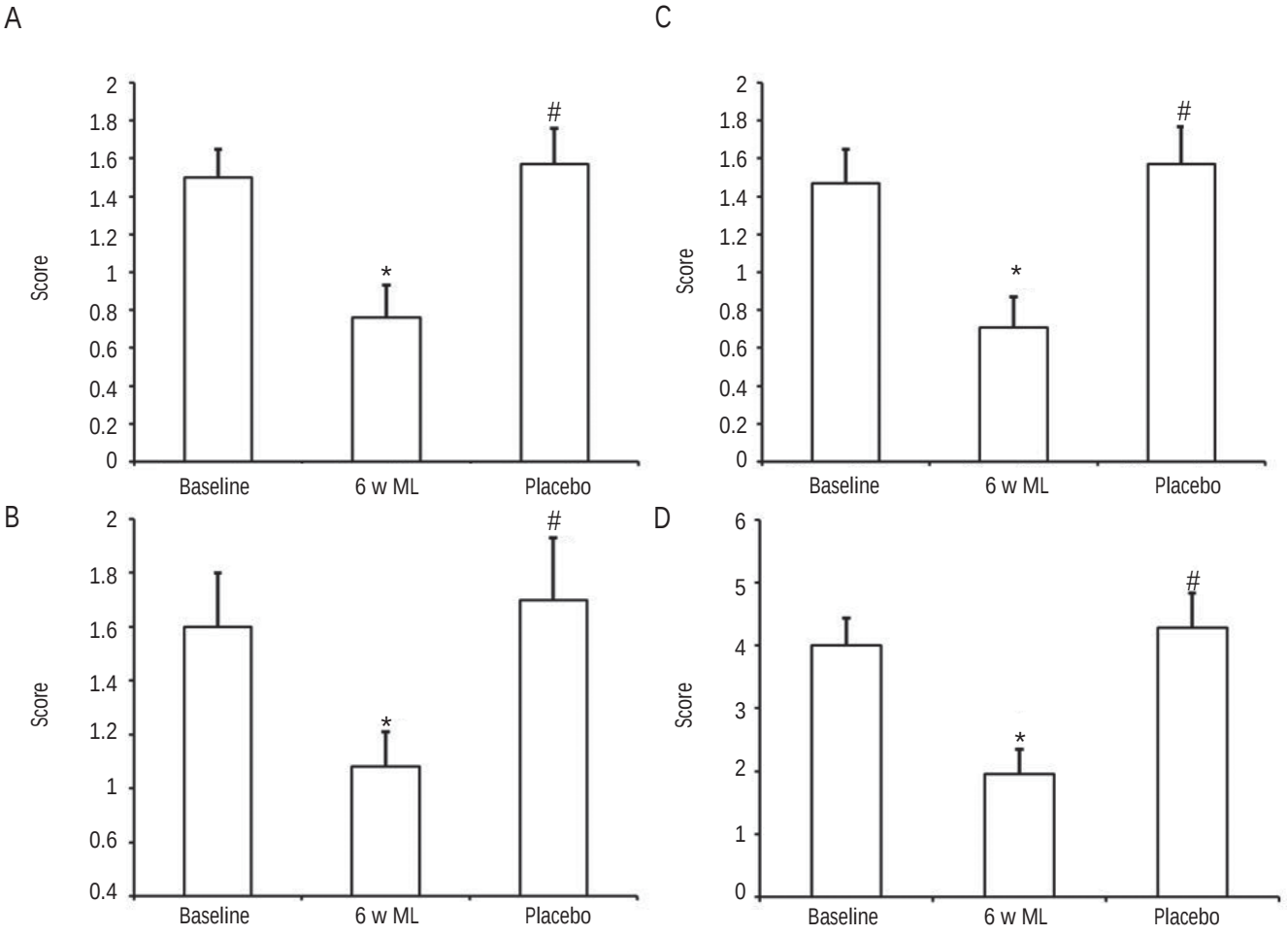

Figure 1. A, Secretion score measured by anterior rhinoscopy; baseline vs 6 weeks (6 w) of treatment vs placebo. B, Irritation score measured by anterior rhinoscopy; baseline vs 6 weeks of treatment vs placebo. C, Obstruction score measured by anterior rhinoscopy; baseline vs 6 weeks of treatment vs placebo. D, Total symptom score measured by anterior rhinoscopy; baseline vs 6 weeks of treatment vs placebo. *P<.05 baseline vs treatment group (Wilcoxon test). #P<.05 treatment group vs placebo (Mann-Whitney U test).

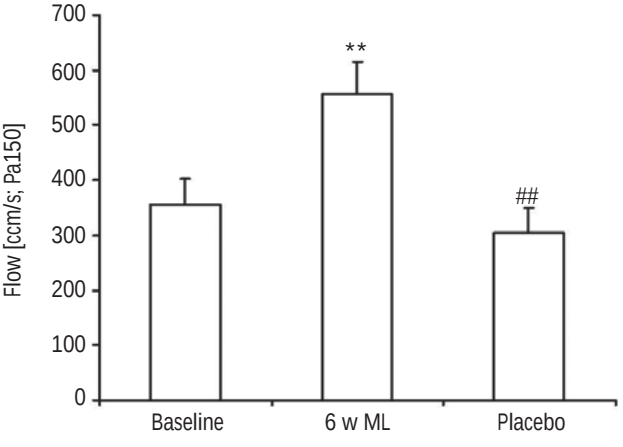

Figure 2. Nasal airway flow (ccm/s) at a pressure of 150 Pa; baseline vs 6 weeks (6 w) of treatment vs placebo. **P<.01 baseline vs treatment group (Wilcoxon test). ##P<.01 treatment group vs placebo (Mann-Whitney U test).

Table 1. Mediator Concentrations Measured in Nasal Lavage Fluid[a]

	Baseline (Groups I/II) (n=24)	MLPT (Groups I/II) (n=24)	Placebo (Groups I/II) (n=24)
SP, pg/mL	36.3±10.1	13.9±3.1**	34.8±8.5##
NKA, ng/mL	1.2±0.3	0.20±0.1***	2.0±0.7##
cICAM-1, ng/mL	0.8±0.1	0.66±0.1***	0.92±0.1##
ECP, ng/mL	46.9±22	9.1±4.2**	29.8±13##
CysLTs, pg/mL	120±32	54.3±14.4*	105.3±24.6#
HSA, µg/mL	40.4±6.1	20.1±4.3**	48.7±7.3

Abbreviations: cICAM, circulating intercellular adhesion molecule-1; CysLTs, cysteinyl-leukotrienes (LTC4, LTD4, LTE4); ECP, eosinophil cationic protein; HSA, human serum albumin; MLPT, montelukast posttreatment; NKA, neurokinin A; SP, substance P.

[a]Data are shown as means±SEM.

*P<.05;

**P<.01;

***P<.001. Baseline vs treatment group (Wilcoxon test).

#P<.05;

##P<.01. MLPT vs placebo (Mann-Whitney U test).

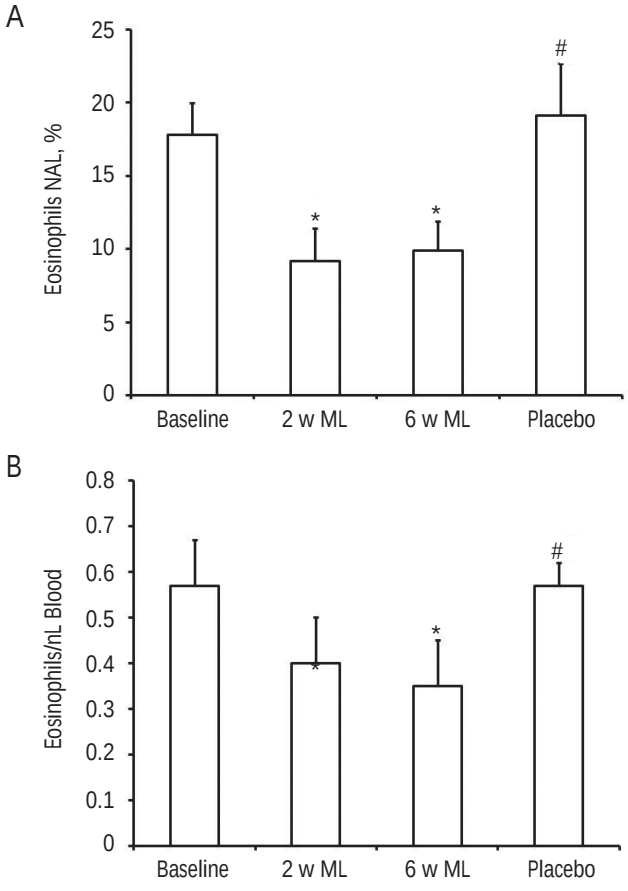

Figure 3. Eosinophils in nasal lavage (NAL) fluid as a %; baseline vs 2 weeks (2 w) of treatment with 10 mg montelukast (ML) once daily (OD) vs 6 weeks of treatment with 10 mg ML OD vs placebo; *P<.05 baseline vs treatment group (Wilcoxon test); #P<.05 treatment group vs placebo (Mann-Whitney U test). B, Eosinophils in blood per nL; baseline vs 2 weeks of treatment with 10 mg ML OD vs 6 weeks of treatment with 10 mg ML OD, vs placebo; *P<.05 baseline vs treatment group (Wilcoxon test); #P<.05 treatment group vs placebo (Mann-Whitney U test).

Daily use of $ß_2$-agonists was significantly reduced with montelukast treatment compared to placebo. There was also a significant improvement in pulmonary symptoms and PEF (Table 2) after 6 weeks of treatment.

No significant differences in signs, symptom scores, endoscopic findings, or mediator concentrations were found between patients with ASA intolerance and those without, regardless of whether they had started with montelukast or placebo first.

Additional statistical tests made with subgroups showed that the results obtained were not due to the sequence of participation in the different groups (data not shown).

Discussion

The observed decrease in inflammatory mediators (LTs, ECP, sICAM-1, and neuropeptides) and HSA in NAL and the reduction in eosinophils in nasal smears in the present study indicate the ability of montelukast to reduce inflammatory mediators and cell migration in the nose. The onset of action is prolonged, with the maximum therapeutic effect seen after 6 weeks of treatment. These improvements are probably based on the control of nasal polyp inflammation and possibly of polyp growth. The anti-inflammatory effect of montelukast observed in our study was accompanied by significant improvements in nasal symptoms, nasal airway flow, lung function parameters (FEV_1 % of predicted not significant, PEF) and pulmonary symptoms.

The above results indicate that monotherapy with the leukotriene1-receptor antagonist montelukast is an effective treatment for patients with polyposis nasi. The results are compatible with earlier reports in patients with bronchial asthma or aspirin triad disease. Dahlen et al [25] showed in a double-blind, placebo-controlled study that the 5-lipoxygenase inhibitor Zileuton, given at 600 mg once daily for 6 weeks, decreased pulmonary and especially nasal symptoms, supporting the theory that LTs are the main inflammatory mediators in this disease. In the present study, there were no

Table 2. Lung Function Tests and Peak Expiratory Flow Measurements[a]

	Group	Baseline	Montelukast		Placebo	
			2 wk	6 wk	2 wk	4 wk
FEV1, % predicted	I[b]	88.1±11.6	92±10.5	93.1±12.2	87.6±11.4	87.8±11.2
	II[c]	87.4±9.8	90.1±9.3	91±8	86.1±9.2	85.7±9.6
FEV_1, L	I[b]	3.4±1.0	3.5±0.8	3.6±0.9	3.3±0.8	2.9±0.8
	II[c]	3.0±0.9	3.1±0.8	3.2±0.8	2.9±0.8	2.8±0.8
PEF, L/min	I[b]	436±122	490±150	510±102d	484±122	476±113
	II[c]	462±99	500±100	509±91d	456±111	447±110

Abbreviations: FEV_1, forced expiratory volume in the first second; PEF, peak expiratory flow.
[a]Data are shown as means±SEM.
[b]Placebo for 4 weeks followed by montelukast for 6 weeks (10 mg once daily).
[c]Montelukast for 6 weeks (10 mg once daily) followed by placebo for 4 weeks.
[d]P<.05; Wilcoxon test, baseline vs 6 weeks treatment.

differences between patients with or without ASA intolerance. In the study by Dahlen et al, nasal symptoms significantly improved compared to placebo, with increasing improvement noted over the 6-week study period [25]. Parnes et al [26] reported that 26 (72%) of 36 patients with nasal polyps treated with zarfikulast or zileuton experienced a significant improvement in nasal symptoms. Ragab et al [27], in turn, demonstrated that an additional three months of montelukast therapy combined with intranasal and inhaled corticosteroids produced subjective and objective improvements in nasal symptoms and function as well as significant improvements in lung function in patients with nasal polyposis, with or without ASA intolerance. In our study, we only saw an improvement in peak flow values after 6 weeks of therapy. The reduction in $ß_2$-agonist use and improvement in asthma symptoms and FEV_1 (none of which were significant) varied between 1% and 15% for the variables recorded and might be explained by successful asthma treatment before the add-on therapy with montelukast.

However, our study extends previous observations by examining inflammatory components that contribute to eosinophil accumulation in nasal polyps such as cysLTs, sICAM-1, and neuropeptides such as substance P. The pathophysiology of nasal polyps is still not completely understood, although a number of contributing factors have been proposed including recurrent infections, allergies, ASA intolerance, and genetic factors [16].

Bachert et al [28] found, along with elevated IL-5, ECP, and eotaxin, increased amounts of albumin in polyp tissue compared to normal nasal mucosa; the combination was proposed as a matrix phenomenon responsible for polyp formation. The authors, however, were unable to name specific mediators as the pathophysiological facilitators behind polyp formation. In our study, the neurogenic component via the release of the neuropeptides SP and NKA was significantly reduced. This can be explained by the reduced release of neuropeptides by LTs from c-sensory nerve fibres and reduced local eosinophil inflammation with a consequent reduction in the release of SP or NKA or reduced release from peripheral cells such as eosinophils or mast cells. These findings predominantly explain the clinical improvements observed in terms of reduced nasal blockage, secretions, and itching as well as improved smell, all objectively evaluated by anterior rhinoscopy, olfactometry, and rhinomanometry. Furthermore, in bronchial asthma an additional effect of bronchodilatation was observed.

The reduction in cysLTs in NAL after therapy with montelukast is probably the main reason for the improved nasal airflow noted, as in human studies, increased nasal blood flow has been seen after intranasal challenge with LTs [29].

The decreased levels of cysLTs, ECP, and HSA in the NAL fluid as well as the reduction in eosinophils with the improvement of nasal symptoms show the importance of these mediators and cells in the pathophysiology of nasal polyps.

CysLTs promote eosinophil recruitment in the airways, and eosinophils, in turn, release these LTs. Montelukast indirectly leads to a decrease in LT concentration in the airways by reducing mucosal leakage, with a subsequent reduction in eosinophil migration and LT and ECP formation [3,4]. The reduction of eosinophils by montelukast could be due to a reduction in transendothelial eosinophil migration, a shortening of eosinophil survival, or a combination of both; this question remains to be answered in further studies.

In the post-montelukast placebo period, the beneficial effect was reversed. We were unable to find any predictive parameter for responsiveness to montelukast.

The results of the present study show that various components in nasal polyp inflammation are affected by montelukast.

Receptor blockade led to a significant decrease in eosinophil inflammation accompanied by a reduction in mediators linked to neurogenic inflammation in the NAL fluid of patients with nasal polyps and asthma, with or without aspirin intolerance. The improved symptoms, the rhinoscopic findings, and the bronchial/nasal flow demonstrate clinical relevance and emphasize a potential role of montelukast in nasal polyposis.

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Christoph Schäper

Department of Internal Medicine B
Friedrich-Loeffler-Str. 23a
17475 Greifswald, Germany
E-mail: christoph.schaeper@googlemail.com

