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DOSE ESCALATION OF MONTELUKAST IN THE TREATMENT OF NINE NASAL POLYPOSIS PATIENTS

AN OPEN PILOT STUDY

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INTRODUCTION

The recurrence of nasal polyposis is a common clinical problem. Leukotriene antagonists (LTRAs) have an effect on asthma¹ and allergic rhinitis symptoms². A review on LTRAs and nasal polyposis (from 356 studies) concluded that the risk of polyp relapse following surgery is reduced by treatment with antileukotrienes³.

In earlier studies on severe asthma, use of montelukast in doses up to 200 mg daily for 22 weeks⁴ and up to 900 mg daily for one week (unpublished data Merck & Co, 1998) has been reported, without marked clinical side effects. After one of the investigators (OT) had met several patients who unprompted had increased the dose of montelukast and found a decrease of symptoms, we decided to test, in an investigator-driven open pilot study, the effects of >10 mg montelukast daily on patients with severe nasal polyposis.

STUDY DESIGN

We performed an open pilot study, in which nasal polyposis patients were treated by montelukast, first increasing the dose up to 40 mg/per day and then descending the dose down to 20 mg/per day. The follow-up time was eight weeks. The study was performed between October 2009 and February 2011 at the Department of Otorhinolaryngology of Helsinki University Central Hospital.

PATIENTS AND METHODS

Ethical consideration

The study was approved by the Research Ethics Board of the Helsinki University Central Hospital.

Patients

Inclusion criteria:

The patients had to have polyps at least beyond middle meatus on both sides, after having had polypectomy at least once before this study and having received maximal conventional therapy with nasal and oral steroids (at least prednisolone 30 mg daily for one week, then 15 mg daily for another week and 2 months fluticasone nose drops) without good stable response with nasal blockage grade remaining $>3/5$ in Sinonasal Outcome Test-22 (SNOT-22)⁵.

Exclusion criteria:

Patients with positive antineutrophil cytoplasmic antibodies (ANCA) or type I diabetes mellitus, primary or secondary hypogammaglobulinemia necessitating immunoglobulin therapy, HIV, other immunodeficient conditions, severe mental disorders, liver or kidney disease, gravidity, breast feeding, or age less than 18 years were excluded.

The use of montelukast may be associated with a small increased risk of Churg-Strauss syndrome and severe eosinophilia⁶. In hematologic diseases, blood eosinophil counts above 1.5×10^9 can cause direct organ toxicity. We arbitrarily chose blood eosinophil count $> 0.8 \times 10^9$ as an exclusion criteria for this trial.

The previous use of montelukast 10 mg daily was not an exclusion criteria.

Of consecutive twenty patients with severe nasal polyposis, eleven were excluded. Notably six patients were found to have high blood eosinophils ($1.04 - 2.36 \times 10^9/L$), of whom three had positive ANCA (one with MPOAbG in ELISA, two with ANCA in immunofluorescence)

without Churg-Strauss vasculitis in biopsies or clinically⁶. Other causes for exclusion were earlier high blood eosinophil counts and severe stomachache from montelukast 10 mg daily (one patient), headache, stomachache and sleeplessness from montelukast (one patient), two patients were excluded before therapy (one for respiratory infection and oral steroids for obstruction after recruitment, one did not learn to perform peak nasal inspiratory flow, PNIF), and one patient was excluded from the final analysis due to having only had previous septoplasty and radio-frequency-assisted inferior turbinoplasty and no polypectomy. Nine patients with nasal polyps were included (Table 1).

Methods

The study protocol is shown in Table 2. The SNOT-22, Visual Analogue Scale (VAS), PNIF, Sniffin' Sticks screening smell test, anterior rhinoscopy, nasal endoscopy (both done by the same investigator every time), and acoustic rhinometry (ARM), were performed. Previous nasal or paranasal sinus operations, aspirin (ASA)-hypersensitivity, asthma-like symptoms, and other diseases and medications were recorded.

Medication was started 1-3 weeks after the recruitment. The treatment lasted eight weeks. During the first week, patients took Singulair (montelukast) 20 mg/day, during the second week 30 mg/day and from third to fifth weeks 40 mg/day, and from sixth to eight weeks 20 mg/day.

Symptom diary (VAS), SNOT-22 and PNIF

The patients filled in a symptom diary at home. The diary was started 1-3 weeks before medication and was continued for the length of study medication. By using VAS the patients recorded self-assessed symptom scores of sense of smell, nasal itching, sneezing, runny nose,

nasal blockage, eye symptoms, cough, asthma symptoms, crusting of the nasal mucosa, and bloody nasal secretions. VAS grades symptoms on a 10 cm line. Zero represents no complaints and 10 the worst imaginable symptoms. SNOT-22 was filled at the recruitment appointment, at the start of the study and at the fifth and eight week follow-up visits. SNOT-22 consists of 22 questions of sinonasal symptoms⁵. Patients performed PNIF every day (the best of three inhalations was recorded) from recruitment to the end of the study.

Smell test

Olfactory function was tested by Sniffin' Sticks Screening 8 Test, using pen-like odour dispensing devices and multiple forced choice from four verbal items per each of the eight common odorants⁷. Both nasal cavities were tested.

Anterior rhinoscopy and nasal endoscopy

At follow-up visits, anterior rhinoscopy was performed. Mucosal swelling and nasal secretions were estimated using the following visual scale: 0 = normal, 1 = slightly abnormal, 2 = moderately abnormal and 3 = heavily abnormal. After ARM measurements (which included nasal decongestion) nasal endoscopy was performed using a rigid endoscope. Polyps were evaluated using the following scale: 0 = no polyps, 1 = polyps at the lowermost level of the middle turbinate but no larger, 2 = polyps beyond middle turbinate, 3 = polyps extending to the bottom of nasal cavity. If the patient had polyps between the middle turbinate and septum meaning that polyps are coming from posterior ethmoid cells one point was added, but not if the polyp scale was already 3. The grade of polyps in each nasal cavity of all patients was taken into account in the results.

Acoustic rhinometry

The volume between the distances of 2 to 5 cm from the nostrils was measured with an A1/2 ARM (G.M. Instruments Ltd., Glasgow, UK). Unilateral volumes were calculated for all patients. The measurements were made before and after nasal decongestion. The nasal mucosa was decongested by inhalation of 0.5% xylometazoline hydrochloride nasal spray in each nasal cavity 15 minutes before the measurements.

Laboratory tests

Complete blood count with differential, ANCA with immunofluorescence test, creatine, alanine aminotransferase (ALAT), and aspartate aminotransferase (ASAT) were investigated before and at the end of the study. Blood eosinophil count was assessed at the fifth week follow-up as well.

Statistics

Change in anterior rhinoscopy, nasal endoscopy, SNOT-22, and ARM (decongested mucosa) were analyzed with Friedman's non-parametric repeated measures ANOVA. Sniffin' Sticks smell test, VAS and PNIF were analyzed using parametric repeated measures ANOVA. Power transformations were applied to variables with non-normal distributions. In VAS, all graded symptom scores during the previous week before each follow-up visit was counted.

RESULTS

The small number of patients successfully recruited into study precluded meaningful statistical analyses. There were seemingly no differences in any objective measurements

including anterior rhinoscopy, nasal endoscopy, Sniffin' Sticks odor identification test, ARM or PNIF during the study time.

However, improvements in subjective VAS measurements on runny nose, nasal crusts, bloody nasal secretions, asthma symptoms, cough, and eye symptoms were reported by patients, but not in sense of smell, nasal itching, sneezing or nasal blockage.

In the evaluation of SNOT-22 the median score was 49,5 at the start of the study, 45,5 at the fifth week follow-up visit and 45,0 at the eight week follow-up visit. The scores suggested that patients felt better during the treatment but the difference was not statistically significant ($p = 0,66$).

Interestingly, montelukast acted differently in ASA-hypersensitive patients compared to ASA-tolerant patients. From objective measurements there was statistically significant interaction between ASA-hypersensitivity and sense of smell in Sniffin' Sticks smell test and between ASA-hypersensitivity and weeks in PNIF (Fig. 1).

There was statistically significant interaction between ASA-hypersensitivity and weeks in VAS items concerning the sense of smell, nasal blockage, itching, nasal crusts, cough and eye symptoms (Fig. 2).

In the beginning of the study ASA-hypersensitive patients had worse VAS items than ASA-tolerant in sense of smell but their VAS items improved during the whole treatment time. This was not seen in ASA-tolerant patients, they felt sense of smell as same the whole time.

DISCUSSION

This is far as we now the first study where the effect of the higher than the normal asthma-dose of montelukast was used in the treatment of recurrent nasal polyps. Interestingly, montelukast acted differently in ASA-hypersensitive patients compared to ASA-tolerant patients. Also in the earlier studies it has been found that polyp patients with ASA-hypersensitivity have different disease expression than ASA-tolerant patients. In 20-year follow-up study of 41 polyposis patients eight patients had underwent > 11 surgeries during the 20-year period and 88% (7/8) belonged to the ASA-hypersensitivity group⁸. In another study we found a clear difference between the ASA-tolerant and ASA-hypersensitivity groups, with the effect of triamcinolone acetonide being significant among the ASA-tolerant group⁹.

It has been speculated that montelukast does not directly cause Churg-Strauss. All Churg-Strauss patients receiving LTRA have been treated for moderate/severe asthma with corticosteroid but actually they have had unmasked underlying vasculitic syndrome¹⁰.

The excluded patients with eosinophilia had also moderate/severe asthma in our study and they would have needed something else than conventional treatments.

The study could be affected by treatment bias as all patients were offered the treatment and the observer was aware of this

There is a need for controlled randomised trial where ASA-hypersensitivity is an independent cofactor.

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CONFLICT OF INTEREST

None to declare.

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Table 1.

PATIENTS	
-all	9
-women	3
-men	6
AGE	
-mean	45,7
-range	38-54
HYPERSENSITIVITY	
asthma.	3
ASA	4
EARLIER POLYP OPERATIONS	
-once	2
-2 to 4	3
-5 to 10	4

Table 2

	-1 visit (1-3 weeks prior to 0 visit)	0 visit	5 weeks	8 weeks
Visit at hospital	ENT out-pt. cl.	ENT out-pt. cl.	ENT out-pt. cl.	ENT out-pt. cl.
Patient information	X			
Informed consent	X			
Medication		X		
Symptom diary (VAS), PNIF	X	X	X	X
SNOT-22	X	X	X	X
Anterior rhinoscopy	X	X	X	X
Nasal endoscopy	X	X	X	X
Acoustic rhinometry		X	X	X
Smell test		X	X	X
Lab. tests				
ASAT		X		X
ALAT		X		X
Creatinine		X		X
Complete blood count with eosinophils		X		X
p-ANCA		X		X

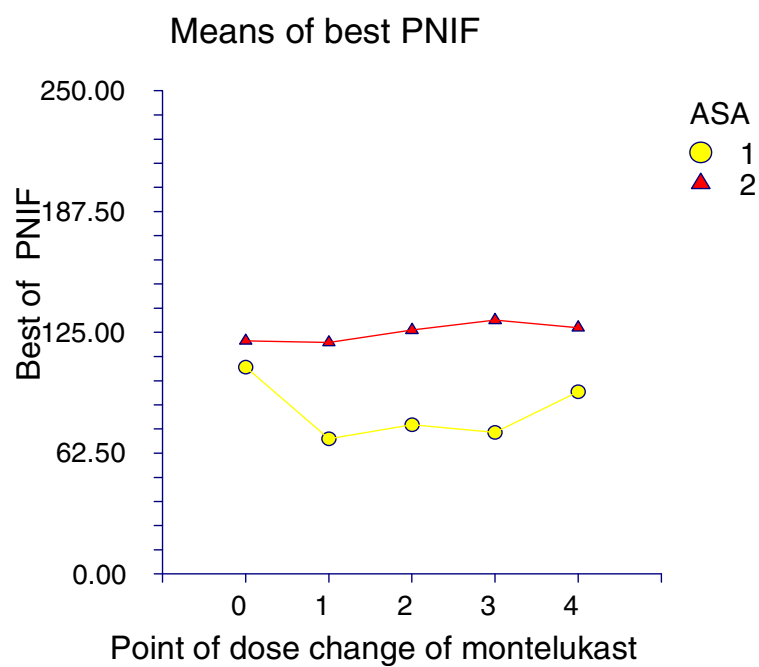
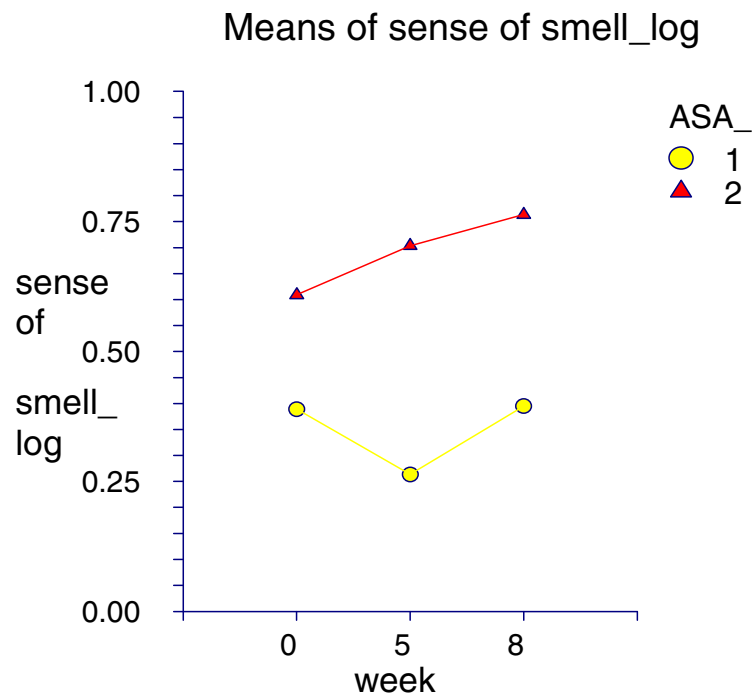


Fig.1

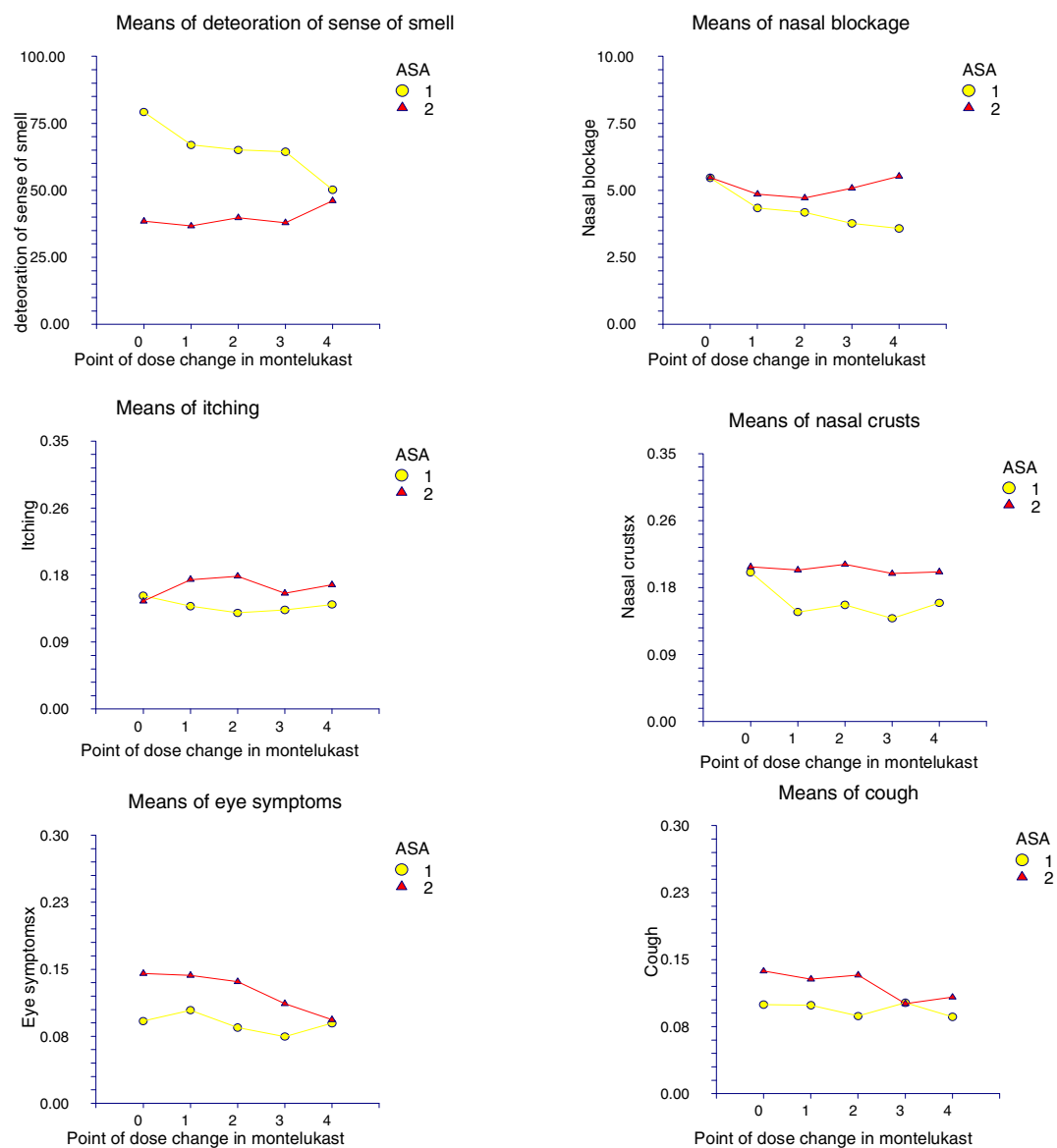


Fig. 2