Efficacy of nasal mometasone for the treatment of chronic sinonasal disease in patients with inadequately controlled asthma

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Background: Chronic sinonasal disease is common in asthmatic patients and associated with poor asthma control; however, there are no long-term trials addressing whether chronic treatment of sinonasal disease improves asthma control.

Objective: We sought to determine whether treatment of chronic sinonasal disease with nasal corticosteroids improves asthma control, as measured by the Childhood Asthma Control Test and Asthma Control Test in children and adults, respectively.

Methods: A 24-week multicenter, randomized, placebo-controlled, double-blind trial of placebo versus nasal mometasone in adults and children with inadequately controlled asthma was performed. Treatments were randomly assigned, with concealment of allocation.

Results: Two hundred thirty-seven adults and 151 children were randomized to nasal mometasone versus placebo, and 319 participants completed the study. There was no difference in the Childhood Asthma Control Test score (difference in change with mometasone − change with placebo [ΔM − ΔP], −0.38; 95% CI, −2.19 to 1.44; $P = .68$; age 6-11 years) or the Asthma Control Test score (ΔM − ΔP, 0.51; 95% CI, −0.46 to 1.48; $P = .30$; age ≥12 years) in those assigned to mometasone versus placebo. In children and adolescents (age 6-17 years) there was no difference in asthma or sinus symptoms but a decrease in episodes of poorly controlled asthma defined by a decrease in peak flow. In adults there was a small difference in asthma symptoms measured by using the Asthma Symptom Utility Index (ΔM − ΔP, 0.06; 95% CI, 0.01 to 0.11; $P < .01$) and in nasal symptoms (sinus symptom score ΔM − ΔP, −3.82; 95% CI, −7.19 to −0.45; $P = .03$) but no difference in asthma quality of life, lung function, or episodes of poorly controlled asthma in adults assigned to mometasone versus placebo.

Conclusions: Treatment of chronic sinonasal disease with nasal corticosteroids for 24 weeks does not improve asthma control. Treatment of sinonasal disease in asthmatic patients should be determined by the need to treat sinonasal disease rather than to improve asthma control. (J Allergy Clin Immunol 2015;135:701-9.)

Key words: *Asthma, rhinitis, sinusitis, sinonasal, asthma control, lung function, asthma exacerbation*

Poor asthma control is a significant cause of morbidity. One important factor thought to affect asthma control is disease of the upper airway, such as rhinitis and sinusitis.[1-5] Therefore chronic sinonasal disease is often treated in asthmatic patients in an effort to improve asthma control. However, although acute and severe sinonasal disease clearly warrant treatment directed toward upper airway disease, it is not clear whether treating chronic sinonasal disease improves asthma control.

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Abbreviations used
ACT: Asthma Control Test
cACT: Childhood Asthma Control Test
ΔM − ΔP: Change with mometasone − change with placebo
SNOT-22: Sino Nasal Outcomes Test 22

Rhinitis, sinusitis, and asthma are closely linked. At least 70% of asthmatic patients have rhinitis,[6,7] and 30% to 40% report sinusitis.[6] A number of mechanisms link sinonasal disease and asthma, which might represent a common immune disorder affecting the whole respiratory system. Allergen challenge in one region produces inflammation in the other,[8,9] postnasal drip of inflammatory mediators can occur,[10] and a nasobronchial reflex might produce bronchoconstriction.[11] Chronic sinonasal disease is very common in asthmatic patients and might be part of a common disease process.

Despite sinonasal disease and asthma being closely related disease processes, it is not clear whether treatment of sinonasal disease affects the course of asthma. Treatment of severe and acute sinonasal disease is clearly warranted and might improve asthma control,[12,13] but most studies have been observational because such sinonasal disease requires treatment regardless of the effect on asthma.[12] Some small studies suggest that treatment of acute rhinitis improves airway reactivity,[14,15] whereas others do not,[16,17] and some observational studies report that long-term treatment for sinonasal disease improves asthma outcomes.[18] However, there are no controlled studies suggesting that long-term treatment of chronic sinonasal disease improves asthma control, although this is often done in clinical practice.[19]

One barrier to understanding the interaction between sinonasal disease and asthma is the lack of simple tests to diagnose rhinitis and sinusitis in asthmatic patients. We previously developed a clinical tool to identify chronic rhinitis and sinusitis in patients with inadequately controlled asthma. This questionnaire, which specifically asks about symptoms experienced over the last 3 months, identifies patients with chronic rhinitis and sinusitis, with a sensitivity of 0.90 and specificity of 0.94.[20] This questionnaire accurately diagnoses chronic sinonasal disease in asthmatic patients, is inexpensive and simple to use, and therefore facilitates the study of the relationship between chronic sinonasal disease and asthma.

Chronic sinonasal disease is common in asthmatic patients and can be associated with severe disease, but the effect of long-term treatment of sinonasal disease on asthma control is not known. The purpose of this study was to determine the efficacy of treating chronic sinonasal disease in children and adults with inadequately controlled asthma, as is common medical practice. There is supportive but inconclusive evidence that such treatment reduces asthma morbidity, and therefore this clinical trial addresses an important and practical issue that has extensive implications for public health and health care costs.

The trial was registered at ClinicalTrials.gov as NCT01118312 under the acronym Study of Asthma and Nasal steroids (STAN).

METHODS

Study design

This was a multicenter, randomized, placebo-controlled, double-masked, parallel-design (allocation ratio 1:1) trial conducted at 19 clinical centers from June 2010 through February 2013. Randomization was stratified by center and age (6-17 years or ≥18 years) by using permuted blocks of varying sizes. Participants aged 12 years and older received 2 sprays of mometasone or placebo per nostril daily (50 μg of mometasone per spray vs vehicle control; Merck, Whitehouse Station, NJ); those aged 6 to 11 years received 1 spray per nostril daily. After a 2-week run-in period, participants were randomized and followed for 24 weeks while receiving treatment. Allocation concealment was enforced as follows: clinical center personnel keyed eligibility data into a centralized Web-based randomization system to receive a study kit number that corresponded to the assigned treatment. Unique drug assignment numbers were used to distribute and track the study drug. Personnel at the data-coordinating center involved in randomization and drug distribution to the centers had access to the treatment information; no personnel at the clinical sites had access to the treatment codes. Analysts looked at treatment identity after data collection was completed and were aware of treatment assignment when performing the analyses of the completed data set.

Participants

Participants were aged 6 years and older with a history of physician-diagnosed asthma and either a positive methacholine challenge result (20% decrease in FEV_1 at <16 mg/mL methacholine) in the previous 2 years or documentation of at least 12% and 200-mL increase in FEV_1 with bronchodilator in the previous 2 years. Subjects were required to meet the following inclusion criteria: poor asthma control was defined as a score of 19 or less on the Childhood Asthma Control Test (cACT; age 6-11 years)[21] or Asthma Control Test (ACT; age ≥12 years[22]; ACT and cACT scores of 19 or less identify "not well controlled asthma," which is defined as an asthma specialist's rating of not controlled at all/poorly controlled/somewhat controlled)[21,23] and chronic symptoms of rhinitis and sinusitis as measured by a mean score of 1 or greater on the Sino-Nasal Questionnaire.[20] Participants were excluded if they had comorbidities predisposing to complicated rhinosinusitis; chronic illnesses that, in the judgment of the physician, would interfere with study participation; history of upper airway symptoms for less than 8 weeks at the time of randomization; temperature of greater than 38.3°C within the prior 10 days; sinus surgery within the prior 6 months; use of systemic or nasal corticosteroids within the prior 4 weeks or antileukotriene medication within the prior 2 weeks; FEV_1 of less than 50% of predicted value before bronchodilator; a greater than 10 pack year smoking history or active smoking within the last 6 months; or cataracts, history of glaucoma, or other conditions resulting in increased intraocular pressure. Other exclusion criteria were nonadherence (<80% completion of daily diaries during the run-in period); inability to take study medications, perform baseline measurements, or be contacted by telephone; or pregnancy.

Participants underwent allergen skin testing at baseline. Percutaneous allergen scratch skin testing was performed with a Multi-Test II device (Lincoln Diagnostics, Decatur, Ill) and 16 allergens (mite mix, cockroach mix, mouse, rat, *Penicillium* species, *Alternaria* species, *Aspergillus* species, *Cladosporium* species, cat, and dog; 4 local center-specific allergens; and positive and negative controls; Greer Laboratories, Lenoir, NC). A positive test result was defined as a wheal 3 mm larger than that elicited by the negative control.

Participants were asked to refrain from taking nonstudy medications (other than topical decongestants or saline) for their nasal symptoms. They were trained to exhale all orally inhaled corticosteroids through the mouth to avoid any potential benefit of orally inhaled corticosteroids on the nasal mucosa.

Participants continued their usual asthma medications during the trial. After randomization, participants kept daily diaries to record morning peak expiratory flow, medication use, and asthma symptoms and returned for assessments at 4, 12, and 24 weeks. Procedures performed at each visit included an interval medical history interview, asthma and sinus symptoms questionnaires, and spirometry (Koko Spirometer; Ferris Respiratory, Louisville, Colo), according to American Thoracic Society standards.[24] At baseline and the 24-week follow-up visits, fraction of exhaled nitric oxide values were measured with the Insight eNO System (Apieron, Menlo Park, Calif), and methacholine challenge testing was performed. Allergen skin testing and the sinonasal questionnaire were administered at baseline.