

Editorial

Will a nasal corticosteroid improve control for patients with step 3 or higher persistent asthma?

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For patients with persistent asthma who are categorized as having step 3 or higher disease by the Expert Panel Report 3 of the National Heart, Lung, and Blood Institute¹ or the Global Initiative for Asthma,² there is uncertainty as to what interventions should be recommended when asthma symptoms are not controlled. The Expert Panel Report 3 advises patient education (eg, inhaler technique), evaluation of medication adherence, environmental control, management of comorbidities at each step (from 2-4), and consideration of “subcutaneous allergen immunotherapy for patients who have allergic asthma.”¹ Step-up therapy can include moving up the medication ladder. The “Global Initiative for Asthma pocket guide”² includes the option of using low-dose beclomethasone dipropionate/formoterol or budesonide/formoterol as maintenance and reliever therapy, which is not in agreement with the guidelines of the US Food and Drug Administration. In the European Academy of Allergy and Clinical Immunology position statement on asthma exacerbations and severe asthma, patients with uncontrolled asthma in primary care were separated into 5 categories: (1) patients with treatment-resistant disease, (2) noncompliant patients, (3) patients who are unable to appreciate deteriorations, (4) patients with a physician who underestimates the level of control and undermanages, and (5) patients who do not have asthma.³ In particular, obese patients with severe asthma might have relative inhaled corticosteroid insensitivity or have been given a misdiagnosis of asthma.

To date, a number of randomized controlled studies focusing on interventions for patients whose symptoms are uncontrolled at step 3 or higher (either while receiving inhaled corticosteroid/long-acting β -adrenergic agonist combination therapy or a medium-dose inhaled corticosteroid) have yielded either negative^{4,5} or positive⁶⁻⁹ results. The positive results are associated with some degree of improved patient health. However, the magnitude of change can be modest, whether in terms of improved peak expiratory flow⁷ or FEV₁,^{7,8} fewer exacerbations,⁶ or prolonged time without an exacerbation.^{7,9} Considered from a

system perspective, a major and continuing unmet need is reducing exacerbations requiring emergency department visits and hospitalizations for asthma. Indeed, the rate of emergency department visits and hospitalizations per 100 patients with asthma was unchanged from 2001 to 2009, whereas the number of deaths from asthma has decreased.¹⁰

The synergistic and concurrent interactions between the upper and lower airways and effects of pharmacotherapy and immunotherapy support using the term united (also known as unified or integrated) airways disease. About 75% to 90% of patients with persistent asthma have allergic rhinitis and might have concomitant chronic rhinosinusitis or intermittent exacerbations of acute rhinosinusitis. Abnormalities on computed tomographic examination of the sinuses are frequently present in patients with persistent asthma.¹¹ In particular, ethmoid sinus involvement has been identified in 61% of adult patients with persistent mild or moderate asthma and in 97% of patients with corticosteroid-dependent asthma.¹¹

In this issue we learn the results of a trial of intranasal mometasone treatment of the upper airways to improve control of inadequately controlled asthma.¹² Most research subjects were at the level of step 3 or higher asthma and had to report sinonasal symptoms for at least 8 weeks. The primary outcome marker was the anticipated improvement in Asthma Control Test (ACT) or Childhood Asthma Control Test (c-ACT) scores. After 24 weeks of planned treatment, the primary outcome was not achieved in either adults or children.¹² The investigators incorporated multiple other secondary outcomes, including the Sino-Nasal Outcome Test 22 for patients aged 18 years and older and the Sino-Nasal Survey 5 for children aged 6 to 17 years, pulmonary physiologic measurements, and episodes of poor asthma control.¹² In analyzing the study and lack of efficacy, a number of questions can be posed:

1. Is the study important scientifically? Yes, the study hypothesis is clinically pertinent.
2. Is the study novel? Yes, the literature is without controlled studies focusing on this intervention in patients with inadequately controlled asthma.
3. Is the study relevant to improving patient care? Yes.
4. Did the investigators study an important patient population? Yes, the patients had asthma symptoms that were not well controlled based on ACT scores, were diverse in sex and race, and had exacerbations in the past year. It is worth noting that patients had a baseline percent predicted FEV₁ of 85%, despite the low ACT or c-ACT scores, emphasizing the discordance between FEV₁ and measures of control, which characterizes asthma.
5. Does the protocol test an intervention that is plausible at the right dose and duration from a pharmacologic or biologic perspective? This is debatable because intranasal mometasone has an onset of action in 7 hours for reducing

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nasal symptoms of seasonal allergic rhinitis,¹³ but in this study of patients with persistent uncontrolled asthma, patients had to have sinus symptoms for at least 8 weeks and not have had sinus surgery in the past 6 months. In children with poorly controlled asthma, intranasal mometasone did not reduce sinus symptoms (by using the Sino-Nasal Survey 5 or sinus symptom score instrument), whereas in adults there was a reduction in symptoms. The sinus symptom score instrument ($P = .03$) and changes in Sino-Nasal Outcome Test 22 scores approached significance, but the magnitude of change for the Sino-Nasal Outcome Test 22 was about half of the minimally important difference of 8.9. Thus if the rationale for improved control of asthma is a direct effect to reduce sinonasal symptoms, then monotherapy with intranasal mometasone was not sufficient, its effects were overweighted, or the questionnaire tools were insensitive to change. A case could be made for the active intervention to include treating with mometasone plus implementing avoidance measures at home for allergens and attempting to reduce exposure to secondhand smoke, which was present at baseline for 26% of adults and 21% of children. In other words, one should demonstrate that there were meaningful reductions in sinus symptoms to explore any evidence for a united airway in patients with asthma of step 3 or greater severity. Would some subjects benefit from aspirin desensitization? We are not told the number of patients with aspirin-exacerbated respiratory disease or chronic sinusitis with or without nasal polyps.

6. Did the subjects in the control group receive usual care? A sobering finding was that 28% of randomized subjects were not receiving inhaled corticosteroid/long-acting β -adrenergic agonist or inhaled corticosteroid therapy at enrollment. Leukotriene antagonist therapy was not permitted 2 weeks before or during the study so as not to interfere with the active intervention with mometasone. By protocol, the study subjects had poorly or uncontrolled asthma yet were not receiving typical controller therapy and were not required to receive such during 6 months of observation. The initial management decisions for worsening or exacerbations of asthma were made by the primary physician managing the patient's asthma and not the investigators (who were available as backup). From the study interpretation perspective, it would be informative to know whether there had been previous sinonasal responses/nonresponses to intranasal steroids and whether the results were comparable in the 2 groups.
7. Did the investigators overinterpret their findings? No.

The investigators and their research teams should be complimented for the great effort that went into this study. At first, they had to screen 1567 prospective subjects to identify 388 for randomization who had asthma with ACT scores of 19 or less, at least 8 weeks of sinonasal symptoms, and bronchodilator

responsiveness or methacholine hyperreactivity. Then they had to verify in a 2 week run-in period that symptom score diaries, peak expiratory flow measurements, and medications were recorded reliably. After randomization, data were generated in a serial manner from age-focused asthma and sinonasal questionnaires, patients' diaries, and other outcome markers over the 24 weeks.

On the basis of this trial, when asthma symptoms are not controlled in patients with concomitant sinonasal symptoms, prescribing intranasal mometasone alone to improve control of asthma will be ineffective. It is my hope that we can make a concerted effort to insert 1 or 2 descriptive words in the assessment section of our progress notes, specifically whether asthma is "controlled," "not controlled," or "poorly controlled." These few words have significant meaning and hopefully will lead to thoughtful patient care and present a challenge for investigators to find the breakthrough interventions for step 3 and higher asthma.

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