

patients undergoing functional endoscopic sinus surgery for chronic inflammatory sinusitis. Although these patients had pathology in their sinuses, the ostial tissue itself was completely free of inflammation, as determined by our pathologist.

John W. Steinke, PhD

Larry Borish, MD

Asthma and Allergic Disease Center
University of Virginia Health System
Charlottesville, VA 22908-1355

REFERENCES

1. Ferguson BJ. Clarification of terminology in patients with eosinophilic and noneosinophilic hyperplastic rhinosinusitis. *J Allergy Clin Immunol* 2003;112:221-2.
2. Steinke JW, Bradley D, Arango P, Crouse CD, Frierson H, Kountakis SE, et al. Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophils and asthma. *J Allergy Clin Immunol* 2003;111:342-9.
3. Bresciani M, Paradis L, Des Rouches A, Vernhet H, Vachier J, Godard P, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;107:73-80.
4. ten Brinke A, Grootendorst DC, Schmidt JT, de Bruine FT, van Buchern MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;109:621-6.
5. Peters E, Hatley TK, Crater SE, Phillips CD, Platts-Mills TAE, Borish L. Sinus computed tomography scan and markers of inflammation in vocal cord dysfunction and asthma. *Ann Allergy Asthma Immunol* 2003;90:316-22. doi:10.1067/mai.2003.1568

Effects of salmeterol on smooth muscle versus inflammatory outcomes

To the Editor:

We wish to pass comment on the study of Busse et al,¹ which concluded that fluticasone-salmeterol combination conferred steroid-sparing properties compared with twice the dose of fluticasone alone.

This was based on the primary efficacy measure of the proportion of patients who did not withdraw because of the lack of efficacy, with the criteria being a 20% or greater decrease in peak expiratory flow or FEV₁ or a worsening of asthma that required additional asthma medication.

Because the primary efficacy measure was largely determined on the basis of airway caliber, the results would always be biased toward adding salmeterol, which improves smooth muscle responsive end points, such as lung function. Indeed, this was evident by the significantly greater improvements in morning peak expiratory flow with the fluticasone-salmeterol combination compared with those with fluticasone alone.

Pointedly, no measurements were made of any surrogate inflammatory markers in this study, which makes it rather difficult to assess what was happening to the underlying asthmatic inflammatory process in the patients taking combination therapy. For example, we have recently compared the 250 µg fluticasone-salmeterol combination (Diskus) administered twice daily versus use of 500 µg of fluticasone alone (Diskus) administered twice daily, each given in randomized cross-over fashion for 2 weeks in patients with persistent asthma, with a 2-week run-in and washout period before each

randomized treatment when patients took their usual inhaled steroid therapy (mean daily beclomethasone equivalent dose of 460 µg/d).² For the primary outcome measure of adenosine monophosphate PC₂₀, fluticasone alone but not the fluticasone-salmeterol combination conferred a significant ($P < .05$) improvement, amounting to a 1.72 and 0.53 doubling dilution shift from baseline, respectively, along with a significantly ($P < .05$) greater effect conferred by fluticasone alone. For exhaled nitric oxide, both fluticasone alone (a 2.3 geometric mean fold reduction) and fluticasone-salmeterol (a 1.5 geometric mean fold reduction) produced significant changes, with the reduction being significantly ($P < .05$) greater than that with fluticasone alone.

It is therefore important to carefully consider end point selection when evaluating the effects of combination inhalers, especially when the outcome might be biased toward smooth muscle-responsive end points. This might be especially relevant to reviewing patients in the clinic, where lung function, symptoms, or reliever use might be relatively disconnected from the underlying inflammatory process in patients using such combination inhalers. This point was recently demonstrated by Green et al,³ who showed that titrating inhaled steroid therapy against sputum eosinophils resulted in better outcomes in terms of exacerbations, airway hyperresponsiveness, and exhaled nitric oxide.

The Asthma and Allergy Research Group has received financial support from GSK for attending postgraduate scientific meetings and for equipment. The spouse and mother of Brian Lipworth are both stockholders of GSK.

Brian J. Lipworth, MD^a

Catherine M. Jackson, MRCP^b

^aNinewells University Hospital
Dundee, Scotland
DD1 9SY

^bTayside Centre for General Practice
University of Dundee
Dundee, Scotland
DD1 9SY

REFERENCES

1. Busse W, Koenig SM, Oppenheimer J, Sahn SA, Yancey SW, Reilly D, et al. Steroid-sparing effects of fluticasone propionate 100 µg and salmeterol 50 µg administered twice daily in a single product in patients previously controlled with fluticasone propionate 250 µg administered twice daily. *J Allergy Clin Immunol* 2003;111:57-65.
2. Currie GP, Bates CE, Lee DKC, Lipworth BJ. Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients [online publication]. *Eur J Clin Pharmacol* March 22, 2003 (DOI 10.1007/s00228-003-0571-9).
3. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21. doi:10.1067/mai.2003.1571

Reply

To the Editor:

Drs Lipworth and Jackson¹ raise an important question regarding measurements that should be assessed for

asthma control. Asthma guidelines state that one of the goals of asthma therapy is reduction of exacerbations while maintaining normal or near-normal lung function. Our study² demonstrates that this can be achieved in patients with persistent asthma whose symptoms are uncontrolled with low-dose inhaled corticosteroids (ICSs). Exacerbation rates were similar between patients with asthma treated with 250 µg of fluticasone propionate and those treated with 100 µg of fluticasone propionate and 50 µg of salmeterol both administered twice daily. The latter group also had improvements in FEV₁, symptom-free days, and rescue-free days that were sustained over the 24-week study period.

It must be noted that to successfully control asthma and prevent exacerbations, the underlying disease must be controlled. In this regard Green et al³ demonstrated that therapy targeted toward decreasing sputum eosinophilia was associated with a reduction in asthma exacerbation rates. Likewise, clinical studies have clearly demonstrated that exacerbation rates are lower with ICSs plus long-acting inhaled β-agonists (LABAs) versus with higher-dose ICSs alone and that control of inflammation is at least as good with ICSs plus LABAs as with higher-dose ICSs alone.⁴ Although inflammatory markers were not directly assessed in the present study, the fact that rates of exacerbations, worsening asthma, or both were comparable with ICSs plus LABAs and higher-dose ICSs alone suggests that inflammation was controlled.

The suggestion by Drs Lipworth and Jackson that the primary efficacy measure was largely determined on the basis of airway caliber is not consistent with the results of this study or others that used exacerbations and not a bronchodilator-sensitive outcome, such as lung function, as the primary outcome. For example, Lazarus et al⁵ demonstrated no differences in bronchodilator-sensitive outcomes in patients receiving salmeterol versus in those receiving an ICS, yet there were more exacerbations in the salmeterol group, thus contradicting the notion that improvements in smooth muscle control drive clinical outcomes.

Selecting any primary end point obviously limits the global relevance of the intervention, be that end point pulmonary function or airway responsiveness. Drs Lip-

worth and Jackson have indicated that various therapies might have distinct effects on markers of asthma severity (ie, AMP responsiveness). However, different components of inflammation might contribute to altered airway function depending on the stage or phase of the disease. Therefore it is unlikely that one outcome or biomarker will provide the pivotal end point for ideal control of asthma. That being said, it is important that surrogate markers be linked to lung physiology or key outcomes (ie, exacerbations) to have relevance to asthma. The comments of Drs Lipworth and Jackson are relevant because they confirm the complexity of asthma.

In summary, there is disagreement that the primary findings of this study resulted from salmeterol-mediated improvements in smooth muscle-sensitive outcomes in that exacerbation rates were as low with low-dose ICS plus salmeterol as with higher doses of ICS alone. There is agreement that biopsy results would be ideal, and 2 studies in similar patient populations nearing completion will provide such data.

William Busse, MD
University of Wisconsin
Medical School
K4/912 CSC
600 Highland Ave
Madison, WI 53792

REFERENCES

1. Lipworth BJ, Jackson CM. ••• J Allergy Clin Immunol 2003;112:223.
2. Busse W, Koenig SM, Oppenheimer J, et al. Steroid-sparing effects of fluticasone propionate 100 µg and salmeterol 50 µg administered twice daily in a single product in patients previously controlled with fluticasone propionate 250 µg administered twice daily. J Allergy Clin Immunol 2003;111:57-65.
3. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. Lancet 2002;360:1715-21.
4. Kips JC, O'Connor BJ, Inman MD, et al. A long-term study of the anti-inflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. Am J Respir Crit Care Med 2000;161:996-1001.
5. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting β₂-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma. A randomized controlled trial. JAMA 2001;285:2583-93.

doi:10.1067/mai.2003.1572