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In vitro* synergism of inhaled corticosteroid and long-acting β_2 -agonist is not translated clinically *in vivo

To the Editor:

Pace et al¹ provide impressive data on the *in vitro* synergism of fluticasone propionate and salmeterol on T-cell activation and apoptosis in patients with asthma. However, it is important to stress that no such synergy has ever been demonstrated clinically in asthma. Studies evaluating the effects of fluticasone propionate alone versus the combination of fluticasone propionate plus salmeterol *in vivo* have failed to demonstrate any potentiation of effects of combination therapy on surrogate inflammatory biomarkers.^{2,3} The superior bronchodilator response seen with the combination of an inhaled corticosteroid and a long-acting β_2 -agonist is merely a result of the predictable additivity of response on separate pathways of inflammation and smooth muscle, respectively. Moreover, in a pooled analysis of studies comparing fluticasone propionate plus salmeterol combination versus concurrent separate inhalers at the same dose, the former afforded a significantly greater effect on morning peak expiratory flow, amounting to a clinically irrelevant difference of 5 L/min.⁴ Salmeterol may reduce asthma exacerbation by stabilizing airway smooth muscle without having to invoke the putative potentiation of anti-inflammatory effects of fluticasone propionate.⁵ In summary, although there appears to be *in vitro* synergism demonstrated by the combination of fluticasone propionate and salmeterol, these effects are not translated *in vivo*, thus calling into question the clinical relevance of such findings.

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Reply

To the Editor:

We thank Lee et al¹ for the generally positive comments on our article.² However, we have some criticisms about their comment concerning the absence of existing evidence demonstrating *in vivo* anti-inflammatory synergy between steroids and long-acting β_2 -agonists. The authors state that this “[i]n *in vitro* synergism of inhaled corticosteroid and long-acting β_2 -agonist is not translated *in vivo*” on the basis of their previous reports focused on the effects of combined therapy on surrogate markers of airway inflammation such as exhaled nitric oxide and serum eosinophil cationic protein (ECP).^{3,4}

The clinical benefits of combining salmeterol and inhaled corticosteroid (ICS) certainly raise the question of whether salmeterol can, independently of its well-known long-lasting bronchodilator activity, add or complement the anti-inflammatory activity of ICS in patients with asthma. Three studies have addressed this question, providing direct information on changes in airway inflammation evaluated on biopsies^{5,6} or on bronchoalveolar lavage.⁷ Briefly, Li et al⁵ demonstrated, together with significant clinical benefits assessed as symptom score, PD₂₀, and morning peak flow, a significant reduction in airway eosinophilic infiltrate in biopsies after 12 weeks of