

Correspondence

Bronchoprotective tolerance with inhaled corticosteroid/long-acting β -agonist treatment

To the Editor:

We read with interest the study by Cardet et al,¹ which showed that 38% of asthmatic patients receiving an inhaled corticosteroid (ICS) and a long-acting β -agonist (LABA; ie, fluticasone/salmeterol) experienced loss of bronchoprotection. We believe that their results need to be interpreted in light of the potential interaction between the LABA moiety and the arginine/glycine genotype at position 16 (Arg16Gly) of the β_2 -adrenoceptor. For example, a *post hoc* genotype-stratified pooled analysis of 152 patients from randomized placebo-controlled trials showed that the degree of protection after chronic dosing with ICS/LABA treatment was 1.49 (95% CI, 0.5-2.48) doubling dose less in patients who possessed ArgArg or ArgGly genotypes (comprising about 60% of patients) compared with those who had the GlyGly genotype (about 40% of patients).² Moreover, chronic exposure to the higher-efficacy agonist formoterol was associated with 3.0 (95% CI, 1.01-4.99) doubling-dose lower protection compared with the lower-efficacy agonist salmeterol. In terms of individual responders as change from placebo after the last dose of ICS/LABA, there were 60% of patients with the Arg genotype who had more than 1 doubling-dose decrease in protection with formoterol compared with 18% with salmeterol, whereas in the Gly genotype there were 29% and 11%, respectively.

The results of Cardet et al¹ also suggested that downregulation of airway β_2 -adrenoceptors was not reflected by commensurate changes in PBMCs. This is not consistent with findings in asthmatic patients taking an ICS with formoterol, in whom loss of bronchoprotection and its acute restoration by a 1600- μ g bolus

of budesonide was mirrored by changes seen in PMBC β_2 -adrenoceptor density.³

Hence we believe that it might not be possible to generalize the findings of Cardet et al¹ to different ICS/LABA combinations, such as fluticasone furoate and vilanterol, the latter also being a higher-efficacy β_2 -agonist.⁴

Brian Lipworth, MD

Chris RuiWen Kuo, MBChB

From the Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee, United Kingdom. E-mail: b.j.lipworth@dundee.ac.uk.

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REFERENCES

1. Cardet JC, Jiang X, Lu Q, Gerard N, McIntire K, Boushey HA, et al. Loss of bronchoprotection with ICS+LABA, beta-receptor dynamics, and the effect of alendronate. *J Allergy Clin Immunol* 2019 [Epub ahead of print].
2. Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 beta2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. *Br J Clin Pharmacol* 2004;57:68-75.
3. Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and β_2 -adrenoceptor down-regulation after regular inhaled formoterol. *Chest* 1999;115:623-8.
4. Slack RJ, Barrett VJ, Morrison VS, Sturton RG, Emmons AJ, Ford AJ, et al. In vitro pharmacological characterization of vilanterol, a novel long-acting beta2-adrenoceptor agonist with 24-hour duration of action. *J Pharmacol Exp Ther* 2013;344:218-30.

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