CORRESPONDENCE

Systemic safety of fluticasone furoate/vilanterol combination

The recent article by Busse *et al*[1] on the safety of fluticasone furoate/vilanterol combination (FF/VI) in asthma reported no significant changes in geometric mean 24 h urinary cortisol (24UC) compared with baseline, perhaps giving a false impression that FF is devoid of systemic adverse effects. The interpretation of these data should be put in context of the patients who were already taking inhaled corticosteroids (ICS 500–1000µg/day) and, as such, would have suppressed adrenal function prior to randomisation with FF/VI. This, in turn, makes the possibility for detecting subtle changes in 24UC less likely while taking FF/VI.

An estimated count from inspection of the individual data reveals that after 52 weeks of treatment, there were approximately n=16/143 (11.2%) with FF/VI 100/25 µg and n=16/143 (11.2%) with FF/VI 200/25 µg who had persistently abnormal low values for UC<40 nmol/24 h.[2] Indeed, the observed number of abnormal low values is clinically relevant because it reflects the individual susceptibility to dose-related adrenal suppression.[3 4] Moreover, the presence of a low urinary cortisol value is a strong predictor of an impaired response to dynamic stimulation testing, in turn indicating the possibility of impaired adrenal reserve.[5 6]

The absorption of FF from the lungs is dependent on airway calibre such that one would expect less observed suppression in the present cohort with a mean FEV1 of 74% predicted,[7] as compared with patients with more preserved pulmonary function. The high degree of lipophilicity of FF will result in prolonged systemic retention at steady state, as reflected by a terminal elimination half life of 14 h for the intravenous route, and 17–24 h for the inhaled route.[8] This pharmacokinetic profile would, in turn, predict a propensity for dose-related systemic adverse effects including adrenal suppression. Further carefully conducted trials are indicated to more accurately quantify the degree of dose-related adrenal suppression with FF in asthmatic patients who have previously been washed out of their ICS prior to baseline, as well as using 24UC corrected for creatinine excretion to obviate potential problems with incomplete collections.

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