Efficacy of an inhaled corticosteroid/long-acting β_2-agonist combination in symptomatic COPD patients in GOLD groups B and D

To the Editor:

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 recommendations stratified patients with chronic obstructive pulmonary disease (COPD) into four severity groups (A–D) [1]. However, the clinical trials on which these recommendations were based did not use this patient classification. Within group D, patients may be stratified into subgroups according to the criteria that determine their inclusion: either forced expiratory volume in 1 s (FEV_1), frequency of exacerbations or both [2–4]. These D-subgroups display significantly different treatment outcomes [2]. The current report determined whether budesonide/formoterol prevented exacerbations more effectively than formoterol alone in symptomatic patients with COPD at high and low risk of exacerbations according to GOLD 2011 severity groups D and B [1], respectively, and in the group D subgroups.

This *post hoc* analysis was performed on pooled 3- and 6-month data from three studies of 6 [5] and 12 months' duration [6, 7] that investigated the efficacy of budesonide/formoterol 160/4.5 μg×2 inhalations twice daily (320/9 μg; pressurised metered-dose inhaler) or formoterol 4.5 μg×2 inhalations twice daily (9 μg; dry powder inhaler), in patients with moderate-to-very-severe COPD. Salbutamol (albuterol) was allowed as rescue medication. The analysis included patients who met the criteria for GOLD 2011 groups D and B [1]. Group D patients were further subdivided as proposed by Han *et al* [2]. Patients in subgroup D1 meet FEV_1 criteria (post-bronchodilator FEV_1 <50% predicted) only; those in subgroup D2 meet exacerbation criteria (two or more exacerbations in the previous year) only, *i.e.* patients have post-bronchodilator FEV_1 >50% predicted; and subgroup D3 meets both FEV_1 and exacerbation criteria (post-bronchodilator FEV_1 <50% predicted and two or more exacerbations in the previous year).

Outcomes were: 1) time to first COPD exacerbation; and 2) a composite outcome of time to first COPD exacerbation or study drop-out, whichever came first. COPD exacerbation was defined as worsening of COPD symptoms that required oral corticosteroid treatment and/or hospitalisation, recorded using diary cards [5–7]. Study drop-out was defined as any event resulting in patient withdrawal from the study. Time to first exacerbation or drop-out was the time difference between randomisation and the date of the first COPD exacerbation or drop-out. Both outcomes at 3 and 6 months were analysed using Cox regression analysis for budesonide/formoterol *versus* formoterol in group D and B patients, as well as subgroups D1–D3. Results are expressed as hazard ratios (HR) with 95% confidence intervals.

Overall, 2346 patients met the criteria for GOLD 2011 groups B (n=252) or D (n=2094). Mean±SD age (63.2±9.2 years) and smoking history (47.9±27.2 pack-years) were comparable between groups B and D, but group B contained a higher percentage of females (46.4% *versus* 35.4%). In group D, 1129 patients met the criteria for D1 (FEV_1 only), 156 patients for D2 (exacerbations only) and 809 patients for D3 (FEV_1 and exacerbations). Mean age and smoking history were comparable between subgroups, but subgroup D2 contained patients with a higher mean±SD post-bronchodilator FEV_1 (as expected, based on subgroup criteria; budesonide/formoterol: 55.1±4.1% predicted; formoterol: 56.8±6.4% predicted) and a higher percentage of females than other subgroups.

Fewer budesonide/formoterol-treated patients had one or more exacerbation than formoterol-treated patients in groups D (250 (24%) *versus* 330 (31%)) and B (21 (16%) *versus* 24 (19%)) (table 1). In group D, budesonide/formoterol significantly prolonged time to first exacerbation *versus* formoterol, corresponding to a risk reduction for exacerbation of 41% (HR 0.59, 95% CI 0.48–0.73) and 31% (HR 0.69, 95% CI 0.58–0.81) at 3 and 6 months, respectively (table 1). Budesonide/formoterol also significantly prolonged time to first exacerbation or drop-out *versus* formoterol, corresponding to a risk reduction for exacerbation or drop-out of 41% (HR 0.59, 95% CI 0.50–0.70) and 29% (HR 0.71, 95% CI 0.62–0.82) at

TABLE 1 Primary outcomes for exacerbations at 3 and 6 months in patients with chronic obstructive pulmonary disease who received budesonide/formoterol or formoterol

	Group D[#]		Group B[¶]		Group D subgroups					
					D1[+]		D2[§]		D3[f]	
	BUD/FORM	FORM	BUD/FORM	FORM	BUD/FORM	FORM	BUD/FORM	FORM	BUD/FORM	FORM
Patients n	1044	1050	128	124	564	565	69	87	411	398
Patients with ⩾1 event n (%)										
Time to first exacerbation										
3 months	142 (14)	226 (22)	9 (7)	14 (11)	64 (11)	103 (18)	10 (14)	17 (20)	68 (17)	106 (27)
6 months	250 (24)	330 (31)	21 (16)	24 (19)	117 (21)	154 (27)	13 (19)	24 (28)	120 (29)	152 (38)
Time to first exacerbation or drop-out										
3 months	203 (19)	320 (30)	18 (14)	28 (23)	98 (17)	153 (27)	14 (20)	22 (25)	91 (22)	144 (36)
6 months	364 (35)	461 (44)	35 (27)	46 (37)	177 (31)	229 (41)	23 (32)	32 (37)	163 (40)	199 (50)
Risk reduction % (hazard ratio, 95% CI)[##]										
Time to first exacerbation										
3 months	41 (0.59, 0.48–0.73)		41 (0.59, 0.23–1.36)		41 (0.59, 0.43–0.80)		26 (0.74, 0.34–1.61)		43 (0.57, 0.42–0.77)	
6 months	31 (0.69, 0.58–0.81)		24 (0.76, 0.43–1.37)		31 (0.69, 0.55–0.88)		33 (0.67, 0.34–1.32)		33 (0.67, 0.52–0.85)	
Time to first exacerbation or drop-out										
3 months	41 (0.59, 0.50–0.70)		42 (0.58, 0.32–1.06)		40 (0.60, 0.46–0.77)		20 (0.80, 0.47–1.55)		44 (0.56, 0.43–0.72)	
6 months	29 (0.71, 0.62–0.82)		33 (0.67, 0.43–1.04)		30 (0.70, 0.58–0.85)		11 (0.89, 0.52–1.52)		44 (0.56, 0.43–0.72)	

Group D (high risk of exacerbations): post-bronchodilator (post-BD) forced expiratory volume in 1 s (FEV_1) <50% predicted and/or two or more exacerbations in the previous year, and modified Medical Research Council (mMRC) dyspnoea score of ⩾2. Group B (lower risk of exacerbations): post-BD FEV_1 ⩾50% predicted and one or fewer exacerbations in the previous year, and mMRC score of ⩾2. D1: post-BD FEV_1 <50% predicted. D2: two or more exacerbations in the previous year. D3: post-BD FEV_1 <50% predicted and two or more exacerbations in the previous year. BUD: budesonide; FORM: formoterol. [#]: n=2094; [¶]: n=252; [+]: n=1129; [§]: n=156; [f]: n=809; [##]: hazard ratio and 95% confidence intervals for reductions in time to first exacerbation, and time to first exacerbation or drop-out for BUD/FORM *versus* FORM, as calculated using SAS v9.2 (SAS Institute Inc., Cary, NC, USA).

3 and 6 months, respectively (table 1). Both outcomes favoured budesonide/formoterol and HRs were greater at 3 months, but remained significant at 6 months.

In group B, comparable HRs to Group D were observed for both outcomes, which resulted in comparable risk reductions (table 1). However, the absolute number of events was much smaller in group B and risk reductions did not reach statistical significance for either outcome at 3 or 6 months (table 1).

Fewer budesonide/formoterol-treated patients had one or more exacerbations than formoterol-treated patients in subgroups D1–D3 (table 1). In subgroups D1 and D3, budesonide/formoterol significantly prolonged time to first exacerbation, and time to first exacerbation or drop-out, at 3 and 6 months compared with formoterol. Risk reductions for both outcomes in the D1 and D3 subgroups were similar to those in group D overall (table 1). In subgroups D1 and D3, HRs favoured budesonide/formoterol and were generally larger for both outcomes at 3 months, but remained significant at 6 months. In subgroup D2, risk reductions did not reach statistical significance at 3 or 6 months, and were generally smaller than those seen in groups B and D and the other subgroups (*i.e.* there was less benefit in patients with frequent exacerbations but better lung function).

The data presented here address a recent call for evidence by the *European Respiratory Journal* about treatment efficacy within the new GOLD categories [8]. Our analysis is the first publication exploring the efficacy of inhaled corticosteroid/long-acting β_2-agonist combinations in symptomatic patients with COPD defined by the GOLD 2011 severity grading and supports the current recommendations [1]. Budesonide/formoterol significantly prolonged time to first exacerbation, and time to first exacerbation or drop-out, *versus* formoterol in patients at high risk of exacerbations, *i.e.* group D and both group D subgroups with post-bronchodilator FEV_1 <50% predicted (D1 and D3). Statistical significance was not reached in subgroup D2, *i.e.* in patients allocated using exacerbation history alone and who had better baseline lung function. This observation requires further elucidation in prospective studies focussed on a larger D2 patient population to establish whether this finding is due to marked heterogeneity in treatment response or small patient numbers.

Differences in both outcomes were not statistically significant in group B patients, who at run-in had mean post-bronchodilator FEV_1 values in the range of 50–80% predicted. This was a smaller group and further analyses are required to assess the efficacy of budesonide/formoterol on exacerbations in patients with less severe airflow obstruction.

This analysis has some limitations. Our studies recruited patients with a modified Medical Research Council dyspnoea score of ⩾2, which limited our analysis to GOLD groups B and D. Furthermore, our criteria restricted the analyses of group B and subgroup D1 to patients with a single exacerbation within the previous year; however, the frequent exacerbator patient cohort is of particular interest when making treatment decisions and our data suggest greater benefit with budesonide/formoterol than formoterol in patients at high risk of exacerbations.

In conclusion, combination budesonide/formoterol significantly prolonged time to first exacerbation or drop-out compared with formoterol alone in COPD patients defined as GOLD 2011 group D and D subgroups with post-bronchodilator FEV_1 <50% predicted (D1 and D3). This observation suggests that the inclusion of budesonide had an additional benefit to formoterol alone and is consistent with the GOLD 2011 treatment recommendations even when the patient categorisation is changed. Differences in time to first exacerbation or drop-out favoured budesonide/formoterol in group B and subgroup D2 patients but did not reach statistical significance. Further trials are needed to inform future treatment recommendations using the revised GOLD classifications.

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Budesonide/formoterol reduced exacerbation risk *versus* formoterol alone in patients with GOLD 2011 group D COPD http://ow.ly/LRtis

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Occupational exposures and fluorescent oxidation products in 723 adults of the EGEA study

To the Editor:

Occupational asthma can be induced by a variety of agents, including high and low molecular weight sensitisers, and respiratory irritants [1]. The role of exposure to cleaning products and disinfectants in work-related asthma is increasingly recognised, although the specific substances that increase asthma risk are not well identified [2]. Some of the numerous agents contained in these products are chemical sensitisers, but most are hypothesised to act as respiratory irritants [2]. While high molecular weight sensitisers are known to cause occupational asthma through a typical allergic response, the pathophysiological mechanisms involved in occupational asthma induced by low molecular weight (LMW) chemicals, and in irritant-induced asthma, remain poorly understood [1, 3, 4].

Oxidative stress is one of the potential mechanisms causing epithelial injury, which may be especially relevant in irritant-induced asthma [1, 4]. In this context, we sought to investigate the associations between occupational exposure to potentially asthmogenic chemicals and irritants, and the level of fluorescent oxidation products, a global marker of damage due to oxidative stress [5], in adults from the Epidemiological study on the Genetics and Environment of Asthma (EGEA).

The French EGEA combines a case–control and family-based study [6]. The baseline study (EGEA1; 1991–1995, n=2047) included cases with asthma, their first degree relatives, and population-based controls. The study protocol was approved by the relevant institutional review board committees (Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris, France) and all participants gave written informed consent. The current analysis used data from the follow-up study (EGEA2; 2003–2007) and included only adults who had never had asthma (n=888), in order to distinguish occupational exposures from the oxidative stress generated by the disease. 723 participants (328 men and 395 women) had fluorescent