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The relationship between COPD severity, inhaled corticosteroid use and the risk of pneumonia

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Abbreviations List

COPD – chronic obstructive pulmonary disease

FEV₁ – forced expiratory volume in 1 second

GOLD – Global Initiative for Chronic Obstructive Lung Disease

ICS – inhaled corticosteroids

To the Editor:

The use of inhaled corticosteroids (ICS) has been associated with an increased risk of pneumonia when administered to patients with chronic obstructive pulmonary disease (COPD).^{1,2} However, there is evidence to suggest that the risk of pneumonia may vary depending on which ICS is prescribed.³ A meta-analysis of seven studies compared inhaled budesonide, administered with or without the long-acting β_2 -agonist, formoterol, with a non-ICS control and did not find an increased risk of pneumonia in patients with COPD treated with budesonide.⁴ Pneumonia becomes more common as airflow obstruction worsens⁵ and any treatment-related increase in the risk of pneumonia should be most evident in patients with the worst airflow obstruction.¹ In this analysis we determined the relationship of budesonide to incident pneumonia according to the severity of airflow limitation in patients with COPD.

Methods. As previously described,⁴ seven studies of inhaled budesonide, with or without formoterol, versus a non-ICS control regimen (formoterol or placebo) in patients with stable COPD and at least 6 months of follow-up were identified. Results of an eighth trial that fulfilled the inclusion criteria were also included in this current pooled analysis.⁶ Duration of treatment ranged from 6 to 36 months in patients with mild-to-very-severe COPD. The analysis was right censored to 12 months since only two trials were of longer duration. In three of the eight studies, patients received either budesonide (640–1280 $\mu\text{g}/\text{day}$) or placebo. In the remaining five studies, patients received either budesonide/formoterol (320/18 or 640/18 $\mu\text{g}/\text{day}$), budesonide (640 $\mu\text{g}/\text{day}$), formoterol (18 $\mu\text{g}/\text{day}$) or placebo.

Pneumonia adverse events or serious adverse events, which started either during, or within 15 days of completion of, randomised treatment, were recorded. For the purposes of this analysis, pneumonia adverse events were identified as any adverse event coded to the MedDRA (version 9) preferred terms “Pneumonia”, “Bronchopneumonia”, “Lobar pneumonia”, “Lung infection”, “Pneumonia staphylococcal” or “Pneumonia pneumococcal”. A serious adverse event was defined as an adverse event that resulted in death or hospitalization. Patients who experienced more than one adverse event were counted only once.

Pneumonia risk was stratified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade (grade 1: mild, post-bronchodilator forced expiratory volume in 1 second [FEV₁] ≥80% predicted; grade 2: moderate, FEV₁ ≥50% to <80% predicted; grade 3: severe, FEV₁ ≥30% to <50% predicted; grade 4: very severe, FEV₁ <30% predicted),⁷ for patients receiving budesonide versus non-ICS control (formoterol or placebo). Patients who received budesonide/formoterol were included within the budesonide treatment group. Overall relative risk was calculated using a Mantel-Haenszel approach, stratified by study and adjusted for treatment exposure. Results were expressed as the pooled Mantel-Haenszel relative risk and 95% confidence intervals (CIs).

Results. Data were available for 8260 patients; 4616 patients who received inhaled budesonide (3394 patient-years of exposure) and 3644 patients who received non-ICS control (2646 patient-years of exposure). Mean (± standard deviation) age of participants was 62±10 years and mean (± standard deviation) post-bronchodilator FEV₁ was 49±18% predicted; 69% of patients were male and 49% were current smokers at enrolment. Overall,

34% of patients (n=2825) were classified as GOLD grade 1 or 2, 48% (n=3987) GOLD grade 3, and 17% (n=1426) GOLD grade 4. GOLD grade was not available for 12 patients who received budesonide and 10 patients who received non-ICS control; however, no pneumonia events were reported in these patients.

The incidence of pneumonia increased with increasing severity of airflow limitation for patients who received budesonide or a non-ICS control, in terms of both pneumonia AEs per 100 treatment-years and pneumonia serious adverse events per 100 treatment-years (Table 1). No statistically significant difference in the risk of pneumonia with budesonide or non-ICS control was observed in the total population or in any severity subgroup (Figure 1, Table 1). The overall relative risk for pneumonia adverse events and serious adverse events was 1.12 (95% CI: 0.89, 1.42) and 1.01 (95% CI: 0.72, 1.42), respectively.

This analysis evaluated whether there was any effect of COPD severity on pneumonia risk from budesonide. Pneumonia assessed as either an adverse event or serious adverse event increased with increasing severity of COPD. While there were numerical differences for pneumonia reported as an adverse risk, risk of pneumonia was not significantly different in patients treated with either budesonide, with or without formoterol, or a non-ICS control across all COPD severities. This is consistent with the findings of the aforementioned meta-analysis, which included data from seven of the eight studies investigated here.⁴ Other inhaled glucocorticoids have been associated with increased risk of pneumonia that increases with GOLD grade.⁸ Why budesonide differs is unknown; however, a database study suggests that the risk of pneumonia in COPD patients is related to the relative effective dose of administered ICS.³

Our results have a number of limitations. Firstly, the analysis was stratified by the GOLD spirometric classification of airflow limitation only (post-bronchodilator FEV₁ ≥50% versus ≥30% to <50% versus <30% predicted), which is only one dimension of the GOLD severity grade. Other measures of COPD severity include symptoms, exacerbation history, presence and extent of emphysema, presence of chronic bronchitis, hypoxemia, functional status and associated co-morbidities, none of which were assessed in the current analysis.⁹ Secondly, the eight studies investigated were not specifically powered to detect pneumonia. Thirdly, pneumonia was identified as an adverse event or a serious adverse event from reports submitted by investigators; however, these events were not systematically validated. Fourthly, our analysis censored patient data at 12 months despite data being available from studies extending up to three years. Therefore, the long-term effects of inhaled budesonide (>12 months) on the risk of pneumonia were not assessed.

In conclusion, the current analysis extends the previous evaluation assessing pneumonia risk in COPD patients. An overall increased risk for pneumonia with COPD severity assessed by FEV₁ was demonstrated. However, for each GOLD severity group, no difference in pneumonia risk was demonstrated with budesonide treatment.

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Table

Table 1

Pneumonia as AEs and SAEs per 100 treatment years and relative risk for pneumonia AEs and SAEs in patients who received budesonide versus non-ICS control

GOLD grade	Budesonide				Non-ICS				Relative risk (95% CI) ^a	
	N	Treatment years	Pneumonia AE per 100 treatment years	Pneumonia SAE per 100 treatment years	N	Treatment years	Pneumonia AE per 100 treatment years	Pneumonia SAE per 100 treatment years	Pneumonia AEs for budesonide vs non-ICS	Pneumonia SAEs for budesonide vs non-ICS
N/A ^b	12	7	-	-	10	3	-	-	-	-
GOLD 1+2	1499	1218	4.3	1.1	1326	1085	3.4	1.0	1.19 (0.77, 1.83)	0.92 (0.42, 2.06)
GOLD 3	2277	1630	5.6	2.6	1710	1192	5.2	2.6	1.06 (0.76, 1.48)	1.03 (0.64, 1.67)
GOLD 4	828	540	6.7	4.8	598	365	5.8	4.7	1.12 (0.65, 1.92)	0.95 (0.51, 1.78)
All patients	4616	3395	5.3	2.4	3644	2645	4.5	2.2	1.12 (0.89, 1.42)	1.01 (0.72, 1.42)

^aRelative risk and exact confidence intervals for pneumonia events (budesonide vs non-ICS) as calculated using StatXact 8.0.0 (Cytel® Inc, Cambridge, USA).

^bGOLD grade was not available for 12 patients who received budesonide and 10 patients who received non-ICS control; no pneumonia events were reported in these patients.

Figure Legend

Pneumonia reported as adverse events (Panel A) or Serious adverse events (Panel B) for subjects treated with budesonide (blue) or placebo (red) separated by GOLD Spirometry Severity. No differences for budesonide vs non-ICS reached statistical significance. See Table 1 for confidence intervals.

Figure 1

