Budesonide and the risk of pneumonia: a meta-analysis of individual patient data

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Summary

Background Concern is continuing about increased risk of pneumonia in patients with chronic obstructive pulmonary disease (COPD) who use inhaled corticosteroids. We aimed to establish the effects of inhaled budesonide on the risk of pneumonia in such patients.

Methods We pooled patient data from seven large clinical trials of inhaled budesonide (320–1280 µg/day), with or without formoterol, versus control regimen (placebo or formoterol alone) in patients with stable COPD and at least 6 months of follow-up. The primary analysis compared treatment groups for the risk of pneumonia as an adverse event or serious adverse event during the trial or within 15 days of the trial end. Cox proportional hazards regression was used to analyse the data on an intention-to-treat basis. Data were adjusted for patients' age, sex, smoking status, body-mass index, and postbronchodilator percent of predicted forced expiratory volume in 1 s (FEV_1).

Findings We analysed data from 7042 patients, of whom 3801 were on inhaled budesonide and 3241 were on control treatment, with 5212 patient-years of exposure to treatment. We recorded no significant difference between treatment groups for the occurrence of pneumonia as an adverse event (3% [n=122 patients] *vs* 3% [n=103]; adjusted hazard ratio 1·05, 95% CI 0·81–1·37) or a serious adverse event (1% [n=53] *vs* 2% [n=50]; 0·92, 0·62–1·35), or for time to pneumonia as an adverse event (log-rank test 0·94) or a serious adverse event (0·61). Increasing age and decreasing percent of predicted FEV_1 were the only two variables that were significantly associated with occurrence of pneumonia as an adverse event or a serious adverse event.

Interpretation Budesonide treatment for 12 months does not increase the risk of pneumonia in patients with COPD during that time and therefore is safe for clinical use in such patients.

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Introduction

Inhaled corticosteroids, given with and without longacting β_2 agonists, reduce the occurrence of disease exacerbation and improve quality of life for patients with chronic obstructive pulmonary disease (COPD), but they have also been associated with increased risk of pneumonia.[1] Results from the largest clinical trial so far showed that inhaled corticosteroids increase the risk of pneumonia by nearly 50%.[1] In an observational study of a large health database, Ernst and colleagues[2] reported a 70% increase in the risk of hospital admission for pneumonia in patients who used inhaled corticosteroids. Findings from a meta-analysis indicated that on average, inhaled corticosteroids raised the risk of pneumonia by 34%;[3] however, results differed widely between studies with some trials reporting increased risk,[1,4] whereas others reported reduced risk.[5,6] The excess risk seemed to be mainly restricted to patients who received doses of inhaled corticosteroids exceeding 1000 µg/day beclometasone or equivalent.[3]

Although these data are striking, several important limitations have affected this meta-analysis and previous meta-analyses.[3,7,8] First, the trials included in the meta-analyses were heterogeneous in terms of study drug and duration, which will probably have contributed to the large variability in results. Indeed in one meta-analysis, use of a random-effects model to correct for heterogeneity across studies yielded a confidence interval that included the possibility of no difference.[7] Second, none of the previous meta-analyses had access to data about patient characteristics and thus could not adequately adjust for potential confounders such as age, lung function, or other clinical features. Third, the previous analyses largely focused on any pneumonia event documented as an adverse event. However, the diagnostic accuracy of this endpoint is uncertain since many events were not validated with established criteria for pneumonia, including an opacity on chest radiographs.[7] Moreover, many such events are not associated with significant morbidity or mortality.[9] Conversely, hospital admissions for pneumonia are usually better documented with imaging studies and laboratory investigations, and are associated with substantial morbidity and mortality.[10,11] Since all hospital admissions due to pneumonia will be reported as serious adverse events, pneumonia as a serious adverse event might be a more accurate and clinically relevant endpoint.

To address these limitations, we pooled data for patient characteristics and results from seven large clinical trials of inhaled budesonide to establish the effects of treatment on the risk of any adverse and serious adverse events of pneumonia in patients with COPD.

Panel: **Countries studied**

Szafranski et al (2003)[12]
Argentina, Brazil, Denmark, Finland, Italy, Mexico, Poland, Portugal, South Africa, Spain, and UK

Calverley et al (2003)[13]
Belgium, Brazil, China, France, Greece, Hungary, Malaysia, Norway, Poland, Portugal, South Africa, Sweden, Taiwan, Thailand, and UK

Rennard et al (2009)[14]
Bulgaria, Denmark, Germany, Greece, Hungary, Iceland, Mexico, Romania, and USA

Tashkin et al (2008)[15]
Czech Republic, Netherlands, Poland, South Africa, and USA

Bourbeau et al (1998)[16]
Canada

Pauwels et al (1999)[17]
Belgium, Denmark, Finland, Italy, Netherlands, Norway, Spain, Sweden, and UK

Vestbo et al (1999)[6]
Denmark

Methods

Data sources, search strategy, and study selection

US and AT searched Medline, EmBase, and an internal AstraZeneca product database of published studies, Planet, for randomised controlled trials of inhaled budesonide, with or without the longacting β_2 agonist formoterol, compared with a control regimen (placebo or formoterol alone) for patients with COPD. We searched using the seach term "COPD" in combination with "budesonide", "Pulmicort", "budesonide and formoterol", "Symbicort", "placebo", "formoterol", "Oxis", or "Foradil". No language or publication date restrictions were placed on the searches. COPD was defined as either a clinical diagnosis of COPD, or a current or former smoker (≥10 pack-year smoking history) with a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of less than 0·7 from postbronchodilator spirometry. Full details of the search strategy are in webappendix pp 1–2. We restricted the search to studies with follow-up of at least 6 months because the overall risk of pneumonia would be very small and the confounding effects of seasonal variation in the occurrence of pneumonia would have been difficult to account for in trials of shorter duration.[8]

See Online for webappendix

We identified seven studies[6,12–17] that were suitable for inclusion in the meta-analysis (webappendix p 3). More than 30 countries had been investigated in the studies, of which 29 contributed to patient recruitment (panel). All these studies were of high quality (Jadad score ≥4)[18] and were listed in the AstraZeneca clinical trials database of individual patient records. AstraZeneca sent anonymous patient data from these trials to the University of British Columbia, Vancouver, BC, Canada, for analysis. The primary analysis on pneumonia was right censored to 12 months since only two trials[6,17] were of longer duration. All trials fulfilled our inclusion criteria, except for Vestbo and colleagues' study,[6] which did not include the criterion that patients had to have at least 10 pack-years smoking history. Participants in all trials were: stable at the time of enrolment, masked to random assignment to a treatment group (double-blind), and seen by study investigators at least every 3 months. At each visit, patient-reported pneumonia information was identified by study personnel and

	Inhaled budesonide dose (μg/day)	Patients	Age (years)	Men	Current smoker	FEV_1 (L)*	FEV_1 (% of predicted)*†	Pneumonia	Follow-up (days)	Duration of total exposure (patient-years)‡
Szafranski et al (2003)[12]	640	812	64·2 (8·9)	641 (79%)	280 (34%)	0·99 (0·31)	36% (10)	34 (4%)	290 (119)	645
Calverley et al (2003)[13]	640	1022	64·0 (9·0)	770 (75%)	353 (35%)	0·99 (0·33)	36% (10)	24 (2%)	268 (135)	750
Rennard et al (2009)[14]	640 or 320	1964	63·2 (9·1)	1255 (64%)	834 (42%)	1·04 (0·35)	37% (10)	82 (4%)	295 (119)	1587
Tashkin et al (2008)[15]	640 or 320	1704	63·4 (9·1)	1161 (68%)	724 (42%)	1·06 (0·36)	37% (10)	35 (2%)	176 (49)	822
Bourbeau et al (1998)[16]	1280	75	65·4 (7·8)	58 (77%)	30 (40%)	0·97 (0·33)	38% (11)	6 (8%)	290 (105)	60
Pauwels et al (1999)[17]†	640	1175	52·6 (7·6)	854 (73%)	1175 (100%)	2·56 (0·66)	78% (14)	22 (2%)	339 (74)	1091
Vestbo et al (1999)[6]†	640	290	59·1 (9·0)	175 (60%)	221 (76%)	2·38 (0·82)	80% (19)	22 (8%)	324 (94)	257
Total	NA	7042	62·0 (10·0)	4914 (70%)	3617 (51%)	1·34 (0·75)	46% (20)	225 (3%)	270 (116)	5212

Data are number (%) or mean (SD), unless otherwise indicated. For continuous variables, an arithmetic mean was calculated with individual patient data from every trial. FEV_1=forced expiratory volume in 1 s. NA=not applicable. *Postbronchodilator values. †Truncated to 365 days of follow-up for this analysis. ‡Number of patients on each treatment multiplied by the number of years on treatment.

Table 1: **Baseline characteristics and follow-up of participants**

	Inhaled budesonide	Control (placebo or formoterol)
Patients	3801	3241
Age (years)	61·8 (9·6)	61·3 (9·9)
Men	2641 (69%)	2273 (70%)
Body-mass index (kg/m²)	26 (5)	26 (5)
Current smoker	1917 (50%)	1700 (52%)
Postbronchodilator FEV_1 (% of predicted)	45% (20)	46% (21)
Follow-up (days)	254 (235)	240 (218)
Duration of total exposure (person-years)*	2817	2397

Data are number (%) or mean (SD), unless otherwise indicated. Data are at baseline unless otherwise indicated. For continuous variables, an arithmetic mean was calculated with individual patient data from every trial. FEV_1=forced expiratory volume in 1 s. *Number of patients on each treatment multiplied by the number of years on treatment.

Table 2: **Variables included in primary analysis**

recorded in the trial databases as an adverse event or serious adverse event.

Definition of adverse and serious adverse events

An adverse event was defined as development of an undesirable disorder or deterioration of a pre-existing disorder, irrespective of severity, and was assessed by study investigators. A serious adverse event was defined as an adverse event that resulted in death or hospital admission, or fulfilled any other criteria described in webappendix p 4. These definitions, which are independent of drug treatment, were used previously in the TORCH[1] and UPLIFT[19] trials. The term adverse event included all adverse events that were and were not judged to be serious.

For **MedDRA** see http://www.meddramsso.com/MSSOWeb/index.htm

Cases of pneumonia were identified by searching for predefined adverse event terms from MedDRA (version 9.0; webappendix p 5); most frequently reported terms were "pneumonia" and "bronchopneumonia". For the primary analysis, we chose any adverse events that occurred during the trial and within 15 days of the trial end. The cutoff of 15 days was based on several factors including: (1) the duration of the pharmacodynamic effects of glucocorticoids, especially with respect to the regulation of transcription factors participating in pro-inflammatory or anti-inflammatory pathways, or both; (2) the natural history of bacterial pneumonia associated with immunosuppressive drugs; and (3) our intent to make our analysis comparable to previous studies.[1,3,8] We used the same principle for primary analysis of serious adverse events.

For more on **R software** see http://cran.r-project.org

Across the trials, we recorded some heterogeneity in the method by which adverse events and serious adverse events were gathered during the period after treatment (webappendix pp 6–7). As a sensitivity analysis, we assessed: (1) any adverse events and serious adverse events occurring during the treatment phase of the trial, thus censoring all events occurring after the patient withdrew or finished the study; and (2) any adverse events and serious adverse events occurring during the treatment phase of the trial and up to 2 months after the study end, at the discretion of the reporting investigator. We also analysed the full pneumonia data without right censoring at 12 months.

Statistical analysis

For the primary analysis, we compared the risk of pneumonia as an adverse event or serious adverse event between patients who were assigned to inhaled budesonide and control regimens. We based our analysis on the original allocation of participants in the individual trials (ie, intention to treat), irrespective of whether they did or did not have complete follow-up. Patients who were not given inhaled budesonide were regarded as the control group. Participants in each trial were followed up from the date of enrolment to the date of withdrawal, pneumonia event, or study completion, whichever came first.

We generated Kaplan-Meier curves to compare the time to pneumonia as an adverse event or serious adverse event between the steroid and non-steroid groups; a log-rank statistic was used to calculate the difference between the curves. We used Cox proportional hazards regression to estimate the effect of inhaled budesonide on pneumonia as an adverse event or serious adverse event, adjusted for potential confounding variables. These variables were baseline data of participants' age (in quintiles), sex, postbronchodilator percent of predicted FEV_1 (in quintiles), smoking status, and body-mass index (in quintiles). We checked for the proportional hazards assumption visually, and added a time-interaction term to the model and the assumption was met (p=0·13).

In the adjusted model, we stratified by individual trials to allow hazard functions to differ for each trial. The model also controlled for the same confounding variables adjusted for in the risk analysis of adverse and serious adverse events. With these data, we also established clinical risk factors for pneumonia as an adverse event or serious adverse event using a Cox regression model. We used a χ^2 test to compare the difference in reporting of adverse and serious adverse events between countries with data from studies by Szfranski,[12] Rennard,[14] and Pauwels,[17] and their colleagues. Statistical significance was defined as a p value of less than 0·05 (two-tailed). All statistical tests were done with R 2.8 software.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the baseline characteristics and follow-up of participants in the seven trials. We analysed data from more than 7000 participants who had more than 5000 patient-years of exposure. Table 2 shows the overall

	Patients on inhaled budesonide	Patients on control	Adverse event		Serious adverse event		Duration of total exposure (person-years)	
			Inhaled budesonide	Control	Inhaled budesonide	Control	Inhaled budesonide	Control
Szafranski et al (2003)[12]	406	406	19 (5%)	15 (4%)	8 (2%)	10 (2%)	333	312
Calverley et al (2003)[13]	511	511	15 (3%)	9 (2%)	9 (2%)	7 (1%)	395	356
Rennard et al (2009)[14]	988	976	39 (4%)	43 (4%)	16 (2%)	21 (2%)	827	759
Tashkin et al (2008)[15]	1120	584	24 (2%)	11 (2%)	12 (1%)	6 (1%)	553	270
Bourbeau et al (1998)[16]	38	37	2 (5%)	4 (11%)	2 (5%)	4 (11%)	32	28
Pauwels et al (1999)[17]	593	582	15 (3%)	7 (1%)	6 (1%)	1 (<1%)	547	545
Vestbo et al (1999)[6]	145	145	8 (6%)	14 (10%)	0	1 (1%)	130	127
Total	3801	3241	122 (3%)	103 (3%)	53 (1%)	50 (2%)	2817	2397

Data are number (%), unless otherwise indicated.

Table 3: **Occurrence of pneumonia as an adverse event or serious adverse event**

baseline characteristics of participants, which were included in the primary analysis. Mean age of participants was 61·6 years (SD 9·7), and mean postbronchodilator FEV_1 was 45·5% (20·2) of predicted. Overall, 22% (n=1523 patients) of the cohort were in the Global initiative for chronic Obstructive Lung Disease (GOLD)[20] stage IV (FEV_1 <30% of predicted), 52% (n=3635) were in GOLD stage III (FEV_1 30–49% of predicted), 16% (n=1148) were in GOLD stage II (FEV_1 50–79% of predicted), and 10% (n=732) were in GOLD stage I (FEV_1 ≥80% of predicted); for four patients, FEV_1 data were missing and therefore GOLD status could not be established. 70% (n=4914) of participants were men, and 51% (n=3617) were current smokers at enrolment.

In the primary analysis, 225 (3%) participants developed pneumonia as an adverse event and 103 (1%) as a serious adverse event during follow-up (table 3). All patients who had serious adverse events were admitted to hospital and all deaths due to pneumonia occurred in hospital. Risk of pneumonia had some seasonal variation with peaks during February–April and October–November (webappendix p 8). Patients who had pneumonia as an adverse event or serious adverse event, compared with those who did not, were older (63·2 years [SD 9·7] *vs* 61·5 years [9·9], p=0·014) and had lower postbronchodilator FEV_1 (43·0% [18·6] of predicted *vs* 45·6% [20·3], p=0·043) at randomisation.

Occurrence of pneumonia as an adverse event or serious adverse event was similar for patients assigned to inhaled budesonide and control treatment in the primary analysis (table 3) and for the full duration of the study (webappendix p 9). Figure 1 shows Kaplan-Meier curves for time to pneumonia as an adverse event or serious adverse event, which was not significantly different between treatment groups (log-rank test 0·94 for adverse event, 0·61 for serious adverse event). Compared with the control group, participants assigned to inhaled budesonide had a similar risk of pneumonia as an adverse event (figure 2A; p=0·71) and serious adverse event (figure 2B; p=0·66). 3% (51/1880) of patients with mild or moderate COPD (GOLD stages I and II) and 3% (174/5158) of those with severe COPD (GOLD stages III and IV) had pneumonia as an adverse event; severity of COPD was not significantly associated with pneumonia as an adverse event (p=0·19). Conversely, the occurrence of pneumonia as a serious adverse event was higher for patients with severe COPD (2% [90/5158]) than for those with mild or moderate COPD (1% [13/1880]; p=0·0017). No difference was recorded in the number of patients with more than one occurrence of pneumonia as an adverse event between treatment groups (11 [<1%] patients in each group). Only two individuals, both in the inhaled budesonide group, had more than one occurrence of pneumonia as a serious adverse event. Only two variables were significantly associated with the occurrence of pneumonia as an adverse event or serious adverse event: increasing age and decreasing percent of predicted FEV_1 (table 4; webappendix pp 10–11).

In the sensitivity analysis, we used different case definitions of pneumonia as an adverse event or serious adverse event (webappendix pp 6–7), but results were not affected. For the treatment phase of the trial, the hazard ratio was 1·01 (95% CI 0·77–1·33, p=0·92) for pneumonia as an adverse event, and 0·86 (0·57–1·31, p=0·49) for pneumonia as a serious adverse event. For the treatment phase of the trial and up to 2 months after the trial end, the hazard ratio was 1·06 (0·82–1·36, p=0·69) for pneumonia as an adverse event and 0·87 (0·60–1·27, p=0·47) for pneumonia as a serious adverse event.

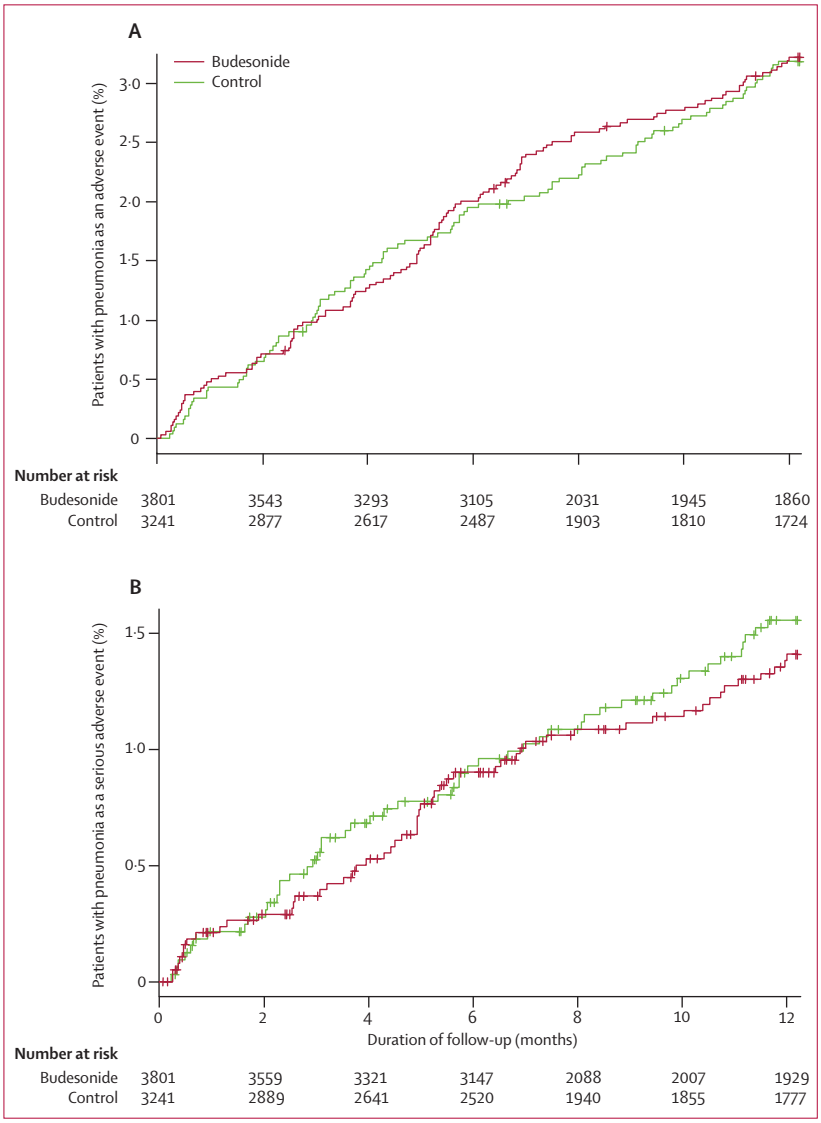

Figure 1: **Kaplan-Meier estimate of risk of pneumonia as an (A) adverse event or (B) serious adverse event between patients given inhaled budesonide or control treatment (formoterol or placebo)**

The proportion of patients who withdrew from study treatment for any reason was higher for the control group than for the inhaled budesonide group (30% [n=961] *vs* 23% [n=877]). Overall, seven patients died from pneumonia (four in the inhaled budesonide and three in the control groups). Additional sensitivity analyses to assess robustness showed that the results were very similar to those of the primary analysis (webappendix p 12–13).

We examined possible differences in the reporting of pneumonia as an adverse event or serious adverse event in the countries investigated in each of the seven trials. Significant heterogeneity was recorded in Denmark only, with up to eight times higher reporting of pneumonia as an adverse event than in all other countries combined. Three of the multinational studies had Danish centres and results showed that the proportion of patients with pneumonia as an adverse event compared with other countries included in these studies (panel) was 11% (12/108) versus 3% (22/704),[12] 22% (21/94) versus 3% (61/1870),[14] and 10% (11/109) versus 1% (11/1066).[17] Collectively, the proportion of patients with pneumonia as an adverse event was about five times higher in Denmark than in the other countries studied (14% [44/311] *vs* 3% [94/3640]; p<0·0001), but no significant differences were shown for the reporting of pneumonia as a serious adverse event (2% [7/311] *vs* 2% [55/3640]; p=0·92).

Discussion

In our study we have shown that budesonide, with or without a longacting β_2 agonist, is not associated with increased risk of pneumonia reported as an adverse event or a serious adverse event. Adjustments for potential confounders such as age, baseline lung function, and smoking status did not affect overall results related to both treatment selection and outcome. Overall, the 1-year risk of pneumonia as an adverse event was low in both treatment groups at about 3%, which is consistent with other published large-scale COPD trials (TORCH[1] and UPLIFT[19]), and exceeds occurrence of pneumonia in patients without COPD by more than ten times (eg, 0·3% in trials of esomeprazole[21]).

These results differ from the meta-analyses of Drummond[3] and Singh,[8] and their colleagues, both of whom reported increased risk of pneumonia as an adverse event and a serious adverse event in patients with COPD on inhaled corticosteroids compared with those on either placebo or longacting β_2 agonists. Although the exact reasons for the discordance in these findings are unknown, several potential explanations exist. First, neither meta-analysis had access to data about patient characteristics and thus could not adequately assess or adjust for potential confounders. Moreover, differential drop-out rates or follow-up periods within and across studies were not adequately adjusted for. Second, these meta-analyses pooled all published randomised controlled trials of inhaled corticosteroids, which were heavily weighted with studies of fluticasone and could not account for possible differences between steroid compounds.

All glucocorticoids act by binding to the same glucocorticoid receptor, but each has its own unique pharmacokinetic properties, which could cause differential clinical effects.[22] Budesonide, for example, is more rapidly cleared from airways than is fluticasone. This difference in clearance might be magnified in individuals with extensive airflow obstruction, leading to increased accumulation of drug particles in central airways and reduced absorbance by peripheral tissues.[23] Therefore, budesonide might be removed from the lungs before it substantially downregulates local immunity and allows proliferation of bacteria, which is advantageous since bacteria are chronically present in the airways of 30–50% of patients with moderate-to-severe COPD.[24]

Moreover, compared with fluticasone, budesonide might be less effective (at least in vitro) in suppressing pro-inflammatory cytokine production by alveolar macrophages and airway epithelial cells in response to lipopolysaccharide stimulation.[25]

Drummond and colleagues[3] suggested that the risk of pneumonia could be dose-dependent; therefore, a decreased glucocorticoid dose could have mitigated the risk of pneumonia in patients receiving budesonide. However, two studies that used reduced doses of fluticasone (500 µg/day instead of 1000 µg/day) reported increased risk of pneumonia, which contradicts this hypothesis.[26,27] Future research should clarify the mechanisms by which inhaled corticosteroids contribute to pneumonia, and how the risk is modified by differences in dosing and pharmacokinetics. Although fluticasone has been associated with increased risk of pneumonia as an adverse and serious adverse event, none of the studies has associated inhaled corticosteroids with increased mortality from pneumonia. Consistently, we did not find any differences in risk of mortality from pneumonia between budesonide and control groups.

We noted that the two most important clinical determinants of pneumonia as an adverse event or serious adverse event were increasing age and reduced lung function, whereas sex, current smoking status, and body-mass index were not significantly associated. We recorded increased reporting of pneumonia as an adverse event but not as a serious adverse event in Denmark. In UPLIFT,[19] the reporting of pneumonia as an adverse event was three times higher in Denmark than in other countries studied (36% *vs* 12%; Argentina, Australia, Austria, Belgium, Brazil, Czech Republic, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, Slovakia, Slovenia, South Africa, Spain, Switzerland, Taiwan, Thailand, Turkey, UK, and USA; Kesten S, Boehringer Ingelheim, personal communication). Findings from two large asthma studies of 7221[28] and 17 862[29] participants similarly reported four times more pneumonia adverse events in Danish centres than in other countries studied (10·3% *vs* 2·7% over 3 years,[28] 4·0% *vs* 1·0% over 6 months;[29] collectively Argentina, Australia, Austria, Belgium, Canada, China, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Indonesia, Israel, Italy, Latvia, Malaysia, Malta, Mexico, Netherlands, Norway, Philippines, Poland, Portugal, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, UK, and USA; Radner F, unpublished data). This discordance could be due to the absence of specificity for identifying pneumonia in Danish—"lungebetennelse" might also encompass bronchitis—which underscores the importance of objective confirmation of diagnosis with imaging and laboratory studies. In future studies of COPD, local language and other regional factors should be considered in the reporting of pneumonia as an adverse and serious adverse event.

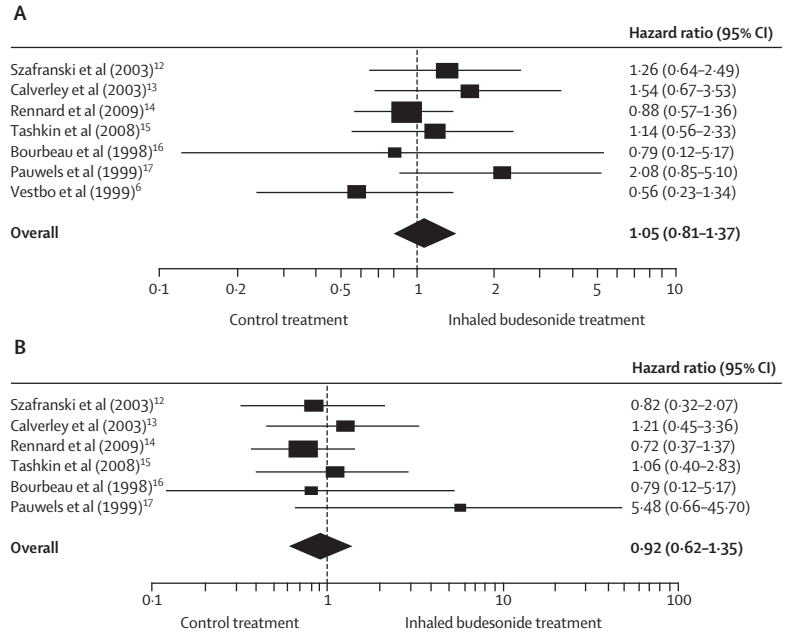

Figure 2: **Adjusted risk of pneumonia as an (A) adverse event or (B) serious adverse event***

Data adjusted for age, sex, smoking status, body-mass index, and percent of predicted FEV_1. *Vestbo and colleagues' study[6] had no reported serious adverse events of pneumonia in the inhaled budesonide group, and one in the control group resulting in an infinitely low hazard ratio and undefined 95% CI.

	Adverse event	p value	Serious adverse event	p value
Age (years)*	1·01 (1·00–1·03)	0·070	1·04 (1·02–1·07)	0·001
Men	0·79 (0·60–1·05)	0·11	0·73 (0·48–1·12)	0·15
Current smokers	0·97 (0·83–1·14)	0·72	0·86 (0·68–1·10)	0·24
Body-mass index (kg/m^2)*	0·98 (0·96–1·01)	0·24	1·00 (0·96–1·04)	0·94
FEV_1 (% of predicted)*	0·98 (0·97–0·99)	0·005	0·97 (0·95–0·99)	0·0005

Data are hazard ratio (95% CI), unless otherwise indicated. Data are adjusted for age, sex, smoking status, body-mass index, and percent of predicted FEV_1. FEV_1=forced expiratory volume in 1 s. *Per 1 unit increase.

Table 4: **Adjusted risk factors for pneumonia as an adverse event or serious adverse event**

Our study had several limitations. First, none of the seven trials studied was powered specifically to detect pneumonia. Pneumonia was instead identified as an adverse event or serious adverse event from reports submitted by investigators, and these events were not systematically validated with well established clinical or radiographic criteria.[30] Thus, the accuracy of the diagnosis based on adverse events is uncertain except for serious adverse events, which were well documented because they were classed as adverse events that resulted in hospital admission or death, and in these cases we had detailed information including a chest radiograph. Therefore, we were reassured that the occurrence of pneumonia as a serious adverse event was similar for patients who did and did not receive budesonide. Diagnostic misclassification could also arise from acute

exacerbation episodes of COPD since the patient symptoms are very similar to those of pneumonia. Although we did not assess exacerbation of COPD, budesonide with or without formoterol has been shown to reduce occurrence of exacerbation.[13] Consequently, we believe that diagnostic misclassification would not have had a substantial effect on our findings.

Second, we noted increased frequency of patient withdrawal in control groups compared with the inhaled budesonide groups. To estimate the effect of differential patient withdrawal, we did a sensitivity analysis of the treatment phase of the trial and the period after treatment (up to 2 months) for such data that were available. However, this analysis did not affect the findings, providing some assurance that differential patient withdrawal did not bias the primary analysis.[31]

Third, our analysis was largely focused on trials that lasted for 12 months. As such, the effects of budesonide on risk of pneumonia in the past 12 months of treatment are uncertain. In the fluticasone trials, however, the risk of pneumonia was evident within 6 months of follow-up, suggesting that signs of pneumonia can be detected within 1 year.[26]

Results from our study have shown that budesonide was not significantly associated with 1-year risk of pneumonia in patients with COPD and therefore is safe for clinical use in such patients.

Contributors

DDS was the principal investigator and obtained funding for the study. All authors contributed to study design, and writing and review of the report. AstraZeneca supplied the completed dataset to DDS. XZ did the primary data analysis, and DDS, FR, PMAC, and SIR participated in further data analysis. All authors interpreted the data. DDS assumes responsibility for the accuracy and integrity of the report. All authors have seen and approved the final version.

Conflicts of interest

DDS has received speaking and advisory fees, and research funding from AstraZeneca and GlaxoSmithKline, which are makers of inhaled corticosteroids. DT has received consulting fees, speaking fees, and grant support from AstraZeneca; and funding from GlaxoSmithKline. FR, US, and AT are employees of AstraZeneca and have shares in AstraZeneca. PMAC has received advisory fees for studies sponsored by AstraZeneca, GlaxoSmithKline, Nycomed, and Boehringer Ingelheim, and spoken at meetings supported wholly or partly by these companies; and received research funding from GlaxoSmithKline, Nycomed, and Boehringer Ingelheim. SIR has received grant support from Almirall, Altana, Astellas, AstraZeneca, Biomarck, Centocor, GlaxoSmithKline, IFSH, Lorrillard, Mpex, Nabi, Novartis, Pfizer, Philip Morris, Reynolds, Roche, Schering-Plough, Talecris, and Wyeth; consulting and advisory fees from Abbott, Adams, Almirall, Altana, Aradigm, AstraZeneca, Bend, Biolipox, Centocor, Critical Therapeutics, Dey, Forest, GlaxoSmithKline, ICOS, Johnson & Johnson, Novartis, Nycomed, Ono Pharma, Paragenix, Pfizer, Pulmatrix, Roche, Sankyo, Sanofi, Schering-Plough, Theravance, United BioSource, and Uptake Medical; and speaking fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Otsuka, Pfizer, and SOMA. XZ declares that he has no conflicts of interest.

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