

# Scientific rationale for the possible inhaled corticosteroid intraclass difference in the risk of pneumonia in COPD

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**Abstract:** Inhaled corticosteroids (ICSs) treatment combined with long-acting  $\beta_2$ -adrenoceptor agonists (LABAs) reduces the risk of exacerbations in COPD, but the use of ICSs is associated with increased incidence of pneumonia. There are indications that this association is stronger for fluticasone propionate than for budesonide. We have examined systematic reviews assessing the risk of pneumonia associated with fluticasone propionate and budesonide COPD therapy. Compared with placebo or LABAs, we found that fluticasone propionate was associated with 43%–78% increased risk of pneumonia, while only slightly increased risk or no risk was found for budesonide. We have evaluated conceivable mechanisms which may explain this difference and suggest that the higher pneumonia risk with fluticasone propionate treatment is caused by greater and more protracted immunosuppressive effects locally in the airways/lungs. These effects are due to the much slower dissolution of fluticasone propionate particles in airway luminal fluid, resulting in a slower uptake into the airway tissue and a much longer presence of fluticasone propionate in airway epithelial lining fluid.

**Keywords:** COPD, pneumonia, inhaled corticosteroids, budesonide, fluticasone

## Introduction

Treatment with inhaled corticosteroids (ICSs) in combination with long-acting  $\beta_2$ -adrenoceptor agonists (LABAs) has been shown to relieve symptoms, improve quality of life, and reduce the risk of exacerbations in patients with COPD.<sup>1–5</sup> The use of ICS/LABA combinations is considered safe and well tolerated. However, an area of potential concern is the increased incidence of pneumonia in COPD patients treated with ICSs, observed for the first time in the Towards a Revolution in COPD Health (TORCH) study published in 2007.<sup>4</sup> There are indications of ICS intraclass differences in pneumonia risk with some evidence of a weaker association of pneumonia with budesonide than with fluticasone propionate therapy.

In randomized, controlled trials, treatment with fluticasone propionate alone or in combination with salmeterol was associated with increased prevalence of pneumonia compared with long-acting bronchodilator monotherapy (salmeterol or tiotropium) or placebo.<sup>4,6–8</sup> This risk appeared to increase with increased lung function impairment.<sup>4,9</sup> Most randomized controlled studies of budesonide alone or in combination with LABA (formoterol) reported no increased risk of pneumonia when compared with formoterol alone or placebo.<sup>1,2,10–12</sup> In a study by Sharafkhaneh et al, however, an association between budesonide treatment and increased risk of pneumonia was found.<sup>13</sup>

A pooled patient-level analysis of 11 double-blind, randomized, controlled trials comparing an inhaled budesonide treatment (ie, budesonide/formoterol or budesonide)

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with a non-corticosteroid-containing comparator (formoterol or placebo), including >10,000 patients with COPD, was conducted. No statistically significant increase in the risk of treatment-emergent pneumonia adverse events or pneumonia serious adverse events was found with inhaled budesonide-containing treatments compared with non-budesonide-containing treatments; however, a small increase in risk with budesonide-containing treatment cannot be ruled out.<sup>14</sup> To date, no randomized, prospective, head-to-head clinical trials have been conducted to compare the risk of pneumonia between budesonide and fluticasone propionate, and between-study differences in underlying pneumonia risk factors and methods for diagnosis and reporting of pneumonia could confound cross-study comparison. In the absence of direct head-to-head studies between fluticasone propionate and budesonide, information regarding potential intraclass differences in pneumonia risk has been provided from observational studies in the real-world setting, as well as from indirect comparison in meta-analyses/systematic reviews of the literature.

In an epidemiological study in a Canadian, new-user COPD population, Suissa et al found a 101% higher risk of pneumonia in COPD patients treated with fluticasone propionate and a 17% increased risk in budesonide-treated patients when compared with controls not treated with ICSs.<sup>15</sup> In a Swedish observational study in almost 5,500 COPD patients followed for up to 9 years (representing >19,000 patient years), patients treated with budesonide/formoterol were compared with matched patients treated with fluticasone/salmeterol. The incidence of exacerbations was lower in patients treated with budesonide/formoterol,<sup>16</sup> and the risk of pneumonia in COPD patients was 73% higher in the fluticasone group than in the budesonide group.<sup>17</sup> It could be argued that predefined diagnostic standards for pneumonia are lacking in most of the observational studies evaluating the association between the risk of pneumonia and ICS treatment, including the study by Janson et al.<sup>17</sup> However, although no chest X-ray-confirmed pneumonia was registered in the study by Janson et al, the difference between fluticasone propionate and budesonide treatments in the risk of pneumonia remained the same when the data of hospitalized patients (where pneumonia was confirmed by chest X-ray) were analyzed.<sup>17</sup>

To better understand the extent of any potential intraclass difference in pneumonia risk between fluticasone propionate and budesonide in patients with COPD, we undertook a systematic review of the literature from January 1, 2010, to June 30, 2016, to identify systematic reviews/meta-analyses

addressing the risk of pneumonia associated with these two ICS treatments. The methodology and results of this search are presented in Table 1. Of the 56 publications identified, 50 did not fulfill the inclusion criteria; the remaining 6 systematic reviews addressed the risk of pneumonia associated with treatment with inhaled fluticasone propionate and budesonide in comparison with placebo or LABAs in patients with COPD, and Table 1 summarizes these 6 systematic reviews.<sup>18–23</sup> In total, this table represents 24 fluticasone propionate and 11 budesonide studies. In all 6 systematic reviews, fluticasone propionate was associated with a statistically significant increased risk of pneumonia (of 43%–78%). None of the 6 systematic reviews found budesonide to be associated with an increased risk of pneumonia; however, in one of them, the risk of nonfatal serious adverse pneumonia events (requiring hospital admission) approached statistical significance (odds ratio [OR]=1.62; 95% confidence interval [CI]=1.00, 2.62).<sup>23</sup>

Within the identified systematic reviews, direct or indirect comparisons between fluticasone propionate and budesonide were sparse. In the Cochrane review by Kew and Seniukovich, an indirect comparison found no significant difference between fluticasone propionate and budesonide monotherapy in the risk of serious adverse events (pneumonia-related or all-cause) or mortality, but a higher risk of any pneumonia event (including less serious cases treated in the community) was found for fluticasone than for budesonide (OR =1.86; 95% CI=1.04, 3.34; Table 1).<sup>23</sup> In the report by Halpin et al, an indirect comparison between budesonide and fluticasone propionate found that adverse pneumonia events and serious pneumonia adverse events were lower for budesonide than for fluticasone (OR =0.47; 95% CI =0.28, 0.80; and OR =0.41; 95% CI =0.19, 0.86, respectively).<sup>19</sup>

These indirect comparisons and meta-analyses/systematic reviews have a number of limitations that may confound data interpretation. These limitations include methodological differences in the studies, such as the definitions of pneumonia events, methods used to confirm pneumonia, drug dosages as well as imbalances in the fluticasone and budesonide groups in terms of study durations, patient numbers, and population differences in the studies. Another limitation is that the sample size is lower for budesonide than for fluticasone propionate studies, which could lead to comparative lack of power when assessing the association between the use of budesonide and pneumonia. The fluticasone propionate studies also include the TORCH study that had a 3-year duration, while all the budesonide studies were of shorter duration. Despite these limitations, the outcomes of these

**Table 1** Summary of 6 systematic reviews, published from 2010 to 2016, addressing the risk of pneumonia associated with inhaled therapy containing treatment with inhaled fluticasone propionate or budesonide compared with placebo or LABAs in patients with COPD

Meta-analyses	Outcome	Fluticasone propionate			Budesonide			Comparator
		Studies (n)	Participants (n)	RR [95% CI]	Studies (n)	Participants (n)	RR [95% CI]	
Singh and Loke (2010) <sup>18</sup>	All reported pneumonia events	16	15,624	RR =1.67 [1.47, 1.89]	7	6,561	RR =1.19 [0.92, 1.53]	LABA; placebo
Halpin et al (2011) <sup>19</sup>	Adverse pneumonia events	8	5,203	Log OR =0.669; variance =0.012	4	2,475	Log OR =-0.082; variance =0.061	Placebo
	Serious pneumonia adverse events	7	5,122	Log OR =0.651; variance =0.018	4	2,475	Log OR =-0.243; variance =0.128	
Spencer et al (2011) <sup>20</sup>	Adverse pneumonia events	1	3,093	OR =1.43 [1.13, 1.81]	2	1,071	OR =0.84 [0.36, 1.96]	LABA
	Serious pneumonia adverse events	4	4,527	OR =1.46 [1.12, 1.92]	1	559	OR =2.42 [0.40, 20.16]	
Nannini et al (2012) <sup>21</sup>	All reported pneumonia events	9	8,242	OR =1.75 [1.25, 2.45]	3	2,834	OR =1.09 [0.69, 1.73]	LABA
Nannini et al (2013) <sup>22</sup>	All reported pneumonia events	9	5,447	OR =1.76 [1.46, 2.14]	3	2,837	OR =0.92 [0.57, 1.47]	Placebo
Kew and Seniukovich (2014) <sup>23,a</sup>	All reported pneumonia events	11	15,377	OR =1.68 [1.49, 1.90]	6	7,011	OR =1.12 [0.83, 1.51]	LABA; placebo
	Serious pneumonia adverse events	17	19,504	OR =1.78 [1.50, 2.12]	7	6,472	OR =1.62 [1.00, 2.62]	

**Notes:** <sup>a</sup>In an indirect comparison, a higher risk of any pneumonia event (including less serious cases treated in the community) was found for fluticasone propionate than for budesonide (OR =1.86; 95% CI =1.04, 3.34). Meta-analyses identified by searching PubMed using the following search strategy: (Mesh Terms "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "pulmonary disease, chronic obstructive") AND "pneumonia" [All Fields] AND "budesonide" [Mesh Term] AND "fluticasone" [Text Word] AND "review" [Publication Type] AND "English" [Language] AND "2010/01/01–2016/06/30" [Date – Publication]. Only articles based on a systematic literature search were included; if more than one systematic review from the Cochrane Library was identified during the time interval, only the last report was included. Studies that reported the "total" risk, ie, the risk of pneumonia due to treatment with ICS without separating the effect of different ICSs, were excluded. Of the 56 articles identified, 50 did not meet the inclusion criteria; the remaining 6 are summarized here.

**Abbreviations:** CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -adrenoceptor agonist; OR, odds ratio; RR, risk ratio.

indirect comparisons and systematic reviews are consistent with the results from observational studies assessing the risk of pneumonia with ICS use and support the hypothesis that budesonide therapy is associated with fewer pneumonia events than therapy with fluticasone propionate.

In April 2016, the European Medicines Agency Pharmacovigilance Risk Assessment Committee completed a review of the known risk of pneumonia in patients with COPD receiving ICSs and reported that they did not find any conclusive evidence of differences in the risk of pneumonia between different ICSs.<sup>24</sup> It is, however, not clear on what scientific evidence this conclusion is based. To date, no randomized, prospective, head-to-head clinical trials are available to provide the conclusive evidence for the intraclass difference between different ICSs. However, a retrospective analysis of the large, 4-year, prospective, randomized Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial has been published recently (March 2017), evaluating differences in incidence of adverse respiratory events among patients entering the study on no ICS, on fluticasone propionate, or on other ICSs.<sup>25</sup> The design

of this study allowed the continuing effects of ICSs on respiratory adverse events to be observed prospectively in a controlled COPD population. The incident rate of pneumonia was significantly higher in patients treated with inhaled fluticasone propionate compared with those not using ICSs ( $p < 0.001$ ) or those on other ICSs (analyzed as one group,  $p < 0.001$ ). The incident rate ratio was 1.38 for fluticasone propionate and 1.05 ( $p = 0.52$ ) for other ICSs as compared to those not using ICSs. The investigation suggests that there are intraclass differences in the risk of pneumonia between fluticasone propionate and other ICSs. It is, however, not possible to draw conclusions on the use of budesonide and the risk of pneumonia from the study.

In summary, there are data from both observational studies in real-world clinical practice and indirect comparisons/systematic reviews of the literature, supporting that there is an intraclass difference between fluticasone propionate and budesonide treatments in terms of pneumonia risk – with a higher risk of pneumonia for fluticasone propionate than for budesonide. This article discusses possible mechanisms for this observed difference.

## Physicochemical and pharmacokinetic differences

The use of ICSs ensures that high concentration of active drug is delivered locally to the airways and lungs with a relatively low systemic burden. After inhalation, corticosteroids are deposited as small particles on the surface of airway mucosa, and they gradually dissolve in mucosal lining fluid before they are absorbed into airway/lung tissue and target cells to exert local immunosuppression and reduction of inflammation.

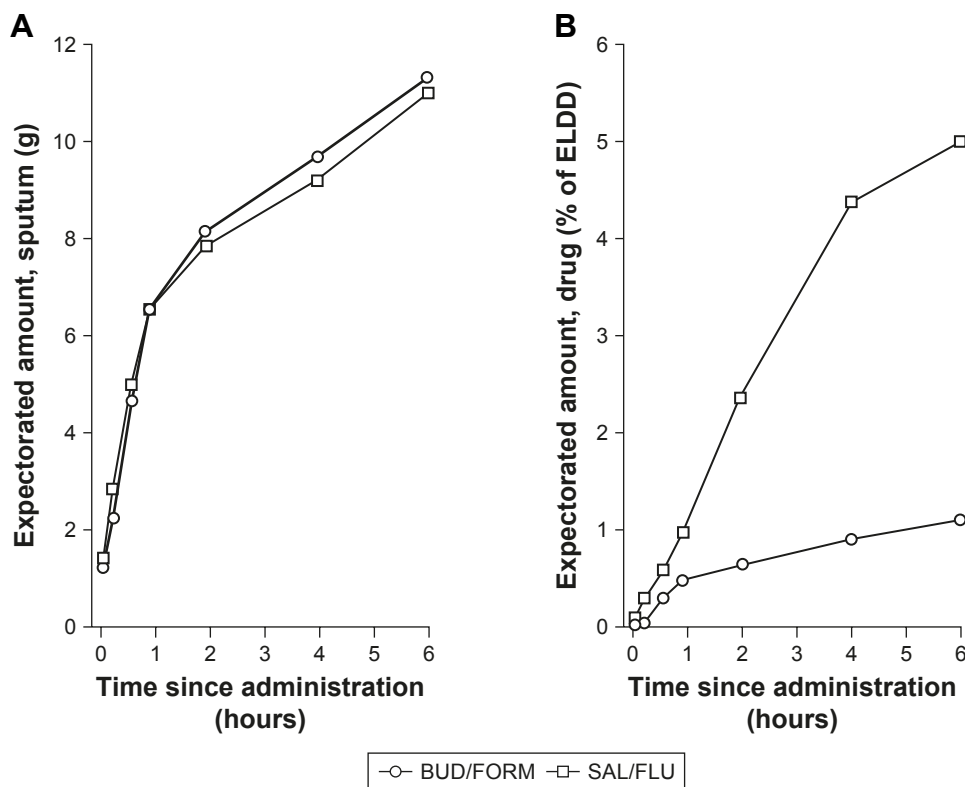
The local pharmacokinetic profile of ICSs, ie, the rate and extent of airway/pulmonary absorption, is strongly dependent on the intrinsic physicochemical properties of corticosteroids, particularly lipophilicity, aqueous solubility, and airway epithelial permeability. The important determinant of dissolution rate of ICS particles in the airway epithelial lining fluid is aqueous solubility, which greatly differs between various ICSs. As the available fluid volume for dissolution in the lungs is small (lung lining fluid volume in humans is estimated to be 10–30 mL),<sup>26</sup> dissolution rates for highly lipophilic corticosteroids are a rate-limiting step in the absorption from the bronchial surfaces. Among ICSs, budesonide has relatively high aqueous solubility (16 µg/mL), whereas the solubility of fluticasone propionate is very low (<0.1 µg/mL).<sup>27</sup> Studies on dissolution rates of budesonide and fluticasone propionate (in vitro and in simulated lung fluid studied in a flow cell) show that budesonide particles were dissolved in 6 minutes, while fluticasone propionate required at least 6 hours<sup>27</sup> or even >8 hours.<sup>28</sup> In agreement with the slow dissolution, only 6%–7% of fluticasone propionate deposited on human bronchial epithelial cell line (Calu-3) was absorbed through the cell monolayer during 4 hours, 93%–94% remained on the cell surface,<sup>29</sup> whereas during the same time 60%–70% of budesonide was transported through the same cell line<sup>30,31</sup> as well as through human primary alveolar epithelial cells.<sup>32</sup> Importantly, in these in vitro studies, commercially available drug powder or suspension aerosol formulations were used for deposition of drugs on the cell surface, and the cells were cultured in air–liquid interface conditions, thus mimicking in vivo context.

The prolonged presence of fluticasone propionate in airway lumen, as compared to budesonide, was also indicated by the study in subjects who inhaled single 1,000 µg doses of both budesonide and fluticasone propionate via dry powder inhalers before surgery (lung or lobar resection due to lung cancer). In this study, fluticasone propionate was detected in several bronchial brush samples for up to 18 hours after inhalation, whereas budesonide was detected only in one brush taken 2 hours after inhalation.<sup>33</sup> Similarly, in patients with COPD, Dalby et al showed that inhaled budesonide was

present in the airway lumen for a much shorter time compared with inhaled fluticasone propionate.<sup>34</sup> This was indicated by the finding that fluticasone propionate was recovered in the spontaneously expectorated sputum over 6 hours after inhalation of salmeterol/fluticasone propionate (50/500 µg), whereas the majority of the expectorated fraction of budesonide was recovered in the first 2 hours after inhalation of budesonide/formoterol (400/12 µg) dose (Figure 1).<sup>34</sup> Deposited undissolved particles of ICSs on the airway walls are exposed to clearance mechanisms by mucociliary escalator. In this study, 5 times greater amount of fluticasone propionate than that of budesonide (calculated as the percentage of estimated lung-deposited dose) was recovered in sputum collected over 6 hours, suggesting that the low dissolution rate of fluticasone propionate delays absorption of fluticasone propionate from the airway lumen.

The prolonged presence of fluticasone propionate in airway lumen is also indicated by the much longer time for systemic absorption of fluticasone propionate than that of budesonide. In COPD patients in the Dalby et al's study commented above, budesonide reached maximal concentration in plasma 15.5 minutes after inhalation compared with 50.8 minutes for fluticasone propionate.<sup>34</sup> In patients with asthma, the mean time for systemic absorption (mean absorption time [MAT]) derived from repeated dose inhalations (1 mg twice daily for 7 days) was 1 hour for budesonide (Turbuhaler®; AstraZeneca, Gothenburg, Sweden) and nearly 7 hours for fluticasone propionate (Diskus®; GlaxoSmithKline, Brentford, UK).<sup>35</sup> After a single dose (1 mg via Diskhaler®; GlaxoSmithKline) given to healthy subjects, the MAT determined for fluticasone propionate was 2 hours.<sup>36</sup> Noteworthy, in the same study in healthy subjects, fluticasone furoate, a highly lipophilic ICS structurally closely related to fluticasone propionate (both containing the S-fluoromethyl carbothioate group conferring high lipophilicity), had a MAT of 7 hours; the time for 90% absorption was 11 hours for fluticasone propionate and 20–30 hours for fluticasone furoate.<sup>36</sup> Importantly, rates of dissolution, absorption, and luminal clearance of lipophilic, slowly dissolving ICSs may be even lower in severe COPD due to emphysema (lower surface area), airway obstruction, fibrosis, and impaired mucociliary clearance.<sup>27</sup>

After absorption from the airway lumen, retention of ICSs within airway/lung tissue is determined by corticosteroid binding to the tissue, which is generally positively correlated to corticosteroid lipophilicity. However, this is different for budesonide, which, despite its only moderate lipophilicity, is retained in the airway/lung tissue for a long time. This is due to intracellular conjugation (esterification)



**Figure 1** Cumulative mean amounts of expectorated sputum (A) and budesonide and fluticasone propionate (B) over 6-hour collection after inhalation of a dose of salmeterol/fluticasone propionate (50/500  $\mu\text{g}$  via Diskus<sup>®</sup>; GlaxoSmithKline, Brentford, UK) or budesonide/formoterol (400/12  $\mu\text{g}$  via Turbuhaler<sup>®</sup>; AstraZeneca, Gothenburg, Sweden). Mean value plots of the amount of (A) expectorated sputum (arithmetic means) and (B) budesonide and fluticasone propionate in the expectorated sputum (percentage of ELDD, geometric means), cumulative over the 6-hour collection period.

**Notes:** Reproduced from Dalby C, Polanowski T, Larsson T, Borgstrom L, Edsbacker S, Harrison TW. The bioavailability and airway clearance of the steroid component of budesonide/formoterol and salmeterol/fluticasone after inhaled administration in patients with COPD and healthy subjects: a randomized controlled trial. *Respir Res.* 2009;10:104. Copyright ©2009 Dalby et al; licensee BioMed Central Ltd. Creative commons license: <https://creativecommons.org/licenses/by/2.0/legalcode>.<sup>34</sup>

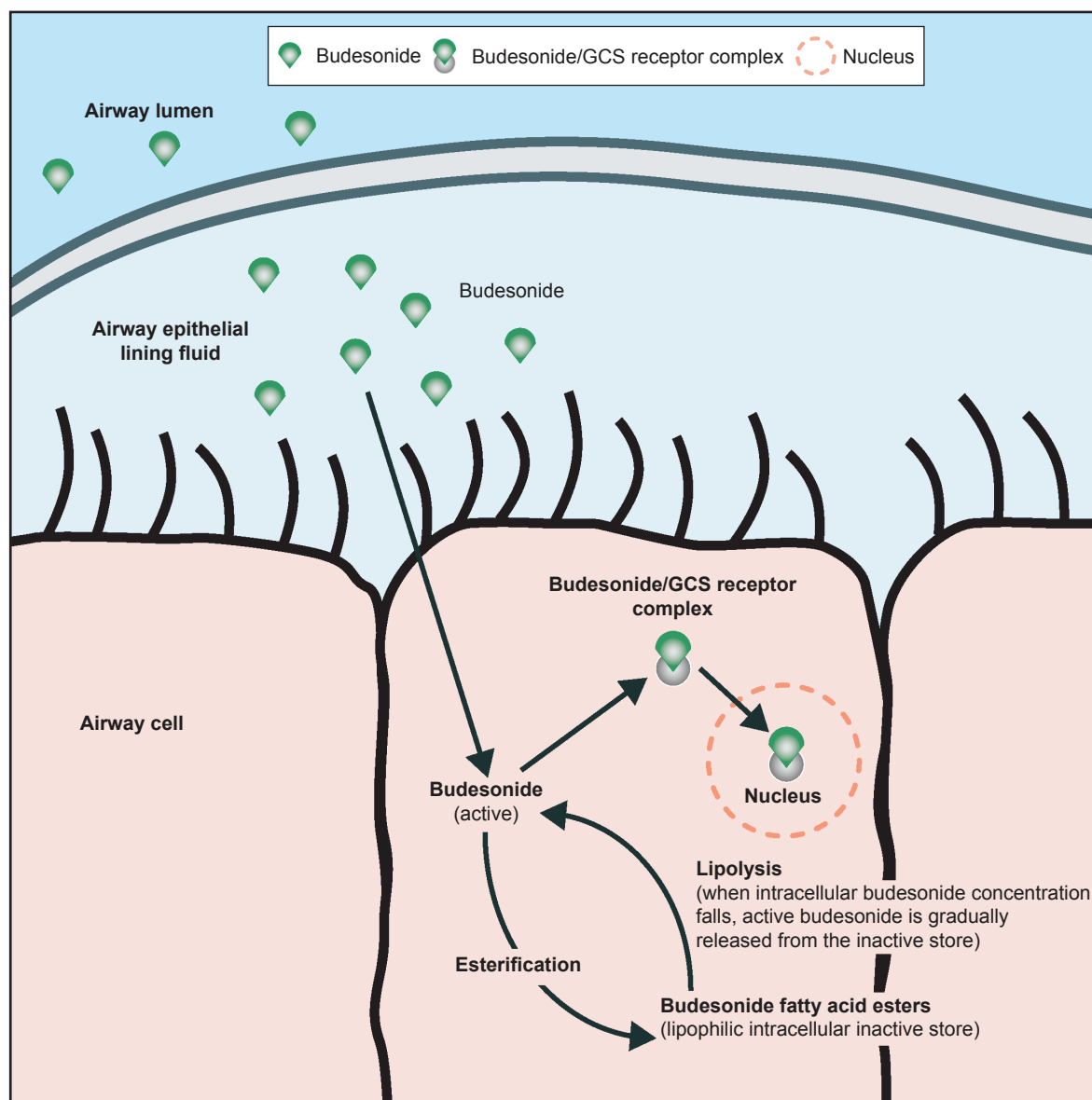
**Abbreviations:** BUD/FORM, budesonide/formoterol; ELDD, estimated lung-deposited dose; SAL/FLU, salmeterol/fluticasone propionate.

of budesonide with fatty acids at C-21 of the budesonide molecule, resulting in the formation of very lipophilic fatty acid esters (mostly oleate) lacking affinity to glucocorticoid receptor and thus making an inactive depot of budesonide in the target airway/lung tissue (Figure 2).<sup>37,38</sup> Budesonide is absorbed into airway/lung tissue within minutes and is rapidly esterified; up to 70%–80% of budesonide is esterified in airway tissue 20 minutes after the start of 5-minute inhalation.<sup>37</sup> Budesonide esters are gradually hydrolyzed back to active drug over an extended time period by the action of intracellular lipases and cholesterol esterases as the concentration of free/active budesonide in the cell decreases. Therefore, although budesonide is rapidly absorbed from the airway lumen, the residence time of budesonide within airway/lung tissue is similar to or even longer than that of fluticasone propionate.<sup>33,37</sup> Budesonide esters provide a slow-release reservoir of active budesonide in the airway/lung tissue, which explains the long duration of action of budesonide over that expected from this drug's general pharmacokinetics and moderate lipophilicity.<sup>37,38</sup> Thus, the long

residence time of budesonide within airway/lung tissue is determined by a long intracellular presence of budesonide fatty acid esters due to their very high lipophilicity. This is in contrast to fluticasone propionate; its long residence time in the airways is determined by two factors: the prolonged presence of slowly dissolving particles of fluticasone propionate in airway luminal fluid and long presence of fluticasone propionate within airway/lung tissue due to high lipophilicity of the fluticasone propionate molecule.

## Differences in immunosuppressive efficacy

From a clinical perspective, fluticasone propionate is considered as a more potent corticosteroid than budesonide; clinical dose of 400  $\mu\text{g}$  budesonide is estimated as comparable to 250  $\mu\text{g}$  fluticasone propionate (1.6-fold ratio). However, fluticasone propionate was shown to be ~10 times more potent than budesonide in suppression of pro-inflammatory cytokines released by human alveolar macrophages and alveolar epithelial cells after in vitro exposure to lipopolysaccharide or



**Figure 2** The reversible process of budesonide endogenous esterification with fatty acids in the airway/lung tissue, showing the intracellular depot of budesonide and illustrating the variable lipophilicity of budesonide, ie, moderate lipophilicity in the airway epithelial lining fluid and very high lipophilicity intracellularly where a portion of budesonide – not bound to GCS receptor – is reversibly converted to highly lipophilic fatty acid esters.

**Notes:** Adapted from *Clin Ther*, 25 Suppl C, Brattsand A, Miller-Larsson A. The role of intracellular esterification in budesonide once-daily dosing and airway selectivity, 28–41, Copyright © 2003 Published by Elsevier Inc., with permission from Elsevier,<sup>38</sup> which was adapted from *Ann Allergy Asthma Immunol*, 88(6), Edsbäcker S, Brattsand R. Budesonide fatty-acid esterification: a novel mechanism prolonging binding to airway tissue. Review of available data. 609–616, Copyright © 2002 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved, with permission from Elsevier.<sup>62</sup>

**Abbreviation:** GCS, glucocorticosteroid.

organic dust.<sup>39</sup> In human alveolar epithelial cells, fluticasone propionate was also 10 times more potent than budesonide in the inhibition of the activity of E-selectin promoter that contains binding sites for a number of transcription factors, including AP-1 and NF- $\kappa$ B, involved in the induction of pro-inflammatory cytokines.<sup>40</sup> Several of these cytokines acutely upregulate the expression of E-selectin (cell surface adhesion protein) on endothelial cells, which contributes to the binding and extravasation of neutrophils. Likewise, in human bronchial epithelial cells, fluticasone propionate

was 80 times more potent than budesonide in the repression of vascular cell adhesion molecule-1 (VCAM-1) that plays a role in the activation and recruitment of leukocytes into infection and inflammatory sites.<sup>41</sup> Fluticasone propionate thus might be 10–100 times more potent than budesonide as an inhibitor of local inflammation and as a suppressor of the local host immune response in the airways and lungs. Of note, in vivo, a 10-fold higher efficacy of fluticasone propionate together with the 5-fold higher concentration of fluticasone in sputum, as detected in Dalby et al's study,<sup>34</sup>

may mean a 50-fold greater efficacy/immunosuppression in luminal immune cells compared with what is attained by budesonide.

Noteworthy, fluticasone furoate is an even more potent corticosteroid than fluticasone propionate as shown *in vitro*<sup>42</sup> and *in vivo*.<sup>43</sup> A recent systematic review of 6 randomized, placebo-controlled trials of >8 weeks of duration, in 15,515 patients with moderate-to-very severe stable COPD, showed that fluticasone furoate alone or in combination with a LABA vilanterol is associated with a significant increased risk of pneumonia in comparison with vilanterol.<sup>44</sup> Although the mechanism behind this association is unknown, it is notable that fluticasone furoate also has a longer duration of anti-inflammatory action and a greater efficacy than fluticasone propionate even under oxidative stress conditions.<sup>42</sup> Importantly, in a response to pathogen invasion, inflammatory response is built up to stop progression of infection. Fluticasone propionate and fluticasone furoate via their local increased anti-inflammatory and immunosuppressive effects might be very potent in the impairment of bacterial clearance from the airways.

## Effects on the systemic host defense

ICSs due to their anti-inflammatory and immunosuppressive effects may impair local and/or systemic host defense. Since an inflammatory response is mounted against invading pathogens, ICSs may promote respiratory infections, especially in subjects with weakened immune system in the airways and lungs, such as COPD patients. However, systemic corticosteroids have been shown in several recent studies to have beneficial effects on community-acquired pneumonia, such as faster recovery, earlier hospital discharge, and decreased treatment failure.<sup>45-47</sup> These beneficial effects were confirmed in the recent meta-analysis comprising 13 randomized controlled trials and 2,005 patients.<sup>48</sup> Therefore, it seems that enhanced risk of pneumonia by ICSs in COPD patients, and differences in pneumonia risk between various ICSs, is not due to the ICS effects on systemic host defense, but on local defense in the airways and lungs.

## Local bronchial immunity – the link to the development of pneumonia associated with ICS use

Immunocompetent cells of the innate defense system in the lungs, such as neutrophils and macrophages, have an important role in maintaining the normal, balanced microbial environment within the lungs. However, airway/lung colonization with various pathogenic bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* is

found in up to 30% of COPD patients with stable disease and in >50% of patients during COPD exacerbations.<sup>49,50</sup>

In stable COPD patients, higher airway bacterial load was shown to be significantly correlated to higher ICS dosage, and this relationship remained significant in a multivariate analysis including age, smoking status, and FEV<sub>1</sub>% predicted.<sup>51</sup> Furthermore, it was shown that ICS use may alter the airway microbiota composition.<sup>52,53</sup> Importantly, according to the “keystone pathogen” hypothesis, even small alterations in the abundance of a few bacterial species can have great effects on microbial community and subsequently modify disease status.<sup>54</sup> The prolonged presence of slowly dissolving particles of fluticasone propionate in the airway epithelial lining fluid compared with budesonide may cause a protracted local immunosuppression. This could impair clearance of airway pathogens, leading to airway/lung colonization with pathogens, which may further develop to pneumonia.

The first-line defense against inhaled pathogens is airway epithelial cells. Recently, it was shown that budesonide (16 nM) fully protected human bronchial epithelial barrier against damage from cigarette smoke and viral mimetic in the presence of smoke, whereas fluticasone propionate (10 nM) had no effect.<sup>55</sup> In the same study, adhesion and/or internalization of *S. pneumoniae*, administered to the apical side of the human bronchial epithelial cells, was doubled by concomitant exposure to viral mimetic. This increase was prevented by treatment with budesonide, but not with fluticasone propionate. Furthermore, preliminary results from a recent study by the same investigator group show that exposure of human bronchial epithelial cells to budesonide for 2 hours followed by exposure to rhinovirus resulted in significantly higher expression of several immune defense genes compared with the treatment with fluticasone propionate.<sup>56</sup> Differential effects of budesonide and fluticasone propionate were also recently reported on bacterial recognition receptors in macrophages derived from blood monocytes of COPD subjects. Preliminary results show that budesonide prevented receptor reductions induced by both *S. pneumoniae* and non-typeable *H. influenzae*, while fluticasone propionate affected only reductions induced by *S. pneumoniae*.<sup>57</sup> The authors of these reports concluded that differential regulation of immune defense genes in human bronchial epithelial cells<sup>56</sup> and bacterial pathogen recognition receptors on macrophages<sup>57</sup> may help to explain the difference between fluticasone propionate and budesonide with respect to the risk of pneumonia. Mechanisms responsible for these differences in gene regulation are not clear; however, recently, it was shown that different corticosteroids express a unique gene “fingerprint”,<sup>58</sup> which

could explain some differences between effects of fluticasone propionate and budesonide.

Airway and alveolar macrophages are host defense key cells responsible for the removal of inhaled pathogens and particles from the respiratory tract through their capacity to phagocytose and subsequently kill microorganisms. This is highly relevant because respiratory infections markedly contribute to the progression of COPD by way of infectious exacerbations and pneumonia. In COPD, alveolar macrophages and macrophages derived from blood monocytes have an impaired ability to phagocytose and kill respiratory pathogens, which may contribute to the increased bacterial colonization in COPD.<sup>59–61</sup> In the study described above,<sup>57</sup> where bacterial recognition receptors in macrophages derived from blood monocytes of COPD subjects were differently affected by budesonide and fluticasone propionate, phagocytosis of bacteria was not studied. However, in the study by Taylor et al, phagocytosis of *S. pneumoniae* and *H. influenzae* by macrophages derived from blood monocytes from COPD patients was increased when cells were treated with budesonide.<sup>61</sup> This effect increased with budesonide concentration, and 3-fold and 5-fold increases of phagocytosis of *S. pneumoniae* and *H. influenzae*, respectively, were obtained at 1  $\mu$ M of budesonide.<sup>61</sup>

The functional in vitro studies described above,<sup>55–57</sup> comparing the effects of budesonide and fluticasone propionate in bronchial epithelial cells and macrophages, were performed with dissolved corticosteroids. Thus, it was not taken into account that fluticasone propionate remains in the airway epithelial lining fluid in the form of particles for many hours after inhalation, while budesonide is dissolved within minutes. Similar to environmental particles, particles of lipophilic ICSs persisting in airway epithelial lining fluid, will be recognized by airway/alveolar macrophages and phagocytosed. Phagocytosis of fluticasone propionate particles by airway/alveolar macrophages might lead to very high concentrations of fluticasone propionate within the phagolysosomes, and this may impair macrophage functions, including phagocytosis and killing of bacteria. This may result in impaired and delayed clearance of bacteria from the airways. The issue of phagocytosis of fluticasone propionate particles would be adequately addressed in studies in vivo with fluticasone propionate administered as powder or suspension into the airways. Thus, further studies are warranted to address the issue of phagocytosis of slowly dissolving lipophilic ICSs, which persist in the airways for many hours, and to answer whether and how it may affect susceptibility to respiratory infections.

A summary of the different mechanisms that may explain the intraclass difference in the risk of pneumonia between

**Table 2** A summary of mechanisms that may explain the intraclass difference in risk of pneumonia between budesonide and fluticasone propionate

Mechanisms	ICS difference	References	
		In vitro	In vivo
<b>Physicochemical properties</b>			
Lipophilicity	Higher for FLU	28	
Aqueous solubility	Higher for BUD	27	
Dissolution rate in lung lining fluid	Higher for BUD	27, 28	33, 34
<b>Airway pharmacokinetics</b>			
Airway epithelial absorption	Higher for BUD	29–32	
Rate of airway absorption	Faster for BUD		33, 34
Intracellular esterification in airway/lung tissue	Only for BUD		37, 38
<b>Immunosuppressive effects</b>			
Suppression of pro-inflammatory cytokines and leukocyte adhesion molecules	Higher for FLU	39–41	
<b>Effects on local immunity</b>			
Protection of airway epithelial barrier	Higher for BUD	55	
Expression of immune defense genes in airway epithelial cells	Higher for BUD	56	
Prevention of adhesion and/or internalization of bacteria to airway epithelial cells	Higher for BUD	55	
Prevention of bacteria-induced reduction of bacterial recognition receptors in COPD macrophages	Higher for BUD	57	
Phagocytosis of bacteria by COPD macrophages	Increased for BUD	61	

**Abbreviations:** BUD, budesonide; FLU, fluticasone propionate; ICS, inhaled corticosteroid.

budesonide and fluticasone propionate is presented in Table 2.

## Conclusion

We suggest that the observed difference in the risk of pneumonia between fluticasone propionate and budesonide is due to greater and more protracted immunosuppressive effects of fluticasone propionate locally in the airways/lungs. This is at least partly explained by the difference between these drugs' local pharmacokinetics in the airways/lungs, where slowly dissolving particles of fluticasone propionate persist for many hours in the airway lining fluid, while budesonide is absorbed into the airway tissue within minutes. Local immunosuppression by fluticasone propionate may enhance susceptibility to respiratory infections and increase the load of pathogenic microbiome in the airways and lungs, and this may further lead to pneumonia.

## Disclosure

CJ has served in an advisory board and/or served as a speaker and/or participated in education arranged from AstraZeneca,



Boehringer Ingelheim, GlaxoSmithKline, Novartis, Chiesi, and TEVA. KL has served in an advisory board and/or served as a speaker and/or participated in education arranged by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Meda, Takeda, Novartis, and Pfizer. TWH has served in an advisory board and/or served as a speaker and/or participated in education arranged from AstraZeneca, Boehringer Ingelheim, NaPP, Vectura, TEVA, and Roche. GS is a fulltime employee of AstraZeneca Nordic. AML is a fulltime employee of AstraZeneca Gothenburg and holds AstraZeneca shares. The authors report no other conflicts of interest in this work.

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