

Fluticasone propionate and increased risk of pneumonia in COPD: is it PAFR-dependent?

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Dear editor

It was with great interest that I read the recent comprehensive review by Christer Janson et al¹ published in the *International Journal of COPD*, where authors discussed the possible mechanisms behind the increased risk of pneumonia in COPD patients using inhaled corticosteroids (ICSs), especially with fluticasone propionate (FP), where the risk was highest.¹ It is an important area, and it is encouraging and reassuring that leading clinical journals are recognizing this. Understanding the fundamental mechanisms behind pneumococcal infections is critical.² I would like to suggest that a broader discussion of new insights into the potential mechanisms contributing to the increased adherence of pneumococcus to airway wall and particularly in response to FP might have been appropriate with this opportunity.

The prerequisite step for any pulmonary microbial infection is the adherence of pathogens to the respiratory mucosa via interaction between the host epithelial cells and the bacterial surface. A possible mechanism is through the interaction of phosphorylcholine, a molecular mimic of platelet-activating factor (PAF) present on the bacterial surface, while PAF receptor (PAFR) is expressed on the airway epithelium.³ Interestingly, both airway pathogens, pneumococcus and *Haemophilus influenzae*, adhere to and are engulfed by airway epithelial cells via the PAFR, thus evading the host immune responses and increasing their chances for colonization and infection.³

Our group previously published that PAFR expression increases in the airways of smokers and COPD patients but especially so in COPD.⁴ Importantly in this study, we also looked at the effects of FP on PAFR expression in COPD patients. Since ICSs increase the risk of pneumonia, we asked the question “Does ICS increase PAFR expression facilitating bacterial adhesion?” We surprisingly found that high doses of FP tend to increase PAFR expression in COPD patients. Overall, increase in epithelial PAFR expression was little, but it was evident that FP can upregulate PAFR expression – though FP certainly did not decrease it over 6 months.⁴ The intervention, though underpowered, still provided interesting inputs on the likely cause of observed vulnerability to pneumococcal infection in COPD patients treated with FP.⁴

We also observed an increased PAFR expression on small airway and alveolar type II pneumocytes and immune cells, suggesting pan airway PAFR expression in COPD.^{3,4} Further, our mechanistic in vitro infection model using immortalized lung epithelial cells demonstrated that a PAFR-specific chemical antagonist such as WEB-2086 significantly decreased the adherence and engulfment of *H. influenzae* and pneumococcus in a dose-dependent manner.⁵

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These observations suggest that PAFR might be an important bacterial adhesion site, which is potentially upregulated in response to ICS treatment. Our findings in COPD might well be applicable to other chronic lung disease such as asthma and interstitial lung diseases.² This recent paper by Christer Janson et al¹ is a timely reminder that understanding of these mechanisms is of utmost importance and will stimulate further research. The main emphasis in the literature has been on bacterial colonizations in airways, but the mechanisms underlying initial bacterial epithelial adherence and consequent infections remain poorly understood.

Acknowledgment

Clifford Craig Foundation supported the work on pathological mechanisms in COPD (grant no 153).

Disclosure

The author reports no conflicts of interest in this communication.

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Authors' reply

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Dear editor

We thank Dr Sohal for his interest in our recently published manuscript discussing the scientific rationale for the possible inhaled corticosteroid (ICS) intraclass difference in the risk of pneumonia in COPD. His own work on platelet-activating factor receptor (PAFR) expression on airway epithelial cells in COPD patients shows a trend toward increased expression of PAFR by 6-month treatment with fluticasone propionate (FP), suggesting an increased rate of pneumococcal adhesion with FP, and hence the possible development of infection or pneumonia.¹ This supports in part the work by Heijink et al² that we cited in our paper.²

Heijink et al² showed that adhesion and/or internalization of *Streptococcus pneumoniae*, administered to the apical side of the human bronchial epithelial 16HBE cells, was doubled by concomitant exposure to viral mimetic, and that this increase was prevented by treatment with budesonide but not with FP at an equivalent dose. In addition, FP had little or no effect on the barrier dysfunction induced by cigarette smoke extract in human bronchial epithelial cells; in contrast, budesonide completely protected barrier function in the same cell line.² This effect of budesonide was likely mediated by reducing inhibitory phosphorylation of the downstream target of

epidermal growth factor receptor (EGFR), while interestingly others have shown that EGFR may be activated by PAFR.³ Additionally, in the Heijink et al's² study, pretreatment with FP significantly reduced mRNA expression of adherens junction protein, E-cadherin, in differentiated primary bronchial epithelial cells exposed to live rhinovirus (RV16), while budesonide preserved this expression. On the basis of these results, Heijink et al² suggested that, in contrast to budesonide, treatment with FP may aggravate RV-induced barrier dysfunction in vivo and therefore increase the risk of a secondary bacterial infection.²

It would be interesting to see whether Dr Sohal's research group could replicate their work to directly compare the effects of budesonide with those of FP on the upregulation of PAFR expression, in light of the findings of Heijink et al.² It would also be of interest to see whether viral infection or viral mimetic affected the results. This could help determine whether another mechanism may be involved in intraclass differences between budesonide and FP in the risk of pneumonia in COPD, beyond the mechanisms discussed in our paper (including greater and more protracted immunosuppressive effects of FP locally in the airways/lungs due to the increased residence time of FP on airway epithelium).

Disclosure

The authors report no conflicts of interest in this communication.

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