Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

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Abbreviations: Burden of Obstructive Lung Disease, **BOLD**; confidence interval, **CI**; tuberculosis, **TB**; inhaled corticosteroids, **ICS**; community-acquired pneumonia, **CAP**; apoptotic cells, **ACs**; alveolar macrophages, **AMøs**; rate ratio, **RR**; long-acting beta2-agonist, **LABA**; budesonide/formoterol combination, **BFC**; fluticasone/salmeterol combination, **FSC**; oral corticosteroid, **OCS**

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Introduction: COPD and Chronic infection

In this issue of Journal Club we examine the relationship between inhaled corticosteroid use and the risk of pneumonia. Over the past several years, investigators have identified a *pneumonia signal* in COPD patients treated with inhaled corticosteroids. Further, some studies have suggested that certain inhaled corticosteroids may present a greater risk than others and that there is a greater association with higher doses of inhaled corticosteroids. The exact nature of the association remains unclear.

Abstract 1
Tuberculosis associates with both airflow obstruction and low lung function: BOLD results

Amaral AF, Coton S, Kato B et al and the BOLD Collaborative Research Group. *Eur Respir J*. 2015 Jun 25. doi: http://dx.doi.org/10.1183/13993003.02325-2014. [Epub ahead of print]

In small studies and case series, a history of tuberculosis has been associated with both airflow obstruction, which is characteristic of chronic obstructive pulmonary disease, and restrictive patterns on spirometry. The objective of the present study was to assess the association between a history of tuberculosis and airflow obstruction and spirometric abnormalities in adults. The study was performed in adults, aged 40 years and above, who took part in the multicentre, cross-sectional, general population-based Burden of Obstructive Lung Disease (BOLD) study, and had provided acceptable post-bronchodilator spirometry measurements and information on a history of tuberculosis. The associations between a history of tuberculosis and airflow obstruction and spirometric restriction were assessed within each participating centre, and estimates combined using meta-analysis. These estimates were stratified by high- and low/middle-income countries, according to gross national income. A self-reported history of tuberculosis was associated with airflow obstruction (adjusted odds ratio 2.51, 95% confidence interval [CI] 1.83-3.42) and spirometric restriction (adjusted odds ratio 2.13, 95% CI 1.42-3.19). A history of tuberculosis was associated with both airflow obstruction and spirometric restriction, and should be considered as a potentially important cause of obstructive disease and low lung function, particularly where tuberculosis is common.

Comments:

This paper from the BOLD study is instructive as it demonstrates that a history of tuberculosis (TB) is associated with spirometric patterns of both obstruction and restriction. There were 14,050 individuals from the BOLD study who met inclusion criteria for this analysis. History of TB was defined as self report if being told by doctor or other provider that they had TB. This could lead to some degree of under-reporting due to the

stigma of the diagnosis. Patients that were on active treatment for TB were excluded. Atypical mycobacterial disease was not included in this study. Confounders such as smoking, passive smoking, education and workplace exposure to dust were considered. There were significant differences from the 19 sites with the strongest association for obstruction in countries with low/middle incomes. The restrictive pattern was evident mainly in countries with low/middle income. The cross sectional nature of the study makes it difficult to rule out reverse causation such as in patients with silicosis or those on inhaled corticosteroids, but as the authors point out, both of these scenarios were relatively uncommon in the countries with low/middle income status where the associations were noted to be the highest. Many patients presenting with obstructive airway disease are started on inhaled corticosteroids (ICS). Given the potential differences in pathogenesis of the airway obstruction, the addition of ICS may be more harmful than helpful.

Abstract 2
Glucocorticoid-augmented efferocytosis inhibits pulmonary pneumococcal clearance in mice by reducing alveolar macrophage bactericidal function

Stolberg VR, McCubbrey AL, Freeman CM, et al. *J Immunol*. 2015;195(1):174-184.
doi: http://dx.doi.org/10.4049/jimmunol.1402217.

Inhaled corticosteroids (ICS) increase community-acquired pneumonia (CAP) incidence in patients with chronic obstructive pulmonary disease (COPD) by unknown mechanisms. Apoptosis is increased in the lungs of COPD patients. Uptake of apoptotic cells (ACs) (*efferocytosis*) by alveolar macrophages (AMøs) reduces their ability to combat microbes, including Streptococcus pneumoniae, the most common cause of CAP in COPD patients. Having shown that ICS significantly increase AMø efferocytosis, we hypothesized that this process, termed glucocorticoid-augmented efferocytosis, might explain the association of CAP with ICS therapy in COPD. To test this hypothesis, we studied the effects of fluticasone, AC, or both on AMøs of C57BL/6 mice *in vitro* and in an established model of pneumococcal pneumonia. Fluticasone plus AC significantly reduced TLR4-stimulated AMø IL-12 production, relative to either treatment alone, and decreased TNF-α, CCL3, CCL5, and keratinocyte-derived chemoattractant/CXCL1, relative to AC. Mice treated with fluticasone plus AC before infection with viable pneumococci developed significantly more lung CFUs at 48 hours. However, none of the pretreatments altered inflammatory cell recruitment to the lungs at 48 hours postinfection, and fluticasone plus AC less markedly reduced *in vitro* mediator production to heat-killed pneumococci. Fluticasone plus AC significantly reduced *in vitro* AMø killing of pneumococci, relative to other conditions, in part by delaying phagolysosome acidification without affecting production of reactive oxygen or nitrogen species. These results support glucocorticoid-augmented efferocytosis as a potential explanation for the epidemiological association of ICS therapy of COPD patients with increased risk for CAP, and establish murine experimental models to dissect underlying molecular mechanisms.

Comments:

This study presents a potential pathogenic mechanism for the increased risk of pneumonia associated with ICS, fluticasone in particular. The study did not compare the effects of different doses of fluticasone nor did it study budesonide or mometasone (ICS formulations found in other ICS/LABA combinations). Hence, one cannot assume that this effect is unique to fluticasone. Further work with this murine model and translational studies that examine these potential mechanisms in humans should be enlightening.

Abstract 3
Discontinuation of inhaled corticosteroids in COPD and the risk reduction of pneumonia

Suissa S, Coulombe J, Ernst P. *Chest*. 2015 Jun 25.
doi: http://dx.doi.org/10.1378/chest.15-0627.
[Epub ahead of print]

Background:
The widespread use of inhaled corticosteroids for COPD treatment has been questioned. Recent studies of weaning some COPD patients off inhaled corticosteroids found little or no loss in adverse consequences compared with long-acting bronchodilators. It is however, unclear whether their discontinuation reduces the elevated risk

of pneumonia associated with these drugs.

Methods:

Using the Quebec health insurance databases, we formed a new-user cohort of COPD patients treated with inhaled corticosteroids during 1990-2005 and followed through 2007 or until a serious pneumonia event, defined as a first hospitalization for or death from pneumonia. A nested case-control analysis of the cohort was used to estimate the rate ratio of serious pneumonia associated with discontinuation of inhaled corticosteroid use, compared with continued use, adjusted for age, sex, respiratory disease severity and co-morbidity.

Results:

The cohort included 103,386 users of ICS, of which 14,020 had a serious pneumonia event during 4.9 years of follow-up (incidence rate 2.8/100/year). Discontinuation of inhaled corticosteroids was associated with a 37% decrease in the rate of serious pneumonia (rate ratio [RR] 0.63; 95% confidence interval [CI)]: 0.60-0.66). The risk reduction was rapidly evident, going from 20% in the first month to 50% by the fourth month after discontinuation. The risk reduction was particularly marked with fluticasone (RR 0.58; 95% confidence interval [CI]: 0.54-0.61), but less so with budesonide (RR 0.87; 95% CI: 0.78-0.97).

Conclusions:

Discontinuation of inhaled corticosteroid use in COPD is associated with a reduction in the elevated risk of serious pneumonia, particularly so with fluticasone.

Comments:

The results of this observation study are consistent with other studies' findings of an association of pneumonia with use of inhaled corticosteroids (and in particular fluticasone) but the magnitude of the risk reduction after withdrawal of inhaled corticosteroids is higher than that reported in prospective randomized controlled trials that have examined this question. This is an observational study and has limitations in interpretation of the results. This study examines ICS withdrawal between 1990 to 2005. Most of the literature on the risk of inhaled corticosteroids and pneumonia has been published after this date and hence, the reasons for the withdrawal of ICS in this study cohort may be important to understand the results. This was a nested case control study with 10 controls matched to each case of pneumonia. While the authors report that they adjusted for differences in COPD severity, there are quite significant differences between the cases and controls in terms of hospitalizations for COPD in the year prior to the index year (41% versus 17.6%), oral corticosteroid prescriptions (1.6 ± 4.4 versus 0.7 ± 2.9) and recent oral corticosteroid use in terms of months before index date (12.8 versus 4.9). Indeed, as the authors state, it is possible that these could lead to an overestimation of the risk reduction. There were also significantly higher numbers of case participants on current fluticasone compared to budesonide (31% versus 5.6%) and a higher percentage of the case group compared to control group with regard to current fluticasone use 31% versus 17%. This is a Canadian-based study and it is possible that some of the patients were using the higher dose 500/50 of fluticasone/salmeterol that has been associated with higher rates of pneumonia than the 250/50 formulation. The authors do not provide data on how many patients were using the higher dose. Nonetheless, this study does suggest that for at least a subset of patients with COPD at high risk for pneumonia discontinuation of ICS may lead to a reduction in future pneumonia episodes.

Abstract 4
Comparative effectiveness of budesonide/formoterol combination and fluticasone/salmeterol combination among chronic obstructive pulmonary disease patients new to controller treatment: a U.S. administrative claims database study

Kern DM, Davis J, Williams SA, et al. *Respir Res.* 2015;16(1):52. [Epub ahead of print]

Background:

Inhaled corticosteroid/long-acting β2-agonist combinations (ICS/LABA) have emerged as first line therapies for chronic obstructive pulmonary disease (COPD) patients with exacerbation history. No randomized clinical trial has compared exacerbation rates among COPD patients receiving budesonide/formoterol combination (BFC) and fluticasone/salmeterol combination (FSC) to date, and only limited comparative data are available. This study compared the real-world effectiveness of approved BFC and FSC

treatments among matched cohorts of COPD patients in a large U.S. managed care setting.

Methods:

COPD patients (≥40 years) naive to ICS/LABA who initiated BFC or FSC treatments between 03/01/2009-03/31/2012 were identified in a geographically diverse U. S. managed care database and followed for 12 months; index date was defined as first prescription fill date. Patients with a cancer diagnosis or chronic (≥180 days) oral corticosteroid (OCS) use within 12 months prior to index were excluded. Patients were matched 1-to-1 on demographic and pre-initiation clinical characteristics using propensity scores from a random forest model. The primary efficacy outcome was COPD exacerbation rate, and secondary efficacy outcomes included exacerbation rates by event type and health care resource utilization. Pneumonia objectives included rates of any diagnosis of pneumonia and pneumonia-related health care resource utilization.

Results:

Matching of the identified 3788 BFC and 6439 FSC patients resulted in 3697 patients in each group. Matched patients were well balanced on age (mean = 64 years), gender (BFC: 52% female; FSC: 54%), prior COPD-related medication use, health care utilization, and comorbid conditions. During follow-up, no significant difference was seen between BFC and FSC patients for number of COPD-related exacerbations overall (rate ratio [RR] = 1.02, 95% CI = [0.96,1.09], $p = 0.56$) or by event type: COPD-related hospitalizations (RR = 0.96), COPD-related ED visits (RR = 1.11), and COPD-related office/outpatient visits with OCS and/or antibiotic use (RR = 1.01). The proportion of patients diagnosed with pneumonia during the post-index period was similar for patients in each group (BFC = 17.3%, FSC = 19.0%, odds ratio = 0.92 [0.81,1.04], $p = 0.19$), and no difference was detected for pneumonia-related health care utilization by place of service.

Conclusion:

This study demonstrated no difference in COPD-related exacerbations or pneumonia events between BFC and FSC treatment groups for patients new to ICS/LABA treatment in a real-world setting.

Comments:

Previous Canadian and European studies that compared pneumonia risk associated with the use of FSC to BFC included patients on both the 500/50 and 250/50 combination of FSC in their cohorts. This U.S. study of a managed care cohort followed patients with new starts of ICS/LABA between 2009 to 2012 that only used the 250/50 FSC formulation (the only formulation with an indication for COPD in the United States) and did not show any difference in the rate of exacerbations nor in episodes of pneumonia. Exacerbations were the primary outcome but the study did prospectively record pneumonia events defined by administrative claims having the diagnostic codes for pneumonia. The results of this study raise the question as to whether or not at least part of the higher rate previously detected with fluticasone may be on the basis of the utilization of the 500/50 FSC formulation in previous studies rather than the 250/50 formulation exclusively.