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Journal Club

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COPD association and repeatability of blood biomarkers in the ECLIPSE cohort.
J.A. Dickens, B.E. Miller, L.D. Edwards, E.K. Silverman, D.A. Lomas, R. Tal-Singer, Eclipse Study Investigators EO. Respir Res. 2011 Nov 4;12(1):146. [Epub ahead of print].

BACKGROUND: There is a need for biomarkers to better characterize individuals with COPD and to aid with the development of therapeutic interventions. A panel of putative blood biomarkers was assessed in a subgroup of the Evaluation of COPD Longitudinally to Identify Surrogate Endpoints (ECLIPSE) cohort.
METHODS: Thirty-four blood biomarkers were assessed in 201 subjects with COPD, 37 ex-smoker controls with normal lung function and 37 healthy non-smokers selected from the ECLIPSE cohort. Biomarker repeatability was assessed using baseline and 3-month samples. Intergroup comparisons were made using analysis of variance, repeatability was assessed through Bland-Altman plots, and correlations between biomarkers and clinical characteristics were assessed using Spearman correlation coefficients.
RESULTS: Fifteen biomarkers were significantly different in individuals with COPD when compared to former or non-smoker controls. Some biomarkers, including tumor necrosis factor-alpha and interferon-gamma, were measurable in only a minority of subjects whilst others such as C-reactive protein showed wide variability over the 3-month replication period. Fibrinogen was the most repeatable biomarker and exhibited a weak correlation with 6-minute walk distance, exacerbation rate, BODE index and MRC dyspnoea score in COPD subjects. 33% (66/201) of the COPD subjects reported at least 1 exacerbation over the 3 month study with 18% (36/201) reporting the exacerbation within 30 days of the 3-month visit. CRP, fibrinogen interleukin-6 and surfactant protein-D were significantly elevated in those COPD subjects with exacerbations within 30 days of the 3-month visit compared with those individuals that did not exacerbate or whose exacerbations had resolved.
CONCLUSIONS: Only a few of the biomarkers assessed may be useful in diagnosis or management of COPD where the diagnosis is based on airflow obstruction (GOLD). Further analysis of more promising biomarkers may reveal utility in subsets of patients. Fibrinogen in particular has emerged as a potentially useful biomarker from this cohort and requires further investigation.

Comment: The ECLIPSE study is an ambitious study to examine biomarkers in COPD that may be useful for the diagnosis and management of COPD. While the preliminary results may seem less helpful than initially hoped, it will be critical to establish common subphenotypes and study biomarkers that may have particular import for specific subsets of COPD patients. Timing of measurements may be critical and these studies will be instructive for designing further investigations that examine this issue.

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Effect of budesonide/formoterol pMDI on COPD exacerbations: A double-blind, randomized study. A. Sharafkhaneh, J.G. Southard, M. Goldman, T. Uryniak, U.J. Martin. Respir Med. 2011 Oct 26. [Epub ahead of print].

BACKGROUND: Treatment with an inhaled corticosteroid (ICS) and long-acting bronchodilator is recommended for severe/very severe chronic obstructive pulmonary disease (COPD) patients with repeated exacerbations. This randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.
METHODS: Following a 2-week run-in during which COPD patients aged ≥40 years with an exacerbation history discontinued medications except ICSs, 1219 patients were randomized 1:1:1 to twice-daily budesonide/formoterol pMDI 320/9 μg, budesonide/formoterol pMDI 160/9 μg, or formoterol dry powder inhaler 9 μg. An exacerbation was defined as COPD worsening requiring oral corticosteroids and/or hospitalization. A post hoc analysis, with antibiotic treatment added to the exacerbation definition, was also performed.
RESULTS: Budesonide/formoterol 320/9 and 160/9 reduced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol ($p \leq 0.002$). Budesonide/formoterol 320/9 prolonged time to first exacerbation versus formoterol, corresponding to a 21.2% reduction in hazard ratio (0.788 [95% CI: 0.639, 0.972]; $p = 0.026$). Exacerbation rates (number per patient-treatment year) including antibiotic treatment (post hoc analysis) were reduced by 25.9% and 18.7% with budesonide/formoterol 320/9 and 160/9, respectively, versus formoterol ($p \leq 0.023$). Both budesonide/formoterol doses were well tolerated with safety profiles similar to formoterol. Pneumonia adverse events occurred in 6.4%, 4.7%, and 2.7% of patients in the budesonide/formoterol 320/9, 160/9, and formoterol groups.
CONCLUSIONS: Over 12 months, both budesonide/formoterol doses reduced the exacerbation rate (defined with or without antibiotic treatment) versus formoterol. Budesonide/formoterol pMDI is an appropriate treatment for reducing exacerbations in COPD patients with a history of exacerbations. (NCT00419744).

Comments: This study demonstrates that Budesonide/Formoterol is capable of reducing exacerbations compared to formoterol alone. Previous studies with combination therapy Fluticasone/Salmeterol 250/50 and 500/50 have also shown reductions in exacerbations and there had been concerns regarding a pneumonia signal in those studies. Interestingly there seems to be a similar trend in this study in that there are higher rates of pneumonia in the groups on the combination ICS/LABA therapy and there seems to be a dose response relationship. While the study was not powered to analyze whether this difference was statistically significant it is consistent with previous findings. At least within the context of this study design, where patients are discontinued from the study after their exacerbation, patients on inhaled corticosteroids may more frequently avoid pure inflammatory exacerbations and as a result when they do develop an exacerbation it is more likely to have an infectious etiology and possibly be diagnosed as pneumonia. This may be the explanation for why despite reduced exacerbation rates and fewer drop outs in the study there is a higher rate of pneumonia in both the Budesonide/Formoterol groups.

Reduced glucocorticoid receptor expression and function in airway neutrophils. J. Plumb, K. Gaffey. B. Kane, B. Malia-Milanes, R. Shah, A. Bentley, D. Ray, D. Singh. Int Immunopharmacol. 2011 Oct 25. [Epub ahead of print].

Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a glucocorticoid resistant condition characterised by airway neutrophilia. Reduced glucocorticoid receptor (GR) expression in COPD airway neutrophils may be a mechanism that contributes to glucocorticoid resistance. Our objective was to investigate the expression and function of GR within COPD airway neutrophils. Dual-label immunofluorescence was used to analyse airway neutrophil expression of GR within peripheral lung tissue samples (11 COPD patients, 7 healthy non-smokers [NS]) and induced sputum (7 COPD patients, 7 NS). TNFa and CXCL8 release were measured in neutrophils isolated from induced sputum and peripheral blood (7 COPD patients) in the presence of dexamethasone. In lung tissue, GR was abundantly expressed in macrophages and lymphocytes, but very low expression was observed in neutrophils (means 6.8% and 4.3% in COPD patients and NS respectively). Similarly low expression was observed in sputum neutrophils (means 3.8% and 6.9% in COPD patients and NS respectively). In contrast, GR was expressed by 100% of blood neutrophils. Dexamethasone had less suppressive effect on TNFa and CXCL8 production in vitro by neutrophils from induced sputum compared to neutrophils from paired blood samples. Airway neutrophils have low expression of GR in both COPD patients and controls. The effects of glucocorticoids on cytokine production from airway neutrophils are reduced. Increased numbers of airway neutrophils lacking GR may contribute to glucocorticoid resistance in COPD patients

Comments: While there is general acceptance of the role of inflammation in the pathogenesis of COPD and acute exacerbations it remains a challenge to find effective treatments for treating this complex process. While the subject numbers are small in this study the findings are intriguing. The fact that neutrophils in the systemic circulation appear to have more glucocorticoid receptors (GR) than neutrophils in the airways may help to explain why systemic steroids tend to be more effective

than inhaled steroids. Perhaps treatment with systemic steroids influences mediators that may be important in signaling the differentiation of airway neutrophils to express less GR. These findings also point out that cell types in different tissues and organs have distinct properties that open opportunities and challenges for more targeted anti-inflammatory and/or disease modifying therapies.

Time course and pattern of COPD exacerbation onset. S.D. Aaron, G.C. Donaldson, G.A. Whitmore, J.R. Hurst, T. Ramsay, J.A. Wedzicha. Thorax. 2011 Oct 18. [Epub ahead of print].

Abstract: Background: The natural history and time course of the onset of exacerbation events of chronic obstructive pulmonary disease (COPD) is incompletely understood. Methods. A prospective cohort of 212 patients with COPD was monitored using daily symptom diaries for a median of 2.8 years to characterise the time course of COPD exacerbation onset. Decision rules based on weighted self-reported symptoms were used to define opening and closing of exacerbation events. Event time intervals were analysed and logistic regression was used to determine the effects of patient covariates on exacerbation events. ResultsPatients recorded 4439 episodes of worsening respiratory symptoms from baseline; 2444 (55%) events resolved spontaneously and 1995 (45%) resulted in a COPD exacerbation. In 1115 of the 1995 COPD exacerbations (56%) the onset was sudden and the exacerbation threshold was crossed on the same day symptoms began. In contrast, 44% of exacerbations were characterised by gradual onset of symptoms (median duration from symptom onset to exacerbation 4 days). Patients who experienced sudden onset exacerbations had greater mean daily symptom scores (7.86 vs 6.55 points, $p < 0.001$), greater peak symptom scores (10.7 vs 10.2 points, $p = 0.003$), earlier peak symptoms (4.5 vs 8.0 days, $p < 0.001$) and shorter median recovery times back to baseline health status (11 vs 13 days, $p<0.001$). Multivariable analysis showed that gradual onset exacerbations were statistically associated with a longer duration of exacerbation recovery (OR 1.28, 95% CI 1.06 to 1.54, $p = 0.010$).Conclusions COPD exacerbations exhibit two distinct patterns-sudden and gradual onset. Sudden onset exacerbations are associated with increased respiratory symptoms but shorter exacerbation recovery times.

Comments: While this study has a fairly small number of subjects and is unlikely to be representative of all sub-phenotypes of COPD it identifies two distinct patterns of COPD exacerbations that may actually warrant different management strategies. Indeed there have been references to rapid decliners and frequent exacerbators in the literature and perhaps they have a tendency to have one of these types of exacerbation patterns. Such information may be helpful in further studies that try to elucidate the biology of these different phenotypes.