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Journal Club

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Persistent Systemic Inflammation is Associated with Poor Clinical Outcomes in COPD: A Novel Phenotype. A. Agusti, L.D. Edwards, S.I Rennard, W. Macnee, R. Tal-Singer, B.E. Miller, J. Vestbo, D.A. Lomas, P.M. Calverley, E. Wouters, C. Crim, J.C. Yates, E.K. Silverman, H.O. Coxson, P. Bakke, R.J. Mayer, B. Celli for the Evaluation of LOPD Longitudinally to Identify Predictive Surrogate Endpoins (ECLIPSE) Investigators. PLoS One. 2012;7(5):e37483. Epub 2012 May 18.

BACKGROUND: Because chronic obstructive pulmonary disease (COPD) is a heterogeneous condition, the identification of specific clinical phenotypes is key to developing more effective therapies. To explore if the persistence of systemic inflammation is associated with poor clinical outcomes in COPD we assessed patients recruited to the well-characterized ECLIPSE cohort (NCT00292552).

METHODS AND FINDINGS: Six inflammatory biomarkers in peripheral blood (white blood cells (WBC) count and CRP, IL-6, IL-8, fibrinogen and TNF-α levels) were quantified in 1,755 COPD patients, 297 smokers with normal spirometry and 202 non-smoker controls that were followed-up for three years. We found that, at baseline, 30% of COPD patients did not show evidence of systemic inflammation whereas 16% had persistent systemic inflammation. Even though pulmonary abnormalities were similar in these two groups, persistently inflamed patients during follow-up had significantly increased all-cause mortality (13% vs. 2%, $p < 0.001$) and exacerbation frequency (1.5 (1.5) vs. 0.9 (1.1) per year, $p < 0.001$) compared to non-inflamed ones. As a descriptive study our results show associations but do not prove causality. Besides this, the inflammatory response is complex and we studied only a limited panel of biomarkers, albeit they are those investigated by the majority of previous studies and are often and easily measured in clinical practice.

CONCLUSIONS: Overall, these results identify a novel systemic inflammatory COPD phenotype that may be the target of specific research and treatment.

Comments: We continue to learn more about the heterogeneity of COPD from ECLIPSE as the data from this ambitious study of biomarkers in COPD is being analyzed and read out. There clearly are COPD patients that are more susceptible to exacerbations, more rapid rate of decline in lung function and extra-pulmonary manifestations than others. This study suggests that those who manifest systemic inflammation appear to be at increased risk of all-cause mortality and it points to the central role that genetic susceptibility likely plays in a subset of COPD patients. While smoking cessation is key, the development of agents that may suppress this response are likely not only to have effects on suppressing the pulmonary consequences of smoking but also on the extra-pulmonary manifestations particularly for the sub-group identified in this report.

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RAGE: a new frontier in chronic airways disease. M.B. Sukkar, M.A. Ullah, W.J. Gan, P.A. Wark, K.F. Chung, J.M. Hughes, C.L. Armour, S. Phipps. Br J Pharmacol. 2012 Apr 17. doi: 10.1111/j.1476-5381.2012.01984.x. [Epub ahead of print]

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous inflammatory disorders of the respiratory tract characterized by airflow obstruction. It is now clear that the environmental factors that drive airway pathology in asthma and COPD, including allergens, viruses, ozone and cigarette smoke, activate innate immune receptors known as pattern-recognition receptors, either directly or indirectly by causing the release of endogenous ligands. Thus, there is now intense research activity focused around understanding the mechanisms by which pattern-recognition receptors sustain the airway inflammatory response, and how these mechanisms might be targeted therapeutically. One pattern-recognition receptor that has recently come to attention in chronic airways disease is the receptor for advanced glycation end products (RAGE). RAGE is a member of the immunoglobulin superfamily of cell surface receptors that recognizes pathogen- and host-derived endogenous ligands to initiate the immune response to tissue injury, infection and inflammation. Although the role of RAGE in lung physiology and pathophysiology is not well understood, recent genome-wide association studies have linked RAGE gene polymorphisms with airflow obstruction. In addition, accumulating data from animal and clinical investigations reveal increased expression of RAGE and its ligands, together with reduced expression of soluble RAGE, an endogenous inhibitor of RAGE signaling, in chronic airways disease. In this review we discuss recent studies of the ligand-RAGE axis in asthma and COPD, highlight important areas for future research, and discuss how this axis might potentially be harnessed for therapeutic benefit in these conditions.

Comments: Our appreciation of innate immunity playing a significant role in the pathogenesis of COPD continues to evolve. As the contributions from RAGE and other endogenous mediators of the tissue injury and inflammatory response to cigarette smoke are elucidated, we will be able to develop targeted therapies that are not only likely to suppress the airway and parenchymal injury/ inflammatory process but also the systemic inflammation that likely contributes to many of the extra-pulmonary manifestations of cigarette smoking.

Brain Structure and Function in Chronic Obstructive Pulmonary Disease. A Multi-Modal Cranial Magnetic Resonance Imaging Study. J.W. Dodd, A.W. Chung, M.D. van den Broek, T.R. Barrick, R.A. Charlton, P.W. Jones. Am J Respir Crit Care Med. 2012 May 31. [Epub ahead of print].

RATIONALE: Brain pathology is a poorly understood systemic manifestation of COPD. Imaging techniques using magnetic resonance (MR) diffusion tensor imaging (DTI) and resting state functional MR imaging (rfMRI) provide measures of white matter microstructure and grey functional activation respectively.
OBJECTIVES: We hypothesized that COPD patients would have reduced white matter integrity and that functional communication between grey matter resting state networks (RSN) would be significantly different to controls. In addition we tested whether observed differences related to disease severity, cerebrovascular co-morbidity and cognitive dysfunction.
METHODS: DTI and rfMRI were acquired in stable non-hypoxemic patients with COPD (n = 25) and compared with age-matched controls (n = 25). Demographic, disease severity, stroke risk and neuropsychological assessments were made.
RESULTS: COPD patients (Mean Age 68; FEV1 53 ± 21 % pred) had widespread reduction in white matter integrity (46% of white matter tracts $p < 0.01$). Six of the seven RSN showed increased functional grey matter activation in COPD ($p < 0.01$). Differences in DTI, but not rfMRI, remained significant after controlling for stroke risk and smoking ($p < 0.05$). White matter integrity and grey matter activation appeared to account for difference in cognitive performance between COPD patients and controls.
CONCLUSIONS: In stable non-hypoxemic COPD there is reduced white matter integrity throughout the brain and widespread disturbance in functional activation of grey matter, which may contribute to cognitive dysfunction. White matter microstructural integrity but not grey matter functional activation is independent of smoking and cerebrovascular co-morbidity. The mechanisms remain unclear, but may include cerebral small vessel disease due to COPD.

Comments: This study further supports the notion of COPD as a systemic illness. Individuals who smoke and develop COPD are more likely to develop several of the other complications of smoking than smokers who do not have COPD. This is a small study sample and clearly further investigations are important to clarify the underlying mechanisms. Of equal and perhaps greater import is the task of elucidating the underlying genetic susceptibility that renders the individual who smokes and develops a lung injury response to also develop these systemic effects. Ongoing research continues to provide evidence that a significant contributing factor is likely related to tissue injury responses in the lung, signaling the evolution of inflammatory and other innate immune responses in the systemic circulation that may cause injury to various vascular beds. While unlikely to be the sole explanation and perhaps having more or less import for various conditions, vasculopathy likely contributes to the extra pulmonary manifestations of cigarette smoking (and indeed COPD) such as cognitive dysfunction, cerebral vascular disease, coronary artery disease, pulmonary hypertension and renal disease.

Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison.
D.A. Mahler, A. D'Urzo, E.D. Bateman, S.A. Ozkan, T. White, C. Peckitt, C. Lassen, B. Kramer; on behalf of the INTRUST-1 and INTRUST-2 study investigators. Thorax. 2012 Apr 27. [Epub ahead of print].

BACKGROUND: Current guidelines recommend treatment with one or more long-acting bronchodilators for patients with moderate or more severe chronic obstructive pulmonary disease (COPD). The authors investigated the approach of dual bronchodilation using indacaterol, a once-daily long-acting β(2) agonist, and the long-acting muscarinic antagonist tiotropium, compared with tiotropium alone.
METHODS: In two identically designed, double-blind, 12-week studies, patients with moderate to severe COPD were randomised to indacaterol 150 μg once daily or matching placebo. All patients concurrently received open-label tiotropium 18 μg once daily. The primary outcome was standardised area under the curve of forced expiratory volume in 1 s (FEV(1)) from 5 min to 8 h post dose at week 12. The key secondary outcome was 24 h post-dose ('trough') FEV(1) at week 12. Resting inspiratory capacity (IC) was measured in a subgroup.
RESULTS: 134 and 1142 patients were randomised in studies 1 and 2; 94% and 94% completed. Compared with monotherapy, concurrent therapy increased FEV(1) (area under the curve by 130 and 120 ml, trough by 80 and 70 ml; all $p < 0.001$) and trough IC (by 130 and 100 ml, $p < 0.01$). Cough was more common with indacaterol plus tiotropium (10% and 9%) than with tiotropium alone (4% and 4%). Most cases (~90%) of cough were mild. Other adverse events were similar for the treatment groups.
CONCLUSIONS: Compared with tiotropium monotherapy, indacaterol plus tiotropium provided greater bronchodilation and lung deflation (reflected by increased resting IC). Adverse events were similar between treatments apart from mild cough being more common with indacaterol plus tiotropium. These results support COPD guideline recommendations to combine bronchodilators with different mechanisms of action. TRIAL REGISTRATION NUMBERS: NCT00846586 and NCT00877383.

Comments: The results of this study are perhaps no surprise to many but they do indeed point to the fact that as newer agents become available for use, (indacaterol has only recently become available commercially in the United States), that our options for individualizing care for our COPD patients increase. There are an ever growing number of reports that outline several sub-phenotypes of COPD. Part of the heterogeneity is reflected by the fact that not all patients respond as well to the various medications and some are more susceptible to adverse effects of some of the medicines used to treat COPD. The convenience of once a day tiotropium has been attractive as a long acting bronchodilator and indeed studies have shown that tiotropium can reduce exacerbations. The ability to optimize bronchodilation with the combination of these two once daily medications as well as potentially reduce exacerbations allows an option for consideration when one is weighing the risks and benefits of the use of inhaled corticosteroids where there may concerns about cataracts, osteopenia, thrush, hoarseness, pneumonia etc. The addition of PDE-4 inhibitors provides another potential anti-inflammatory strategy to be combined with the two bronchodilators. Indeed there are combined formulations of these two once a day bronchodilators being tested and will almost certainly be available in the future. The creation of these various therapeutic options will allow us greater flexibility to individualize care for our COPD patients.