

Interleukin-6 and statin therapy: potential role in the management of COPD

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Dear Editor

We read with interest the article by Ferrari and colleagues showing in a small prospective study of chronic obstructive pulmonary disease (COPD) patients that interleukin-6 (IL-6) is a useful biomarker predicting worsening exercise tolerance and greater mortality [1]. We outline below the significance of this finding and its potential impact on the future management of COPD.

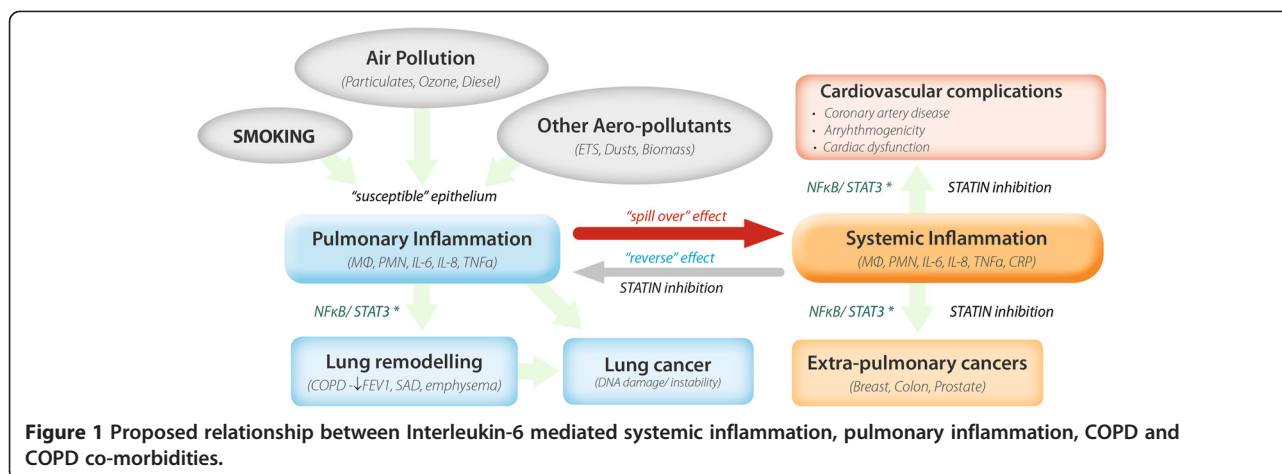
The findings by Ferrari and colleagues concur with other prospective studies, including the recently published ECLIPSE study, showing elevated IL-6 is a clinically useful marker predicting poor outcomes in COPD [2-4]. In large prospective studies a similar utility was found for elevated C-reactive protein (CRP), whose expression is controlled primarily by IL-6 and also associated with poor outcomes in COPD [5-7]. These poor outcomes include poorer exercise tolerance, worsening lung function, greater exacerbation rate, greater comorbidities (lung cancer, pneumonia, diabetes and coronary artery disease) and most importantly, greater mortality. Collectively, these findings suggest that the natural history of COPD and its prognosis can be predicted to some extent by elevated IL-6, a serum marker of systemic inflammation. These observations also suggest that systemic inflammation plays a primary pathogenic role in the natural history of this disease ("reverse" effect, Figure 1), not just a secondary phenomenon from pulmonary inflammation (the "spill over" effect, Figure 1) [8]. In animal models where IL-6 is over-expressed, the clinical phenotype closely resembles that of COPD further suggesting a primary role for IL-6 (and systemic inflammation) in the development of COPD [9]. We have recently reviewed the literature and suggest that IL-6-mediated systemic inflammation is also relevant to many of the COPD-related co-morbidities described above [8]. The prospective study by Ferrari and colleagues provides

further data to suggest that elevated IL-6 plays an active role in the progression of this important disease [1].

If these observations are true, then it follows that HMGCoA reductase inhibitors (statins) might be beneficial in COPD patients through their powerful inhibition of IL-6-mediated systemic inflammation [8]. Indeed, there is a large body of data from numerous observational studies showing that statin therapy reduces both morbidity and mortality in COPD including; reducing the rate of infective exacerbations, slowing the decline in FEV₁, reducing mortality from pneumonia or infective exacerbations and improving exercise tolerance [8]. This last clinical feature of COPD is very important as it significantly affects quality of life. In the first randomized control trial of statin therapy in COPD, exercise tolerance was improved by nearly 50% after 6 months of statin therapy compared to placebo [10]. This improvement correlated with a significant reduction in serum IL-6 level (and CRP) but not lung function [10], suggesting IL-6-mediated systemic inflammation might be one of the primary determinants of poor exercise tolerance. Also of considerable importance, is the recent finding that elevated IL-6 or CRP levels are associated with increased risk of lung cancer [11], particularly in patients with COPD [12], and that lung cancer mortality is reduced by 17% with statin use [Supplementary Figure S11 from ref. [13]. Together with the findings of the observational studies described above, these results make a strong argument for examining the role of statins as adjunct therapy to inhaler therapy in COPD (Figure 1) [8,14]. This is particularly the case as current inhaler therapy in COPD is symptom-based, minimizing breathlessness and reducing exacerbations, while statin-based systemic therapy, inhibiting both systemic and pulmonary inflammation, appears to confer significant disease modifying benefits. It also argues in favor of investigating the utility of measuring serum IL-6 (or its surrogate CRP) in patients with COPD to target and monitor therapy [1-7,14].

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We conclude that the study of Ferrari and colleagues confirms earlier studies showing that outcomes in COPD are related to IL-6-mediated systemic inflammation [1]. This observation not only provides the basis on which to better phenotype patients with COPD [14], but more importantly highlights the important potential utility of statin therapy as a significant disease-modifying therapy in COPD [8]. This hypothesis requires urgent examination in clinical trials.

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