Interleukin-6 as a biomarker for asthma: hype or is there something else?

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Tantalising evidence purports IL-6 to be a biomarker for adult-onset asthma that predicts ICS use and symptoms http://ow.ly/bhra303fg5j

"A biomarker, a biomarker – my kingdom for a biomarker."

Modified from Act V, Scene 14, Richard III, William Shakespeare with apologies to the Bard.

Much of precision medicine research today seeks to find a biomarker, or like King Richard, our kingdom might be lost. The hope is that if one is successful in identifying such a biomarker [1], all will be resolved: diagnosis, prognosis and the best treatment regime identified from the morass of treatment options available. In this context, the research for a single, do-all biomarker is a truly dramatic irony because it may not exist, consider the rise and fall of C-reactive protein (CRP) or exhaled nitric oxide fraction ($F_{E}NO$). Yet such a biomarker could be quite useful in asthma, a syndrome that so often defies definition. With this mythical biomarker, one could clearly decide whether the patient has asthma, assess how severe the disease is, and even guide selection of which of the many available treatment regimens should be employed.

An ideal biomarker should be easy to obtain, be reproducible, be both sensitive and specific, respond to therapy in a way that mirrors the patient's response, and be accepted by the medical community. To meet these requirements, the potential biomarker must be subjected to a long series of studies that include retrospective and, better yet, prospective studies, consistent findings in multiple studies, validation studies against gold standards, treatment studies that assess the sensitivity of the biomarker for change, long-term studies that assess the ability of the biomarker to provide a prognosis, and basic science studies that provide the biological/pathological plausibility needed to gain acceptance in the medical community [2]. Bringing forward a new biomarker for asthma presents a particularly daunting challenge as the disease is really a syndrome that has defied a precise definition and is highly heterogeneous in both its presentation and treatment. Nevertheless, the effect might be worth the time/expense of exploring certain biomarkers for their ability to stage the disease and help focus a treatment regime with a high chance of success, as some asthma treatments are very expensive. $F_{E}NO$ was originally lauded as such a biomarker, but has largely fallen from favour because the pulmonary community was seduced by the hype, as illustrated by the Gartner Hype Cycle [3].

Interleukin (IL)-6 is a pleotropic cytokine that acts as a pro-inflammatory mediator and acute-phase response inducer, but has also been reported to have anti-inflammatory properties. While largely associated with T-cells and macrophages, it is increasingly apparent that the airway epithelium is a major source of IL-6 in the lungs. In its anti-inflammatory role, IL-6 has inhibitory effects on tumour necrosis factor-α and IL-1. Moreover, it has been implicated in the synthesis of prostaglandin E_2. IL-6 is produced downstream from the recognition of microbial- and damage-associated molecular patterns by pattern recognition receptors of the innate immune system [4]. Given recent interest in the role of obesity, IL-6 is

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also a product of adipocytes and linked to the well-known systemic inflammatory biomarker, CRP. As such, IL-6 has strong biological plausibility as a major, pivotal cellular signalling modality in pathways germane to asthma [4, 5].

In disease, circulating IL-6 is elevated in asthmatic patients [6] and elevated in bronchoalveolar lavage fluid (BALF) of patients in whom asthma is clinically active [7] and in patients with intrinsic asthma [8]. The latter finding is significant, as it suggests a more general role of IL-6 assessment in phenotyping asthmatics. IL-6 levels are also affected by viral infections and obesity [4, 5], two important comorbid factors in causing exacerbations and severity, respectfully. Moreover, BALF IL-6 levels correlate with circulating IL-6, suggesting an association [9–12]. As we postulated earlier, IL-6 levels probably reflect an activated state of the lung, specifically the airway epithelium. Lastly, a number of studies show that sputum IL-6 is correlated with forced expiratory volume in 1 s (FEV_1) and FEV_1/forced vital capacity and obesity [9]. Taken together, IL-6 clearly may have a role as a biomarker for asthma.

In this issue of the *European Respiratory Journal*, Ilmarinen *et al.* [13] report a dataset from the ongoing Seinäjoki Asthma Study of a 12-year follow-up of 170 patients with adult-onset asthma. The adult-onset asthma patient often presents as female predilection, without a history suggestive of early-onset (typically allergic) asthma, and most importantly carries a poor prognosis characterised by inadequate asthma control and frequent exacerbations [14–16]. These patients can be quite challenging, with high rates of healthcare obligation, physiological disorders and poor quality of life [16]. Ilmarinen *et al.* [13] postulated that the high prevalence of comorbidities might be related to systemic inflammation or a spillover of the inflamed status of the lung into the circulation. The authors report a high rate of systemic inflammation as assessed by high circulating levels of CRP and/or IL-6. Patients with multiple comorbidities were more likely to be female, with a higher body mass index and higher smoking pack-years, used more inhaled corticosteroids (ICSs), had poor asthma control, and worse lung function. IL-6 levels showed a reasonable correlation to CRP and IL-6 was correlated to lung function, albeit weakly. Of interest, IL-6 levels and eosinophil number were predictors of current ICS dose. The authors conclude that comorbidities and IL-6 levels are predictive of ICS use and asthma symptoms, thereby lending promise to IL-6 as a potentially valid biomarker.

So what is the significance of these findings, in particular to the research for a useful biomarker for the asthmatic patient? This study raises the interesting question of whether the comorbidities are the result of inflammatory products spilling into the circulation and affecting distal sites or whether the severity of the asthma is a result of the total systemic inflammatory product burden derived from other sites, such as a subclinical infectious process, tissue damage, or adipose tissue? Lastly, and perhaps most importantly, is IL-6 the culprit or merely a marker of the process because of its biokinetics?

As a biomarker for asthma, IL-6 has some virtues but also some shortcomings. First, it is hardly specific and it is implicated and elevated in other lung diseases [5] and in many other non-pulmonary diseases. Moreover, the associations in BALF/sputum are strong, reproducible and easily lead to biologic plausibility [5, 9, 13] especially in terms of the loss of lung function where one merely links the IL-6 to transforming growth factor-β, collagen deposition in the airway wall, and a loss of central airway function. Although other mechanisms could be at play, at the moment the best role for IL-6 assessment appears to be as an objective measure of disease activity or of airway injury linked to the prognosis of loss of lung function. Given the well-described role of spirometry (which also can be thought of as a biomarker), it is unclear to what extent IL-6 assessment will add to that tried and true biomarker. At the end of the day, only by manipulating IL-6 by blocking its production, neutralising the protein, or blocking its receptors with the many available therapeutics [17–20], will we begin to bring clarity to the utility of measuring IL-6. Until then, the search for a horse to save our kingdom goes on.

References

1 Vargas AJ, Harris CC. Biomarker development in the precision medicine era: lung cancer as a case study. *Nat Rev Cancer* 2016; 16: 525–537.
2 Pepe MS, Etzioni R, Feng Z, *et al.* Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst* 2001; 93: 1054–1061.
3 Fenn J, Raskino M. Mastering the Hype Cycle. Boston, Harvard Business Press, 2008.
4 Hirano T. Interleukin 6 and its receptor: ten years later. *Int Rev Immunol* 1998; 16: 249–284.
5 Rincon M, Irvin CG. Role of IL-6 in asthma and other inflammatory pulmonary diseases. *Int J Biol Sci* 2012; 8: 1281–1290.
6 Yokoyama A, Kohno N, Fujino S, *et al.* Circulating interleukin-6 levels in patients with bronchial asthma. *Am J Respir Crit Care Med* 1995; 151: 1354–1358.
7 Tillie-Leblond I, Pugin J, Marquette CH, *et al.* Balance between proinflammatory cytokines and their inhibitors in bronchial lavage from patients with status asthmaticus. *Am J Respir Crit Care Med* 1999; 159: 487–494.
8 Virchow JC Jr, Kroegel C, Walker C, *et al.* Inflammatory determinants of asthma severity: mediator and cellular changes in bronchoalveolar lavage fluid of patients with severe asthma. *J Allergy Clin Immunol* 1996; 98: S27–S33.

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9 Neveu WA, Allard JL, Raymond DM, *et al.* Elevation of IL-6 in the allergic asthmatic airway is independent of inflammation but associates with loss of central airway function. *Respir Res* 2010; 11: 28.
10 Dixon AE, Raymond DM, Suratt BT, *et al.* Lower airway disease in asthmatics with and without rhinitis. *Lung* 2008; 186: 361–368.
11 Morjaria JB, Babu KS, Vijayanand P, *et al.* Sputum IL-6 concentrations in severe asthma and its relationship with FEV1. *Thorax* 2011; 66: 537.
12 Dixon AE, Shade DM, Cohen RI, *et al.* Effect of obesity on clinical presentation and response to treatment in asthma. *J Asthma* 2006; 43: 553–558.
13 Ilmarinen P, Tuomisto LE, Niemelä O, *et al.* Comorbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. *Eur Respir J*; 48: 1052–1062.
14 Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006; 368: 804–813.
15 Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178: 218–224.
16 Hanania NA, King MJ, Braman SS, *et al.* Asthma in the elderly: current understanding and future research needs – a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol* 2011; 128: Suppl., S4–S24.
17 Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol* 2015; 16: 448–457.
18 Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy* 2016; 8: 959–970.
19 Casneuf T, Axel AE, King P, *et al.* Interleukin-6 is a potential therapeutic target in interleukin-6 dependent, estrogen receptor-α-positive breast cancer. *Breast Cancer (Dove Med Press)* 2016; 8: 13–27.
20 Kasama T, Isozaki T, Takahashi R, *et al.* Clinical effects of tocilizumab on cytokines and immunological factors in patients with rheumatoid arthritis. *Int Immunopharmacol* 2016; 35: 301–306.