LETTERS TO THE EDITOR

Sputum IL-6 concentrations in severe asthma and its relationship with FEV₁

As asthma becomes more severe it adopts additional characteristics including corticosteroid refractoriness and a neutrophil-predominant inflammatory response implicating Th1 or Th17 responses involving cytokines such as tumour necrosis factor α , interleukin (IL)-6 and IL-8. We have examined the role of IL-6 and IL-8 in severe asthma. Subjects with severe asthma (GINA stage IV) who were exacerbation-free for ≥ 4 weeks with a forced expiratory volume in 1 s (FEV₁) $>30\%$ but $<80\%$ predicted were studied from the baseline parameters of a clinical trial.¹ Cell counts and cytokines were measured in induced sputum (see online supplement for Methods).

Eighteen subjects (9M, 9F) with severe asthma (mean $\pm$ SD age 43.4 $\pm$ 11.4 years (SD), FEV₁ 59 $\pm$ 14% predicted) were studied (see table 1 in online appendix). The median (IQR) levels of sputum IL-8, IL-6, neutrophils (%), macrophages (%) and eosinophils (%) were 1853.8 pg/ml (1376.8–2537.7), 70.0 pg/ml (28.55–127.5), 32.5% (24.1–42.6), 46.8% (39.8–54.8) and 4.4% (3.2–9.4), respectively. We observed significant negative correlations between FEV₁ (% predicted) and sputum IL-8 ($r = -0.912$, $p < 0.001$), IL-6 ($r = 0.717$, $p = 0.002$) (figure 1) and neutrophils ($r = 0.919$, $p = 0.014$). The Asthma Control Questionnaire positively correlated with sputum IL-6 levels ($r = 0.375$; $p < 0.001$). Serum IL-6 and IL-8 were undetectable.

We have demonstrated that subjects with low FEV₁ have raised sputum IL-8 levels and neutrophilia which is in accordance with our earlier reports.² In patients with asthma there is a strong correlation between the levels of IL-8 and bronchoalveolar lavage fluid levels of neutrophils and myeloperoxidase,³ suggesting a role for IL-8 as a chemoattractant and activator of neutrophils in the airway lumen. Now we report that, similar

to IL-8, sputum IL-6 levels also have an inverse relationship with FEV₁. Increased levels of IL-6 have been reported in mice with experimentally-induced allergic airway inflammation.⁴ Others have also shown correlations between levels of soluble intercellular adhesion molecule 1 and IL-6 in nasal provocation fluid in patients with allergic rhinitis and bronchial hyperresponsiveness.⁵ Moreover, in a small recently published prospective cross-sectional study in patients with mild asthma it was reported that sputum IL-6 levels correlated inversely with postbronchodilator FEV₁.⁶ IL-6 is responsible for the modulation of synthesis of acute phase proteins such as C-reactive protein, whose serum level is increased in severe asthma.⁷ IL-6 induces its inflammatory activity by interacting with its receptor and a signal transducing non-ligand (gp130), but also via the soluble IL-6 receptor (sIL-6R).⁸ Of note, sIL-6R/IL-6 is increased after allergen challenge in patients with asthma. More recently, Th17 cells have been identified which require transforming growth factor β and IL-6 for differentiation. IL-17, produced by Th17 cells, has been found to be increased in both asthma and chronic obstructive pulmonary disease, acting by upregulating the expression of a number of CXCR2 chemokines and promoting and sustaining neutrophilic inflammation.

In conclusion, we report strong negative correlations between FEV₁ and sputum IL-6 and IL-8 levels and a weak correlation with asthma control. The raised sputum IL-6 levels seen in patients with severe asthma are probably a characteristic of the inflammatory process in asthma. Local regulation of IL-6 may thus contribute to disease severity, poorer asthma control and the associated systemic inflammatory response. Future studies aimed at examining IL-6/sIL-6R and the role of Th17 cells in varying severities of asthma may help to determine whether IL-6 could serve as a possible therapeutic target in patients with severe asthma where there is a large unmet need.

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J B Morjaria,¹ K S Babu,¹ P Vijayanand,¹ A J Chauhan,² D E Davies,¹ S T Holgate¹

¹Infection, Inflammation and Immunity, Southampton University Hospitals Trust, Southampton, UK;

²Department of Respiratory Medicine, Queen Alexandra Hospital, Portsmouth, UK

Correspondence to Dr J B Morjaria, Mailpoint 810, South Academic Block, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK; jbm@soton.ac.uk

► Additional data are published online only. To view these files please visit the journal online (<http://thorax.bmj.com>).

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A trial of caspofungin salvage treatment in PCP pneumonia

Pneumocystis jirovecii pneumonia (PCP) remains a major cause of mortality in patients with HIV; we read with enormous interest the recent PCP mortality prediction rule stratifying 451 patients by mortality at

Figure 1 Correlation between forced expiratory volume in 1 s (FEV₁) and sputum interleukin 6 (IL-6) levels.