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) >50% but <80% predicted were studied from the baseline parameters of a clinical trial. Cell counts and cytokines were measured in induced sputum (see online supplement for Methods).

Eighteen subjects (9M, 9F) with severe asthma (mean±SD age 43.4±11.4 years (1SD), FEV1 59±14% (predicted) were studied (see table 1 in online appendix). The median (IQR) levels of sputum IL-6, IL-8, neutrophils (%), macrophages (%) and eosinophils (%) were 1853.8 pg/ml (1576.8–2537.7), 70.0 pg/ml (28.55–127.5), 32.5% (24.1–42.6), 46.6% (39.8–54.8) and 4.4% (3.2–9.4), respectively. We observed significant negative correlations between FEV1 (% predicted) and sputum IL-6 (r = -0.912, p < 0.001), IL-6 (r = 0.717, p = 0.0002) (figure 1) and neutrophils (r = 0.919, p = 0.014). The Asthma Control Questionnaire positively correlated with sputum IL-6 levels (r = 0.575; 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. In patients with asthma there is a strong correlation between the levels of IL-8 and bronchoalveolar lavage fluid levels of neutrophils and myeloperoxidase, 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. 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. 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. 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. 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).

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.

Acknowledgements The authors thank Drs D Bagmane, L C Liu and J Ward for help with the laboratory analyses and sample acquisition.

J B Morjaria, 1 K S Babu, 1 P Vijayanand, 1 A J Chauhan, 2 D E Davies, 3 S T Holgate 1

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, Malpoint 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).

Funding This study was supported by an educational grant from Wyeth Pharmaceuticals, UK, who were not sponsors of the study. The study was part of a trial that was investigator-initiated and the sponsors were not involved in the study design, data collection, analysis or interpretation of the data. STH is a UK Medical Research Council funded Clinical Professor.

Competing interests This study was conducted with an educational grant from Wyeth Pharmaceuticals. JBM is funded by the educational grant to conduct this study. AJC in the last 8 years has received research funding, honoraria for lectures and educational grants from Astra Zeneca, Glaxo Smith Kline, Boehringer Ingelheim and Merck and has been on Advisory Boards for Astra Zeneca and Glaxo Smith Kline. STH is a consultant for Novartis, Synargen, Merck, Wyeth and Centocor and has received lecture fees from these companies. The other authors have no competing interests.

Ethics approval This study was conducted with the approval of the SE Hampshire and Isle of Wight Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Accepted 23 March 2010

Published Online First 29 September 2010


REFERENCES


A trial of caspofungin salvage treatment in PCP pneumonia

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

J B Morjaria, K S Babu, P Vijayanand, A J Chauhan, D E Davies and S T Holgate

Thorax 2011 66: 537 originally published online September 29, 2010
doi: 10.1136/thx.2010.136523

Updated information and services can be found at:
http://thorax.bmj.com/content/66/6/537.1

These include:

References
This article cites 9 articles, 2 of which you can access for free at:
http://thorax.bmj.com/content/66/6/537.1#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/