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) ≥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 (28.5–127.5), 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-6 (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 = 0.575; p = 0.001). Serum IL-6 and IL-1 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). 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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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

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the time of illness presentation. The first-line treatment for this infection, cotrimoxazole, is associated with a number of adverse effects, including rash, leucopenia, thrombocytopaenia and interstitial nephritis. Therefore, treatment with cotrimoxazole significantly adds to the morbidity associated with this condition and we note in this study that this was the main treatment used.

One of the identifying characteristics of *P. jiroveci* is the presence of (1,3)-β-D-glucan in its cell wall. As the cell wall of this organism does not contain ergosterol (the target of azoles and polyenes), echinocandins, which target the synthesis of (1,3)-β-D-glucan, are likely to be the only effective antifungals for PCP.

Caspofungin was the first echinocandin licensed for empiric antifungal treatment in candidiasis and aspergillosis. In animal models of PCP echinocandins have demonstrated prophylactic and therapeutic efficacy. Furthermore, there are reports that caspofungin is effective salvage treatment for PCP. Echinocandins are associated with a low incidence of adverse events. Caspofungin does not inhibit the CYP system and does not induce CYP3A4 drug metabolism.

We present our experience of the use of caspofungin in the context of severe PCP in HIV-infected individuals. We performed a retrospective analysis of all patients treated for proven or probable PCP pneumonia over a 4 year period from our unit, the largest HIV cohort in Europe; appropriate ethical approval was obtained. For all patients, baseline demographics, CD4 count, viral load, PCP prophylaxis, radiological features, arterial blood gas analysis, PCP immunofluorescence, PCP treatment, ventilatory support, adverse reactions and outcomes were recorded. Treatment failure was defined as worsening hypoxia or radiographic features after 4 days of first-line treatment.

Over the 4 year study period 80 patients were treated for PCP, of whom 56 of the 76 tested had microbiologically confirmed PCP by immunofluorescence. The mean CD4 count measured at 109 (4-676) cells/ml; nine patients (9.8%) had microbiologically confirmed PCP with a CD4 count of >200, and a further nine had confirmed PCP with an undetectable viral load while receiving highly active antiretroviral therapy (HAART). A total of six patients had been receiving PCP prophylaxis at diagnosis. Overall mortality was 6.25% (5/81) and 5.5% (5/95) for microbiologically confirmed PCP. Five patients died overall (3 from respiratory failure, 1 from persistent pneumothorax and 1 refused all treatment).

Of these patients, 26 received cotrimoxazole as first-line treatment, six with clindamycin/primaqine, with atovaquone, and one patient received intravenous pentamidine. Twelve individuals required a treatment switch due to cotrimoxazole-related toxicities (7 rash, 2 hepatitis, 1 hyponatraemia, 1 diarrhoea and 1 nausea). A total of 12 patients with PCP not responding to first-line treatment received caspofungin in combination with other treatments. Of these patients, 10 had microbiologically confirmed PCP. None of these patients had other relevant fungi such as *Candida* or *Aspergillus* isolated by induced sputum or bronchoalveolar lavage.

Of these 12 patients, 10 individuals received treatment with caspofungin as a component of salvage therapy after first-line treatment failure, and two received caspofungin following first-line drug toxicity. Patients received caspofungin in combination with clindamycin/primaqine (6/12), cotrimoxazole (4/12) or intravenous pentamidine (2/12).

For the 10 patients who received caspofungin as a part of salvage therapy, two died, one from bilateral pneumothoraces which had been present since day 2 of diagnosis and one from Burkitt lymphoma. The patient with Burkitt lymphoma did not have microbiological confirmation of PCP. Therefore, for patients with microbiologically confirmed PCP treated with caspofungin, mortality was 1 in 10 or 10%.

Despite the advent of HAART for the treatment of HIV infection, PCP remains a major cause of mortality even in resource-rich settings. Recent data suggest that in the HAART era, mortality from this infection when microbiologically confirmed is ~10%. Over the last 4 years we have used caspofungin adjunctive treatment for the management of severe or refractory cases of PCP. Caspofungin targets the synthesis of β-glucan, a major component of the *P. jiroveci* cell wall. Furthermore this drug has minimal side effects and drug interactions, allowing its use as adjunctive treatment.

This single cohort study suggests that caspofungin may improve outcomes from PCP, with favourable comparative mortalities in our cohort (5.5%) compared with a recent study (9.7%) of confirmed cases of PCP from a similar cohort of UK patients in the HAART era. Randomised controlled studies of caspofungin for PCP are warranted and further suggest that the prediction rule may require modification in the setting of newer treatments.

**REFERENCES**


**Survey of the use of non-invasive positive pressure ventilation in UK and Australasian children with cystic fibrosis**

Non-invasive positive pressure ventilation (NIPPV) for respiratory failure in cystic fibrosis (CF) is frequently used in adults and has been shown to be of benefit to patients with advanced disease in terms of stabilisation of lung function, reduction in symptoms and increased exercise capacity. When used as an adjunct to physiotherapy, NIPPV increases oxygen saturations (*SpO₂*), tidal volume, maximum expiratory muscle strength and ease of sputum clearance.

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