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.1 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 (15D), FEV₁ 59±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 (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-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 = 0.575, 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.5 In patients with asthma there is a strong correlation between the levels of IL-8 and bronchoalveolar lavage fluid levels of neutrophils and myeloperoxidase,6 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.9

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 Lau and J Ward for help with the laboratory analyses and sample acquisition.

J B Morjaria,1 J S Babu,1 P Vijayanand,1 M J Chauhan,1 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, Malpighit 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 was 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 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

Letters to the Editor

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

Figure 1 Correlation between forced expiratory volume in 1 s (FEV₁) and sputum interleukin 6 (IL-6) levels.
the time of illness presentation. The first-line treatment for this infection, cotrimoxazole, is associated with a number of adverse effects, including rash, leucopenia, thrombocytopenia 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 \emph{P. jirovecii} is the presence of (1,3)-\beta-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)-\beta-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 CYF34A2 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 measured 109 (4–676) cells/ml; nine patients (8.8%) had microbiologically confirmed PCP. 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 \emph{Candida} or \emph{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/primaquine (6/12), caspofungozole (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 \beta-glucan, a major component of the \emph{P. jirovecii} 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.

Darius Armstrong-James, Justin Stebbing, Laurence John, Andrew Murungi, Mark Bower, Brian Gazzard, Mark Nelson

1. Imperial College, St. Stephens AIDS Trust, Chelsea and Westminster Hospital, UK; 2. Department of Infectious Diseases and Immunity, Imperial College London, UK; 3. Department of Infection and Tropical Medicine, Lister Unit, Northwick Park Hospital, Harrow, UK

Correspondence to Professor Justin Stebbing, Imperial College, Imperial College Healthcare NHS Trust, London W12 0NN, UK; j.stebbing@imperial.ac.uk

Competing interests: None.

Ethics approval: This study was conducted with the approval of the Riverside Ethics Committee.

Provenance and peer review: Not commissioned; externally peer reviewed.

Accepted 4 May 2010

Published Online First 29 September 2010


doi:10.1136/thx.2010.135350

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 eurputum clearance.

Miller et al. have shown that NIPPV is effective in improving both short-term and long-term outcomes for children with cystic fibrosis. However, there is a lack of evidence to support its use in the paediatric population, and the potential risks associated with its use must be carefully balanced against the benefits.

In this study, we aimed to assess the current practice of NIPPV in children with cystic fibrosis in the UK and Australasia.

Methods

We conducted a postal survey of all UK and Australasian centres providing respiratory physiotherapy or respiratory services for children with cystic fibrosis. The survey was sent to 20 centres in the UK and 18 in Australasia.

Results

Sixteen centres (78%) completed the survey, representing a total of 722 children with cystic fibrosis. The majority of centres (88%) had experience of using NIPPV, with a median of 5 years of experience (range 1–15 years). The median duration of NIPPV use per patient was 12 months (range 1–24 months).

The most common indications for NIPPV were exacerbations of cystic fibrosis (94%), sleep apnoea (87%), and bronchiectasis (87%). The median duration of NIPPV use per patient was 12 months (range 1–24 months).

Discussion

The results of this survey suggest that NIPPV is widely used in the UK and Australasia for the treatment of respiratory failure in children with cystic fibrosis. The indications for NIPPV use were similar to those reported in previous studies, with exacerbations of cystic fibrosis being the most common indication. The median duration of NIPPV use per patient was 12 months, which is consistent with previous reports.

The results of this survey highlight the need for further research to determine the optimal use and duration of NIPPV in children with cystic fibrosis. Further studies are required to assess the long-term effects of NIPPV on the progression of lung disease and the quality of life of children with cystic fibrosis. The potential risks associated with NIPPV, such as increased oxygen saturations and increased exercise capacity, should be balanced against the benefits of improved respiratory function and reduced symptoms.

Conclusion

This survey provides valuable information on the current practice of NIPPV in children with cystic fibrosis in the UK and Australasia. The results highlight the need for further research to determine the optimal use and duration of NIPPV in this population. Further studies are required to assess the long-term effects of NIPPV on the progression of lung disease and the quality of life of children with cystic fibrosis.