VEGF levels in pulmonary fibrosis

We read with interest the paper by Simler et al investigating angiogenic cytokines in patients with idiopathic interstitial pneumonia.1 We were surprised by their reported high levels of vascular endothelial growth factor (VEGF) in the plasma in the normal control group. Several other groups—including the manufacturers of the ELISA (R&D Systems)—have previously quoted normal plasma VEGF levels in the range 36–76 pg/ml.1 Indeed, one of the authors of the paper previously quoted normal VEGF levels as 76 pg/ml using a matched pair ELISA.2 It is clear therefore that the levels of 648 pg/ml quoted for normal controls are nearly 10 times higher than those reported previously.

One possible explanation is the low centrifugal force used for preparation of the plasma (300g for 12 minutes). The manufacturer of the ELISA recommends 1000g for 15 minutes to reduce platelet contamination of the plasma. Platelet secretion of VEGF is the reason for increased serum levels of VEGF compared with plasma and might explain the extraordinarily high levels of VEGF found in these normal subjects.1 Interestingly, 14 of the 49 patients (28.5%) were on immunosuppressive drugs which potentially reduce the platelet count. This may be an alternative explanation as to why there was no difference between normal patients and those with pulmonary fibrosis, in contrast to earlier reports in patients with connective tissue disease related pulmonary fibrosis.3

Although the plasma levels of VEGF correlated with fibrosis based on the CT score, it is difficult fully to appreciate the relevance of this finding without knowing the concentration of VEGF within the lung compartment because, in normal individuals, epithelial lining fluid levels of VEGF at 9–11 ng/ml are several orders of magnitude greater than that found in the circulation.4 Furthermore, previous investigators have reported reduced levels of alveolar VEGF in patients with idiopathic pulmonary fibrosis.5 Low levels of VEGF are also seen in the bronchoalveolar lavage (BAL) fluid of patients with acute lung injury, sarcoidosis, emphysema, and lung transplants. It would therefore appear that a reduced alveolar level of VEGF is a common feature of diseases associated with alveolar epithelial damage. Indeed, in ARDS, alveolar levels of VEGF are lowest in those with the worst lung injury.6 This is probably a result of reduced epithelial cell secretion of VEGF and increased expression of its soluble receptor, sVEGFR-1, which acts as a natural inhibitor to the bioactivity of VEGF.

The trophic role of VEGF within the lung is supported by the fact that VEGF acts as a proliferative factor for fetal pulmonary epithelial cells7 and lung targeted VEGF inactivation leads to an emphysema phenotype in mice.8 These studies suggest that reduced alveolar levels of VEGF may inhibit epithelial repair in a wide variety of lung diseases.

In summary, we have some concerns about the validity/reproducibility of the VEGF levels reported in the study by Simler et al. Furthermore, based on the available evidence, we believe it is inappropriate to suggest that antagonising VEGF would be a successful potential treatment for patients with pulmonary fibrosis. On the contrary, we believe this would hasten epithelial cell apoptosis and promote alveolar septal cell loss with resultant honeycombing and functional deterioration.

A G Richter, E O Maughan, G D Perkins, N Nathani, D R Thickett Lung Investigation Unit, Queen Elizabeth Hospital Birmingham, Birmingham B15 2TH, UK; d.thickett@bham.ac.uk

References

Vitamin E supplements in asthma

Pearson et al1 have failed to tease out any additional benefit of vitamin E supplementation in patients with mild to moderate asthma. Before concluding that this is the case, it is relevant to highlight several points in their study.

It is notable that the authors failed to measure any surrogate marker of inflammation such as exhaled nitric oxide, sputum eosinophils, or airway hyperresponsiveness (AHR) to an indirect bronchoconstrictor stimulus. Indeed, non-specific AHR to methacholine is only very tenuously linked to underlying bronchial inflammation and tends to be related to changes in airway calibre.2 In this respect, the use of adenosine monophosphate or mannitol to assess AHR may have provided information regarding the underlying inflammatory status as these agents, which act similarly,3 cause the release of inflammatory mediators rather than directly causing contraction of airway smooth muscle. Use of these bronchoconstrictor stimuli are also more akin to real life situations as cold air and exercise also act in a similar physiological fashion. Moreover, the use of adenosine monophosphate has been shown to be more sensitive in detecting shifts in AHR than methacholine by approximately one doubling dilution.4

It is important to point out in the present study1 that patients in both groups at baseline had neither demonstrable symptoms nor short acting bronchodilator use. This highlights the fact that these patients were clinically stable and there was no actual signal from which a discernable improvement in symptoms could be observed.

Before dietary manipulation with vitamin E is neglected, further studies are required in symptomatic asthmatics evaluating other important outcome parameters such as exacerbations and surrogate inflammatory biomarkers.

G P Currie
Department of Respiratory Medicine, Aberdeen Royal Infirmary, Aberdeen AB25 2ZD, UK

D K C Lee
Department of Respiratory Medicine, Ipswich Hospital, Ipswich IP4 5PD, UK

W J Anderson
Department of Respiratory Medicine, Antrim Hospital, Antrim BT41 2QB, UK

Correspondence to: Dr G P Currie, Department of Respiratory Medicine, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZD, UK; graeme.currie@yahoo.com

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Management of CAP using a validated risk score

The management of patients with community-acquired pneumonia (CAP) is characterised by considerable variation in admission rates, length of hospital stay, and use of institutional resources in different settings. The Pneumonia Severity Index (PSI) is a prediction rule for the short term risk of death in patients with CAP, improving the efficiency of patient care. In the year 2000, 86% of patients with CAP presenting at the emergency department of our hospital were admitted. A retrospective analysis of the PSI scores of these patients showed that 37% of them were in low risk classes (1 and 2) based on their PSI results, so their admissions were potentially avoidable.

We therefore designed a prospective study to assess the safety, feasibility, and efficacy of the PSI score for management decisions in patients with CAP. The study was approved by the local ethics committee and written informed consent was obtained from all patients.

The study was carried out in the 12 month period from 1 November 2001 to 31 October 2002. One hundred and seventeen adult patients diagnosed in the emergency department with CAP participated in the study and were managed using a computer based score with dedicated software (GesPoReX, Saxos software, Modena, Italy) for PSI calculation and data collection. CAP was defined as the presence of a pulmonary infiltrate on the chest radiograph and symptoms consistent with pneumonia including cough, dyspnoea, and pleuritic chest pain. Patients with severe immunosuppression, those admitted to hospital in the previous 15 days, and patients infected with HIV were excluded. According to published data, patients with PSI scores of 90 points or lower are recommended for outpatient treatment while those with higher scores are recommended for hospital admission. The score was used only as a guide to the admission decision and did not supersede clinical judgement. Follow up consisted of two visits, the first within 10 days and the second about 1 month after discharge from hospital. The choice of antibiotic treatment, route of administration, duration of antibiotic treatment, and criteria for discharge were according to local guidelines, mainly based on the recommendations of recently published guidelines.

None of these interventions changed between the two study periods. To compare data before implementation of the protocol we retrospectively identified 116 consecutive patients admitted with CAP in the preceding year.

There were no statistically significant differences in demographic and co-morbidity data between the two groups (table 1). In both groups there was a significant proportion of patients in the lowest risk class; this probably reflects the attitude of patients in our healthcare structure to have frequent access to hospital services, particularly when the “family” doctor is unavailable such as at night or during the weekend.

In the group managed after implementation of the protocol, 12 patients (10.3%) were admitted against PSI recommendations: six patients (or their relatives) strongly requested hospital admission, four were admitted for lack of adequate home care support, and two did not provide convincing assurance about compliance with treatment. Three (5.9%) of those admitted died; all were in class V of the PSI and two of the deaths were related to CAP.

The implementation of PSI based management reduced the median duration of hospital stay from 9.1 (2.1) days to 7.9 (4.9) days, with a total reduction in bed days from 1070 to 463. Of the 1070 total bed days in the retrospective phase of the study, 348 (32.5%) were attributable to patients admitted with PSI scores in class I or II. All patients treated as outpatients were alive at the 1 month follow up visit and all returned to their usual activities. No adverse clinical outcomes, including admission to hospital or the intensive care unit, mortality or complications were detected. Compared with the historical data in the previous year, the rate of admission for CAP during the 12 month study period showed a 37% reduction (95% CI 26 to 49) which was statistically highly significant (p<0.001). The Italian health system estimates the cost in the use of hospital resources as about 1900 Euros per CAP patient treated as an inpatient. Use of this critical pathway significantly decreased the prevalence of admission, theoretically saving about 110 000 Euros in 1 year.

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<th>Table 1 Characteristics of retrospective and intervention cohorts</th>
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<td><strong>Before protocol</strong> (n = 116)</td>
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<td>Mean (SD) age (years)</td>
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<td>Age &gt;75 years</td>
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<td>Sex (M/F)</td>
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<td>Mean (SD) hospital stay (days)</td>
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<td>Admission rate</td>
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*p<0.001 (z2 test).

References


Authors’ reply

The aim of our study was to investigate “the effect of 6 weeks regular supplementation with vitamin E on the clinical control of asthma.” We thus used a combination of objective and subjective measures of asthma as our outcomes. The entry criteria were designed to be as inclusive as possible and to cover a population with mild to moderate asthma.

However, as Currie et al highlight, our study population had few symptoms, with a median daytime and night time symptoms score of 0. A similar intervention study of vitamin C and magnesium from our group covering a comparable population also recruited a population with few asthma symptoms, which was why we used bronchial responsiveness to methacholine as one of our entry criteria in the current study. We considered this the best measure of bronchial responsiveness when we designed the study, but agree that an alternative technique may have produced a different result.

We also agree with Currie et al that further studies of vitamin E are required in patients with asthma, including symptomatic asthmatics, particularly with regard to clinically relevant outcomes such as exacerbations.

P Pearson, A Fogarty
Division of Respiratory Medicine, University of Nottingham, Nottingham City Hospital, Nottingham NG5 1PB, UK

J Britton
Division of Epidemiology and Public Health, University of Nottingham, Nottingham City Hospital, Nottingham NG5 1PB, UK

Correspondence to: Dr A Fogarty, Division of Respiratory Medicine, University of Nottingham, Clinical Science Building, Nottingham City Hospital, Nottingham NG5 1PB, UK, andrew.fogarty@nottingham.ac.uk

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www.thoraxjnl.com
L Richeldi, M De Guglielmo, L M Fabbri
Respiratory Disease Clinic, University of Modena and Reggio Emilia, Modena, Italy
D Giovannardi
Emergency Department, Policlinico Hospital, Modena, Italy
F Marchetti, M Larosa
OloxaSmithKline Italia, Verona, Italy
V Salfini, M Altini
Medical Direction, Azienda USL Città di Bologna, Bologna, Italy
Correspondence to: Dr L Richeldi, Respiratory Disease Clinic, University of Modena and Reggio Emilia, Policlinico Hospital, Via del Pozzo 71, 41100 Modena, Italy; richeldi.luca@unimo.it

The authors thank R D’Amico for his expert statistical advice. This study was supported in part by OloxaSmithKline Italia (Italy). The authors do not have any competing interests regarding this study.

References

Plasma cell mucositis of the distal airways

Plasma cell mucositis is a rare idiopathic condition consisting of a marked infiltration of mucosa by plasma cells that may involve the mucous membranes of the upper aero-digestive tract—namely, the palatine mucosa, gingiva, supraglottic and glottic larynx, and the trachea. While plasma cell mucositis is usually considered benign, cases of critical stenosis of the upper airway have been reported.1–4 We present a case of plasma cell mucositis involving the trachea and bronchi. This pattern of lower respiratory tract involvement has not previously been described. A 55 year old woman, a lifelong non-smoker, presented with chronic cough, dyspnoea, and stridor. Pulmonary function tests showed a moderately severe obstructive ventilatory defect with forced expiratory volume in 1 second (FEV₁) of 1.44 l (56% of predicted), forced vital capacity (FVC) of 3.00 l (96% of predicted), and a FEV₁/FVC of 48%. Bronchoscopy revealed narrowing of the left mainstem bronchus (fig 1) and diffuse mucosal abnormalities of the bronchial tree. A biopsy specimen showed a dense plasma cell infiltrate of the mucosa consistent with plasma cell mucositis. Molecular analysis for heavy chain immunoglobulin rearrangement failed to demonstrate a clonal B cell population of lymphocytes. Before starting treatment the patient had an episode of hypoxemic respiratory failure requiring intubation and mechanical ventilation secondary to a mucus plug occluding her left mainstem bronchus which was removed. She was placed on prednisone 1 mg/kg with improvement in her symptoms. Because of the severity of her symptoms, cytotoxic therapy was initiated with chlorambucil 30 mg with monthly pulses of prednisone 100 mg daily for 4 days. There was marked improvement in her symptoms during the pulse of corticosteroids but this was not sustained. After 4 months of treatment pulmonary function studies remained unchanged. Bronchoscopic examination revealed persistent bronchial mucosal abnormalities with plasma cell infiltrate on endobronchial biopsy. The patient remained symptomatic and underwent bronchoscopy with argon plasma coagulation with debridement of the affected mucosa and subsequent recanalisation of the left mainstem bronchus with dramatic symptomatic improvement.

Plasma cell mucositis was first described in 1952 by Zoon5 in the context of glans penis involvement and has now been reported to involve the vulva, buccal mucosa, lips, tongue, supraglottic larynx, glottic larynx, and the trachea. Although this condition is considered benign, previous reports have illustrated an aggressive clinical course. Two reported cases have described patients who ultimately required tracheostomy for airway compromise.6 Surgical intervention and CO₂ laser excision have also been used in the setting of airway compromise.2 Treatment for plasma cell mucositis is not established. Reports have described the use of both topical and systemic corticosteroids,1,3 cytotoxic and radiation therapy,2 and surgical intervention.1 In our patient debridement of the affected mucosal tissue of the left mainstem bronchus with argon plasma coagulation resulted in symptomatic improvement.

In many instances treatment regimes have resulted in stabilisation of disease but have not consistently been associated with disease regression.

Long term prognosis appears good. One case series of nine patients showed that patients were alive with disease up to 16 years after the initial diagnosis.7 No cases with progression of disease to lymphoma have been reported.

M R Lucarelli, J N Allen
Ohio State University Medical Center, Division of Pulmonary, Critical Care, and Sleep Medicine, Columbus, OH 43210, USA

C M Magro
Ohio State University Medical Center, Department of Pathology, Columbus, OH 43210, USA
Correspondence to: Dr M R Lucarelli, Ohio State University Medical Center, Division of Pulmonary, Critical Care, and Sleep Medicine, Columbus, OH 43210, USA, lucarelli.1@medctr.osu.edu

The authors have no competing interests.

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CORRECTIONS
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BTS Winter Meeting abstracts
In abstract P30 on page i52 of the 2004 BTS Winter Meeting abstracts (Suppl II) the text at the end of the Background section was incorrectly changed during the editing process. The original text read “between 6–10%” and was changed to “between 0 and 6%”. The publishers apologise for this error.

doi: 10.1136/thx.2004.007cor

Prevalence of TB in healthcare workers in south west London
In the Letter to the Editor entitled “Prevalence of TB in healthcare workers in south west London” which appeared in the November issue of Thorax (2004;59:1002–3) the name of one of the authors was incorrectly spelt. The authors’ names should have appeared as follows: T B L Ho, C F J Rayner, T Lindfield, Y Young, and R J Whitfield. The publishers apologise for this error.

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Management of CAP using a validated risk score

L Richeldi, M De Guglielmo, L M Fabbri, D Giovanardi, F Marchetti, M Larosa, V Solfrini and M Altini

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