PostScript

LETTERS

Effect of azithromycin on primary bronchial epithelial cells derived from stable lung allografts

Obliterative bronchiolitis (OB), the main cause of lung allograft failure, is characterised by airway inflammation, neutrophilia, remodelling and fibrosis. Recent studies of the macrolide antibiotic azithromycin in OB, including one from our centre, have reported improved lung function with rescue therapy.[1] The mechanism for this improvement remains unclear, but a recent study suggests that neutrophilic inflammation may be an important predictor of clinical response.[2]

Macrolides have anti-inflammatory properties in several pulmonary conditions. We hypothesised that the clinical benefit observed with azithromycin in patients undergoing lung transplantation may be related to the inhibition of factors key to airway neutrophilic inflammation, remodelling and fibrosis. The bronchial epithelium is in a pivotal position as a target and orchestrator of airway inflammation and remodelling. We tested our hypothesis using a unique primary bronchial epithelial cell (PBEC) model.[3] The local research ethics committee approved the study.

Following pre-bronchoscopic assessment, surveillance bronchoscopy and bronchoalveolar lavage microbiology were performed to rule out infection. Bronchial brushings were obtained from subsegmental bronchi for PBEC cultures. Transbronchial specimens were examined to exclude acute vascular rejection. PBECs were established using endobronchial brushings from 10 clinically stable transplant recipients.

Azithromycin (Pfizer Ltd, Sandwich, UK) 20, 10 and 5 ng/ml was added to PBECs for 48 h before removal of cell supernatant and protein analysis with multiplex kits (R&D Systems Europe Ltd, Abingdon, UK) and a Luminex analyser. A methylene blue assay was used to correct data for PBEC cell number and the data were analysed using the Wilcoxon signed rank test.

Azithromycin caused a significant decrease in matrix metalloproteinase (MMP)-2, interleukin (IL)-8, granulocyte-macrophage colony stimulating factor (GM-CSF) and MMP-9 levels, with a trend towards decreased IL-6 production (table 1). Basal MMP-9 (2/10) and MMP-2 and GM-CSF levels (3/10) were below detection limits in some PBEC cultures. These factors are critical in orchestrating neutrophil influx, influencing antigen presenting cells and potentiating airway remodelling, which are relevant to the pathophysiology of OB. IL-8 is a neutrophil chemoattractant with additional roles in angiogenesis and remodelling, while IL-6 plays a part in B cell differentiation, monocyte proliferation, neutrophil recruitment, activation and degranulation, which may have pathophysiological roles in OB. GM-CSF regulates accumulation and activity of neutrophils and is increased in lung disease characterised by neutrophilic infiltration and in the post-transplant airway.[4] It is also associated with an increased number and activity of antigen presenting cells, including activated dendritic cells.

It is assumed that fibroblasts are responsible for the production of scar collagen in chronic transplant rejection. We have shown potential for injured airway epithelial cells from allografts to become fibroblasts through epithelial mesenchymal transition (EMT) and have demonstrated a key role for MMPs in facilitating this phenotypic change.[5] The ability of azithromycin to modulate the epithelial release of these factors is therefore consistent with a potential to influence alloimmunity, neutrophilic inflammation, EMT, remodelling and fibrosis. We therefore suggest that this may underlie the clinical benefit of azithromycin seen in certain patients, but further animal model and in vivo studies including randomised trials are required.

Desmond M Murphy, Ian A Forrest, Chris Ward, Paul A Corris, Gail E Johnson, Debbie Jones, Andrew J Fisher
Institute of Cellular Medicine, The University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Jim J Egan
The Irish Lung Transplant Programme, The Mater Hospital, Dublin, Ireland

Timothy E Cawston, James L Lordan
Institute of Cellular Medicine, The University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Correspondence to: Dr James L Lordan, William Leech Centre for Lung Research, The Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK; Jim.Lordan@nuth.nhs.uk

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Table 1 Effect of azithromycin at concentrations of 5, 10 and 20 ng/ml on IL-8, GM-CSF, IL-6, MMP-2 and MMP-9 levels

Azithromycin concentration (ng/ml)	IL-8 ng/10^6 cells (n = 10)	GM-CSF ng/10^6 cells (n = 7)	MMP-9 ng/10^6 cells (n = 8)	MMP-2 ng/10^6 cells (n = 7)	IL-6 pg/10^6 cells (n = 3)
0	4.4 (0.6–13.0)	1.1 (0.1–5.5)	34.2 (5.5–65.6)	2.2 (0.4–8.7)	54.6 (36.4–238.0)
5	3.4 (0.5–14.5)	0.6 (0.1–4.3)	20.4 (3.9–66.4)*	1.0 (0.4–4.1)	37.0 (24.7–91.6)
10	2.2 (0.4–16.9)	0.4 (0.1–3.3)	20.5 (3.6–93.9)	1.2 (0.4–6.9)*	39.3 (36.8–71.0)
20	1.8 (0.2–7.3)**	0.5 (0.1–2.9)*	14.6 (1.4–35.1)**	0.6 (0.4–5.0)*	35.0 (21.6–46.4)

IL, interleukin; GM-CSF, granulocyte-macrophage colony stimulating factor; MMP, matrix metalloproteinase.
Data shown are median (range) values.
Experiments were analysed for n = 10 for IL-8, n = 8 for MMP-9, and n = 7 for both MMP-2 and GM-CSF. Where azithromycin decreased analyte levels below the assay detection limit, a value halfway between the lowest level of the detection range and zero was assigned. The Wilcoxon signed rank test was used to test for statistical significance with a two-sided p value <0.05 deemed significant. *$p<0.05$; **$p<0.01$. IL-6 data (n = 3) were not statistically analysed.

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Critical care as part of respiratory training in the UK

Experience in critical care medicine is mandatory for all respiratory trainees in the UK with a need for 60 days (3 months) minimum placement in an intensive care unit (ICU). The Respiratory Critical Care Group of the British Thoracic Society[1] recently reported a survey in which there was widespread agreement with this requirement, although it was inadequately provided by a number of programmes. In addition, a proportion of trainees indicated the intention to subspecialise in intensive care medicine and were concerned that their ICU experience was diluted by having responsibilities such as acute general medical takes during their attachment. We recently carried out an email survey of anaesthetic and respiratory trainees and directors of intensive care which provides additional useful information.

The majority of ICUs in the UK operate an admission policy that depends on making initial contact with the duty anaesthetic registrar. One aspect of our survey concerned the interaction between the referring physician and the critical care ''gate keeping'' specialist. Although it might be optimal to involve the appropriate medical, emergency or surgical consultant directly in making a referral to the critical care consultant, it is often specialist registrars who refer patients, especially out of hours.

Our survey investigated whether the specialty of the referring specialist registrar affected the outcome. A total of 108 doctors (97 specialist registrars and 9 ICU lead consultants) from South Thames, West Midlands and Oxford regions were surveyed in 2006. Of the respiratory specialist registrars, 27% indicated they ''commonly'' or ''always'' had difficulty gaining admission for medical patients. No anaesthetic trainee reported difficulty ''commonly'' or ''always'' while 47% reported that

they "rarely" had difficulty. The different experience may reflect a difference between elective or semi-elective postoperative admissions versus acute medical admissions. Perceived or actual experience in intensive care could be another factor; 48% of respiratory specialist registrars had experience of intensive care medicine at the SHO level compared with 100% of anaesthetic trainees, and all the anaesthetic trainees had experience at the registrar level compared with 52% of the respiratory specialist registrars. Both groups underestimated the duration of critical care experience of each other.

Critical care leads considered that the "quality" of referral was better from specialist registrars in anaesthesia than medicine. They strongly supported the need for physicians to receive more training in how to make effective referrals and in achieving a more "realistic" understanding of potential benefit from ICU admission.

Our survey confirms the common perception that medical teams have more difficulty than anaesthetic colleagues in gaining acceptance of their patients to intensive care. Furthermore, this may relate to the perception that they are less able to judge need or prognosis because they have less ICU experience. Critical care training is soon to be integrated into acute care common stem,[2] but additional experience for all medical specialties is probably needed together with an expansion of dual accreditation by medical specialists in intensive care medicine.

B C Creagh-Brown
Department of Respiratory Medicine, St George's Hospital, London, UK

A McD Johnston
Department of Medicine and Royal Centre for Defence Medicine, University Hospital Birmingham, Birmingham, UK

D Pandit
Department of Respiratory Medicine, Princess Royal Hospital, Telford, UK

R J Parker
Department of Respiratory Medicine, Northampton General Hospital, Northampton, UK

A C Davidson
Programme Director South Thames, Guy's and St Thomas' Hospital, London, UK

Correspondence to: Dr B C Creagh-Brown, Department of Respiratory Medicine, St George's Hospital, London SW17 0QT, UK; drbencb@gmail.com

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Breathing techniques in the management of asthma

We welcome the study by Slader *et al*[1] recently published in *Thorax* as the current state of our knowledge on breathing techniques for asthma is deplorable,[2] although such techniques are frequently used by physiotherapists when treating patients with asthma.[3]

Several aspects in this study may have influenced the results and need to be discussed.

First, the absence of evidence that upper body exercises, used as a comparator in this study, have an impact on lung function should not be confused with evidence that such an effect is absent. The two studies identified in the Cochrane review on breathing exercises for asthma,[2] that included forced vital capacity or forced expiratory volume in 1 s as an outcome, had only 8–12 patients in each group. If upper body exercises are in fact effective, the contrast between the two interventions may have been insufficient.

Second, we believe that more attention is needed for the hypothesis that the subjects recruited in this study were a special group. The patients were recruited using a database of volunteers and advertising in the lay press. In our view this may jeopardise the generalisability of the results to patients who consult a doctor for asthma.

Finally, the possibility that the two breathing routines provided a non-specific deferral strategy for reliever use needs further testing by, for example, comparing a breathing exercise with other (non-physical) deferral strategies.

Johannes C van der Wouden, Arianne P Verhagen
Department of General Practice, Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands

Correspondence to: Dr J C van der Wouden, Department of General Practice, Erasmus MC – University Medical Center Rotterdam, P O Box 2040, 3000 CA Rotterdam, The Netherlands; j.vanderwouden@erasmusmc.nl

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NICE guidance for screening for malnutrition: implications for lung cancer services

The National Institute for Health and Clinical Excellence (NICE) guidelines on nutrition support in adults recommends screening all outpatients at their first clinic appointment to identify those who have malnutrition or are at risk of malnutrition.[1] A recent study of inpatients with cancer also suggests outpatient screening to improve the early identification of patients who may benefit from nutritional support.[2] In response to this, we have examined the potential impact of introducing routine screening for malnutrition into the two Combined Lung Oncology Clinics held weekly at the Nottingham University Hospitals NHS Trust. Neither clinic routinely screens for malnutrition, and referrals to a dietician are made—relatively infrequently—on an ad hoc basis. The malnutrition universal screening tool (MUST)[3] was completed in 50 consecutive patients with lung cancer at their first or second outpatient attendance following their histological diagnosis. Using either the NICE or MUST guideline recommendations, about one third of patients had or were at high risk of malnutrition (table 1).[1 3]

Table 1 Screening for malnutrition in 50 outpatients with lung cancer

Mean (SD) age (years)	69 (10)
M:F	28:22
NSCLC:SCLC	39:11
Performance status (East Coast Oncology Group)	
0–1	37
≥2	7
Unknown	6
Mean (SD) BMI (kg/m^2)	24 (5)
NICE recommends nutritional support is considered for any of the following:	
BMI <18.5 kg/m^2; weight loss >10% or	
BMI <20 kg/m^2 and weight loss >5%	
Total meeting one of the above criteria	15 (30%)
MUST score, n (%)	
0 (routine clinical care)	20 (40%)
1 (medium risk, observe)	12 (24%)
≥2 (high risk, needs nutritional treatment)	18 (36%)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; BMI, body mass index.

The introduction of routine screening for malnutrition into lung cancer clinics is therefore likely to identify a large number of patients at the time of their diagnosis who should be considered for nutrition support. The challenge locally is to identify how screening can be implemented routinely and how the dietetic input required can be funded, at a time when financial constraints are limiting service development. The generally nihilistic view of nutritional support will also need to be addressed. Progress cannot be made unless such patients are identified, receive high quality support and have the opportunity to take part in trials that aim to improve outcomes.

Alpna Chauhan, Vanessa Siddall, Andrew Wilcock
Department of Palliative Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK

Sugamya Mallawathantri, David R Baldwin, Ian D Johnston
Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK

Correspondence to: Dr Alpna Chauhan, Department of Palliative Medicine, Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, UK; alpna.chauhan@nuh.nhs.uk

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