

- cardiovascular mortality and cardiovascular risk factors in men. *Eur Heart J* 2000;**21**:1584–90.
- 8 Dahl M, Tybjaerg-Hansen A, Vestbo J, et al. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**164**:1008–11.
 - 9 Engstrom G, Lind P, Hedblad B, et al. Lung function and cardiovascular risk: relationship with inflammation-sensitive plasma proteins. *Circulation* 2002;**106**:2555–60.
 - 10 Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;**107**:1514–9.
 - 11 Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: Data from the third national health and nutrition examination. *Am J Med* 2003;**114**:758–62.

TB screening and anti-TNF α treatment

Reactivation of tuberculosis (TB) is a major concern during treatment with TNF inhibitors.¹ Different guidelines to detect active and latent TB have been recommended in various countries before starting treatment with these drugs. There is evidence that their application has led to a significant reduction in the number of cases of TB,² but we do not know which is the most cost effective strategy.

In our department 69 consecutive patients with rheumatoid arthritis (n = 53), ankylosing spondylitis (n = 10), and psoriatic arthritis (n = 6) considered for treatment with TNF inhibitors have recently been screened for TB infection according to the Italian guidelines. All underwent a careful history, tuberculin skin testing by intradermal injection of 0.2 ml 10 TU PPD (Mantoux method), and chest radiography. In order to enhance the sensitivity of tuberculin testing we had stopped steroid treatment in all patients at least 1 week before performing the test. Patients were considered to be affected by latent TB if they had any of the following conditions: (1) unequivocal history of previous TB; (2) positive tuberculin reaction (at least 5 mm skin induration at 72 hours); (3) radiographic lesions consistent with old TB (calcified nodular lesions, apical fibrosis, pleural scarring). According to our guidelines, patients with latent TB undergoing treatment with TNF inhibitors receive preventive chemotherapy. Our patients were predominantly women (63.8%) with a mean age of 55.8 years (range 21–81). We found a history of previous TB in 2.9% of patients, tuberculin positivity in 8.7%, and radiographic lesions consistent with latent TB in 20.3%. Globally, a diagnosis of latent TB was made in 24.6% of our patients, six of whom underwent treatment with TNF inhibitors (notably, five of the six had a negative tuberculin test). We started preventive chemotherapy with isoniazid in all patients but this drug was discontinued in four because of liver toxicity.

Our data suggest that tuberculin skin testing is not sufficiently sensitive to detect latent TB in patients with rheumatoid arthritis and other spondyloarthropathies or in those with inflammatory bowel diseases.³ In these patients chest radiography is essential if we do not want to miss a significant proportion of cases. The Italian guidelines for TB screening before starting treatment with TNF inhibitors allow recognition of these cases,

increasing the indications for preventive chemotherapy. However, liver toxicity caused by isoniazid may be enhanced in these patients, probably due to concomitant treatment with other drugs such as methotrexate and NSAIDs. This suggests that the risk of chemoprophylaxis should be compared with the chance of contracting TB in the individual patient, and that a cost effectiveness evaluation of the different strategies used to minimise the risk of TB reactivation during treatment with TNF inhibitors is indicated.

G Provenzano, M C Ferrante, G Simon

Department of Internal Medicine and Respiratory Diseases, AO "Villa Sofia-CTO", Palermo, Italy; giuseppe.provenzano5@tin.it

doi: 10.1136/thx.2005.042457

References

- 1 Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum* 2004;**50**:372–9.
- 2 Gomez-Reino JJ, Carmona I, Valverde VR, et al. Treatment of rheumatoid arthritis with tumour necrosis factor inhibitors may predispose to significant increase in tuberculosis risk. A multicenter active surveillance report. *Arthritis Rheum* 2003;**48**:2122–7.
- 3 Mow WS, Abreu-Martin MT, Papadakis KA, et al. High incidence of anergy in inflammatory bowel disease patients limits the usefulness of PPD screening before infliximab therapy. *Clin Gastroenterol Hepatol* 2004;**2**:309–13.

Risedronate induced BOOP complicated with sarcoidosis

Bisphosphonates are synthetic compounds that are taken up preferentially by skeletal tissue and suppress osteoclast mediated bone resorption. They are being used increasingly in the treatment of osteoporosis.¹ Bronchoconstriction caused by bisphosphonates has been described² but drug induced pneumonitis has not previously been reported.³ This is the first report of interstitial pneumonia induced by the bisphosphonate risedronate.

A woman developed an intramuscular mass in her right arm at the age of 51 years. Sarcoidosis was diagnosed by non-necrotising epithelioid granulomas in the resected specimen of the mass, bilateral hilar lymphadenopathy on the chest radiograph, a negative reaction to tuberculin test, and an increase in the serum angiotensin converting enzyme (ACE) level to 27.9 U/ml. She had pain in her right arm due to the mass and was treated with prednisolone for 10 years. The mass disappeared and the ACE level fell to 9.6 U/ml.

At the age of 66 years treatment was started with risedronate for osteoporosis. Two months later she developed a dry cough, high fever, and bilateral infiltrative shadows were seen on the chest radiograph (fig 1A). A high resolution CT scan showed multiple consolidation and ground glass opacity with interlobular and intralobular interstitial thickening (fig 1B). Mediastinal lymph nodes measuring about 1 cm and small amounts of bilateral pleural effusion were visible on the CT scan. Chest auscultation showed no crackles and neither the superficial lymph nodes nor the intramuscular mass lesions were palpable. Laboratory examination showed white blood cell (WBC) count of 9100/ μ l, C-reactive protein (CRP) 7.31 mg/dl, lactate dehydrogenase (LDH) 201 U/ml, ACE

5.3 U/ml, and lysozyme 8.9 U/ml. Total cell count of the bronchoalveolar lavage (BAL) fluid performed on left B⁴ was 4.18 \times 10⁵/ml with 43.4% macrophages, 15.8% neutrophils, 24.2% lymphocytes, and 16.0% eosinophils. The CD4+/CD8+ ratio of lymphocytes in the BAL fluid was 1.37. No pathogenic organisms were detected in the BAL fluid, and trans-bronchial lung biopsy specimens revealed no granulomas but cellular alveolitis with intraluminal polypoid organisation consistent with bronchiolitis obliterans organising pneumonia (BOOP). These findings ruled out reactivation of sarcoidosis.

Treatment with several antibiotics did not improve her symptoms and laboratory findings, so all her drugs (risedronate, pravastatin, neurotrophin, menatetrenone, and sairei-to) were stopped because drug induced pneumonitis was suspected. Her high fever began to resolve about 5 days after stopping the drugs and her symptoms and the abnormal shadows on the chest radiograph disappeared 2 weeks later. The WBC and CRP level were also normalised. A drug lymphocyte stimulation test (DLST) on her peripheral lymphocytes gave a positive reaction only to risedronate with a stimulation index of 265%. There was a negative reaction to the other four drugs, all of which had been administered to her for at least 4 years. She was therefore diagnosed with risedronate induced pneumonitis.

Amino-bisphosphonates including alendronate, pamidronate, and risedronate are reported to induce pro-inflammatory cytokines from macrophages in vitro and in vivo

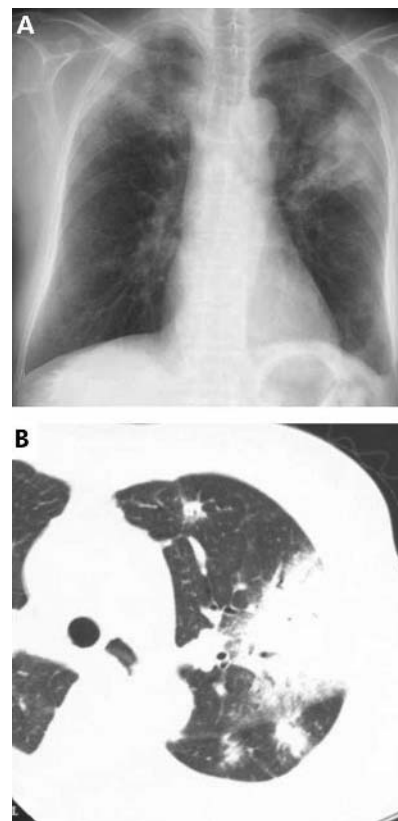


Figure 1 (A) Chest radiograph showing infiltrative shadows. (B) High resolution CT scan of the chest showing multiple consolidation and ground glass opacity with interlobular and intralobular interstitial thickening.

and to cause transient pyrexia, a flu-like syndrome, and serological changes resembling a typical acute phase reaction in some cases.⁴ They are also reported to induce anterior uveitis through these reactions or specific immunological responses.⁵ However, pneumonitis associated with amino-bisphosphonates has not been previously reported. In this case the specific immunological reaction to risedronate by DLST suggested that her lung disease was caused by the drug rather than by non-specific release of pro-inflammatory cytokines.

Osteoporosis is a common disease and bisphosphonates will be prescribed frequently. The possibility of pneumonitis caused by risedronate and other bisphosphonates needs to be kept in mind.

T Arai, Y Inoue, S Hayashi, S Yamamoto, M Sakatani

National Hospital Organization Kinki-chuo Chest Medical Center, Sakai, Japan

Correspondence to: Dr Y Inoue, National Hospital Organization Kinki-chuo Chest Medical Center, 1180 Nagasone-cho, Sakai City, Osaka 591-8555, Japan; giichi@kch.hosp.go.jp

doi: 10.1136/thx.2005.043893

References

- 1 **Peters ML, Leonard M, Licata AA.** Role of alendronate and risedronate in preventing and treating osteoporosis. *Cleve Clin J Med* 2001;**68**:945–51.
- 2 **Rolla G, Bucca C, Brussino L.** Bisphosphonate-induced bronchoconstriction in aspirin-sensitive asthma. *Lancet* 1994;**343**:426–7.
- 3 **Adami S, Zamberlan N.** Adverse effects of bisphosphonates. A comparative review. *Drug Saf* 1996;**14**:158–70.
- 4 **Thiebaud D, Sauty A, Burckhardt P, et al.** In vitro and in vivo study of cytokines in the acute-phase response associated with bisphosphonates. *Calcif Tissue Int* 1997;**61**:386–92.
- 5 **Macarol V, Fraunfelder FT.** Pamidronate disodium and possible ocular adverse drug reactions. *Am J Ophthalmol* 1994;**118**:220–4.

Bacterial denitrification, nitric oxide and airway pH in CF

The recent findings of Ojoo *et al*¹ are of considerable interest. However, one confounding factor that appears to have been overlooked in recent studies of airway pH and exhaled breath nitric oxide (eNO) levels in cystic fibrosis (CF) is that of bacterial respiration. *Pseudomonas aeruginosa* adopts an anaerobic and biofilm mode of existence within the CF lung and, under such environmental conditions, it uses NO rather than oxygen as an electron donor to generate energy via oxidative phosphorylation. This bacterial denitrification results in the stepwise reduction of NO to nitrite (NO₂), nitrate (NO₃), and ultimately ammonium.^{2–3} It is surprising that such an important metabolic process has been ignored as the high energy requirements of large bacterial loads in the CF lung imply substantial consumption of NO. This could explain both the low levels of measured eNO and high (NO₂)/(NO₃) content described in the sputum and exhaled breath condensates of patients with CF. The products of denitrification are likely to alter the chemical milieu substantially, including the pH of the airway. Further research is needed to examine how the metabolic activity of bacteria and the host inflammatory response interact

to change the chemical composition of the lung microenvironment in CF.

D W Reid

Medical School, University of Tasmania, Hobart, Australia 7000; d.e.c.reid@utas.edu.au

References

- 1 **Ojoo JC, Mulrennan SA, Kastelik JA, et al.** Exhaled breath condensate pH and exhaled nitric oxide in allergic asthma and in cystic fibrosis. *Thorax* 2005;**60**:22–6.
- 2 **Wasser IM, de Vries S, Moenne-Loccoz P, et al.** Nitric oxide in biological denitrification: Fe/Cu metalloenzyme and metal complex NO(x) redox chemistry. *Chem Rev* 2002;**102**:1201–34.
- 3 **Ye RW, Averill BA, Tiedje JM.** Denitrification: production and consumption of nitric oxide. *Appl Environ Microbiol* 1994;**60**:1053–8.

Authors' reply

We thank Dr Reid for his interest in our paper.¹ Bacterial denitrification involves the stepwise reduction of oxides of nitrogen to support oxidative phosphorylation.² Gaston *et al*³ have previously proposed that consumption of nitric oxide (NO) during this process might be one factor contributing to the low fractional exhaled NO concentration (F_{ENO}) seen in cystic fibrosis (CF). It is clearly not the only mechanism, however, as decreased F_{ENO} levels have been reported in infants with newly diagnosed CF,⁴ and reduced NO generation is also described in cystic fibrosis transmembrane conductance regulator (CFTR) deficient mice.⁵ Bacterial denitrification would be expected also to deplete nitrate (NO₃⁻) and nitrite (NO₂⁻) levels in the local milieu and to increase its pH.

In our study 14 of the 18 subjects with stable CF were chronically colonised with *Pseudomonas aeruginosa*. Interestingly, F_{ENO} levels were indeed significantly lower in CF subjects with *P aeruginosa* than in those without (2 (1) v 7 (5) ppb; p = 0.015). The median NO₂⁻ and NO₂⁻/NO₃⁻ levels in exhaled breath condensate (EBC) were also lower in subjects with *P aeruginosa*, although this difference did not reach statistical significance. Irrespective of the presence of the organism, values for both NO₂⁻ and NO₂⁻/NO₃⁻ were substantially higher in CF subjects than in healthy controls. There was little difference in the median pH of the EBC between CF subjects with and without *P aeruginosa*.

These further analyses provide support for the suggestion that denitrification by *P aeruginosa* may modulate the nitrogen redox balance in CF airways. They are consistent with the findings of Gaston *et al*³ who described NO consumption and ammonium (NH₄⁺) generation by *P aeruginosa* in vitro and also a reduction in NH₄⁺ levels in the sputum of CF subjects after antipseudomonal treatment. Further comparisons involving larger numbers of CF subjects with and without *P aeruginosa*, and investigation of the relative impact of antimicrobial therapies in the two groups, may help to define the extent to which this mechanism operates in CF airways in vivo. Its relevance to airway pathophysiology, however, will be more difficult to determine.

J C Ojoo, S A Mulrennan, J A Kastelik, A H Morice, A E Redington

Division of Academic Medicine, Postgraduate Medical Institute, University of Hull, Hull, UK

Correspondence to: Dr A E Redington, Department of Respiratory Medicine, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK; aredington@hntt.org

References

- 1 **Ojoo JC, Mulrennan SA, Kastelik JA, et al.** Exhaled breath condensate pH and exhaled nitric oxide in allergic asthma and in cystic fibrosis. *Thorax* 2005;**60**:22–6.
- 2 **Zumft WG.** Cell biology and molecular basis of denitrification. *Microbiol Mol Biol Rev* 1997;**61**:533–616.
- 3 **Gaston B, Ratjen F, Vaughan JW, et al.** Nitrogen redox balance in the cystic fibrosis airway: effects of antipseudomonal therapy. *Am J Respir Crit Care Med* 2002;**165**:387–90.
- 4 **Elphick HE, Demoncheaux EAG, Ritson S, et al.** Exhaled nitric oxide is reduced in infants with cystic fibrosis. *Thorax* 2001;**56**:151–2.
- 5 **Steagall WK, Elmer HL, Brady KG, et al.** Cystic fibrosis transmembrane conductance regulator-dependent regulation of epithelial inducible nitric oxide synthase expression. *Am J Respir Cell Mol Biol* 2000;**22**:45–50.

Exhaled NO in diffuse alveolar haemorrhage

The syndrome of diffuse alveolar haemorrhage (DAH) is associated with a wide variety of diseases. Haemoptysis, falling haemoglobin, and air space opacities on the chest radiograph constitute a triad of features suggestive of DAH which should be confirmed by bronchoalveolar lavage (BAL).¹ However, haemoptysis can be absent in up to one third of patients. A sensitive marker of DAH is a sequential increase in the carbon monoxide lung transfer factor (TlCO). This results from the increased availability of haemoglobin within the alveolar compartment which avidly binds carbon monoxide.² Although informative, the TlCO often cannot be measured in patients with DAH as they might be too ill. Nitric oxide (NO) combines with haemoglobin much faster than carbon monoxide and is continuously produced in the respiratory tract. Exhaled NO can be measured either online or offline even in acutely ill patients by collection of exhalate in a bag for subsequent analysis.³ We reasoned that DAH could be associated with low levels of exhaled NO because of the increased availability of haemoglobin within the alveolar compartment binding NO.

A 52 year old non-smoking man with a history of allergic rhinitis and asthma was admitted with increasing dyspnoea. His asthma had been controlled by maintenance inhalation of salmeterol and fluticasone. In the previous 3 weeks the patient had experienced painful paraesthesias. On admission he was in mild respiratory distress with a peak expiratory flow rate of 415 l/min (92% of his personal best value), arterial oxygen tension (Pao₂) 8.6 kPa (65 mm Hg), haemoglobin 11 g/dl, and WBC 23 000 (eosinophils 23%). Exhaled air was collected in a sample bag according to American Thoracic Society recommendations (inspiratory air NO concentration <5 ppb, expiratory flow rate 350 ml/s)³ and NO was measured within 2 hours of collection using a chemiluminescent analyser (NIOX, Aerocrine, Solna, Sweden). The initial level of exhaled NO was 4 ppb (normal reference value in our laboratory is 12 (2) ppb). Twelve hours later the haemoglobin fell to 9.1 g/dl, Pao₂ was 7.2 kPa (54 mm Hg), and confluent air space opacities were apparent on the chest