COPD, restrictive syndrome and inflammation

In a recent issue of Thorax Gan et al.

published a systematic review and meta-analysis of 14 reports which confirmed the strong association between COPD and biological markers of systemic inflammation. In six reports COPD was diagnosed by the presence of a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV₁/FVC) ratio lower than 0.7. However, in the remaining eight studies this measure was not available, and the authors assumed that all participants in the lowest quartile of FEV₁% (and, in one study, of FVC%) had a diagnosis of COPD. In these cases the corresponding highest quartile group served as control. Since a COPD diagnosis based on a decreased FEV₁/FVC ratio was lacking in eight reports, the possibility cannot be excluded that a certain number of patients included in the meta-analysis did not have COPD but, rather, a restrictive ventilatory defect. This could be particularly true for participants in the study by Engstrom et al.

who were characterised only by a low FVC.

According to the current GOLD guidelines, only an FEV₁/FVC ratio lower than 0.7 indicates airflow obstruction, thus allowing a COPD diagnosis. Indeed, in the absence of particular pulmonary diseases, many subjects show a homogenous decrease in all dynamic lung volumes (FEV₁, FVC, PEF) without any change in the FEV₁/FVC ratio, and are thus considered to have “impaired lung function”. The occurrence of respiratory symptoms, systemic inflammation, and the increased risk of cardiovascular diseases are the only features that subjects with restrictive disease share with COPD. In fact, whereas COPD is characterised by a decrease in body mass index and blood lipids, subjects with restrictive disease often have abdominal obesity, insulin resistance, and other metabolic risk factors.

Although we believe that most of the included patients were affected by COPD, the possible inclusion of patients with restrictive lung disease may have altered the statistical conclusions of the meta-analysis.

In addition, the decision to select patients in the lowest quartile of FEV₁ and FVC prevented the authors from confirming the absence of inflammation in mild COPD (GOLD stage I and II), a finding previously reported by the same group in a study not included in this meta-analysis.

Because patients with restrictive lung disease and those with COPD have different features, the generic term “impaired lung function” should not be used. Future studies of the role of inflammation and other metabolic risk conditions in patients with respiratory disease, and those investigating the outcome in these subjects, should clearly distinguish between these two groups of patients.

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Authors’ reply

We wish to thank Dr Fimognari and colleagues for highlighting the difficult issue of defining chronic obstructive pulmonary disease (COPD). In most circumstances a spirometric cut off is used to define COPD, but there is no uniform consensus on what that should be and different expert panels have promulgated different spirometric cut off values. COPD is a disease characterised by lung inflammation and patient symptoms (most notably dyspnoea). Studies have shown that the relationship between airflow inflammation and patient symptoms with forced expiratory volume in 1 second (FEV₁) is a continuum and is not threshold dependent. Thus, any attempts to impose FEV₁ (or the ratio of FEV₁ to forced vital capacity (FVC)) limits in defining COPD are bound to be arbitrary and contentious. Rather than relying on arbitrary cut off values for large population based studies, it is reasonable (and useful) to compare the outcomes of interest—in this case, systemic inflammation—between extremes of FEV₁ (that is, worst FEV₁, quartile to best quartile group). This method avoids imposing any arbitrary constraints in the definition of COPD and allows maximal utilisation of the data points. However, a potential limitation of this approach is the possibility of diagnostic misclassification between restrictive and obstructive lung diseases. To specifically address this concern, we excluded population based studies in which a FEV₁/FVC ratio was not used to define COPD and reanalysed the C-reactive protein (CRP) and fibrinogen data. Even after the exclusion of these studies, the standardised mean difference in the CRP level between COPD and control subjects was 0.68 units (95% confidence interval (CI) 0.38 to 0.98) or 4.85 mg/l (95% CI 1.92 to 7.78). For the fibrinogen data, the standardised mean difference in COPD and control subjects was 0.48 units (95% CI 0.43 to 0.54) or 0.42 g/l (95% CI 0.00 to 0.84). These results indicate that the possible contamination of individuals with restrictive defect in the groups with low FEV₁, or FVC did not influence the overall findings. Finally, we did not include data from one of our previous reports because the study sample was taken from the same source population as the study by Mannino and colleagues which was included in the meta-analysis.

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TB screening and anti-TNFα treatment
Reactivation of tuberculosis (TB) is a major concern during treatment with TNF inhibitors. 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, 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 after 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 test is insufficient sensitive to detect latent TB in patients with rheumatoid arthritis and other spondyloarthropathies or in those with inflammatory bowel diseases. 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 contaminant 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 the benefit:risk effectiveness evaluation of the different strategies used to minimise the risk of TB reactivation during treatment with TNF inhibitors is indicated.

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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. Bronchoconstriction caused by bisphosphonates has been described1 but drug induced pneumonitis has not previously been reported. This is the first report of interstitial pneumonia induced by the bisphosphonate risedronate.
A woman developed an intramural mass in her right arm at the age of 51 years. Sarcoidosis was diagnosed by non-necrotising epitheloid 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 intramural mass lesions were palpable. Laboratory examination showed white blood cell (WBC) count of 9100/μL, 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 B3 was 4.18×10³/μL 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 transbronchial lung biopsy specimens revealed no granulomas but cellular alveolitis with intraluminal polyloid 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, neurotropin, menatetrenone, and saicri-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 intramural mass. (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. They are also reported to induce anterior uveitis through these reactions or specific immunological responses. 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.

Osteopetrosis 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.

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Bacterial denitrification, nitric oxide and airway pH in CF

The recent findings of Ojoo et al 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 oxides of nitrogen. The redox balance in the cystic fibrosis (CF) lung is clearly not the same when NO is reduced to nitrogen gas (N2), rather than by non-specific release of pro-inflammatory cytokines. 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 who described vasoconstrictor and bronchodilator activity in vitro in the presence of NO. In 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.

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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 high profile of features suggestive of DAH which should be confirmed by bronchoalveolar lavage (BAL). 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 (Tco). This results from the increased availability of haemoglobin within the alveolar compartment which avidly binds carbon monoxide. Although informative, the Tco 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. 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 periaesthesia. On admission he was in mild respiratory distress with 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 23000 (eosinophils 23%). Exhaled air was collected in a sample bag according to American Thoracic Society recommendations (inspiratory air NO concentration <3 ppb, expiratory flow rate >350 l/min) and NO was sampled over 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.
that, in acute pneumonia (which should be considered in the differential diagnosis), exhaled NO levels have been reported to be high, at least in the one published case series.

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Epidemiology and Health Care Practice

The IEA-EEF European Congress of Epidemiology “Epidemiology and Health Care Practice” will be held in Utrecht, The Netherlands, from 28 June to 1 July 2006. The Congress is organised by epidemiologists from Utrecht University in collaboration with the Netherlands Epidemiology Society and will encompass a broad range of themes from the fields of epidemiology, public health and research in health care. For further information visit the website (www.euroepi2006.org) or email euroepi2006@ffu.uu.nl.

The Dr HM (Bill) Foreman Memorial Fund

The TRUSTEES of the above fund invite applications for grants relating to study in Respiratory Disease, and allied fields (for example, microbiology, histopathology, radiology, biochemistry, and molecular biology).

Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own to study Respiratory Disease, and also support for clinical research abroad.

Intending applicants should write for further details to: Dr Brian H Davies, Llandough Hospital, Penarth, Vale of Glamorgan, CF64 2XX.

EXHALED BREATH CONDENSATE IN CHRONIC COUGH

In the March issue of *Thorax* the letter entitled “Exhaled breath condensate in chronic cough” by A Morice, C F Everett, and S A Mulrennan which appeared on page 259 was inadvertently printed also on page 257 under the heading “EBC pH and chronic cough”. The publishers apologise for this error.
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