Lung fibrosis in systemic sclerosis treated with a combination of ciclosporin and azathioprine

Sirs,

Alveolitis is a major complication of systemic sclerosis (SSc) and there is no randomized trial evidence on which to base therapy. Herein we present a patient with SSc-associated alveolitis who responded to azathioprine and ciclosporin.

A 29-year-old woman presented with a three-year history of Raynaud's phenomenon and recent onset digital ulceration. She also reported exertional dyspnoea at about 200m on level ground. She took no medication and was a lifelong non-smoker. Examination revealed sclerodactyly and digital ulceration of the left index finger. She was normotensive and there were bilateral end-inspiratory crackles on chest auscultation. Full blood count, biochemical profile and erythrocyte sedimentation rate (ESR) were all normal. She had a speckled pattern ANA (titre 1/100); anti-centromere and anti-Scl-70 antibodies were negative. Doppler echocardiography was normal with normal pulmonary arterial pressure and a ventilation perfusion scan was normal. Pulmonary function tests (PFTs) revealed a restrictive defect, FEV1 1.92l (58% predicted) and forced vital capacity (FVC) 1.95l (52% predicted). The transfer factor (DLCO) was 4.92 ml/min/mmHg (73% predicted). The chest radiograph revealed increased interstitial markings and high resolution CT (HRCT) scan showed ground glass opacification and traction dilatation of bronchi in both lower zones. A diethylenetriamine penta-acetate (DTPA) scan showed accelerated clearance of 30.3 seconds (normal 40-80 secs). A diagnosis of limited cutaneous systemic sclerosis (LcSSc) with alveolitis and digital ulceration was made. Her respiratory symptoms failed to improve with high dose prednisolone. Intravenous cyclophosphamide was offered but the patient declined because of the risk of premature ovarian failure. She was treated with ciclosporin (2mg/kg) and azathioprine (2.5mg/kg) with symptomatic improvement and stabilization of her PFTs and DTPA clearance (Fig. 1). Repeat HRCT showed evidence of stable fibrosis only.

The reported prevalence of pulmonary fibrosis in SSc varies from 25%-90% depending on the methodology employed (1). Early detection depends on PFT and echocardiographic screening. HRCT scanning allows staging of the extent of fibrosis with typical changes including ground glass opacification (suggesting active inflammation and alveolitis) subpleural and diffuse honeycombing and cylindrical bronchiectasis (2). Abnormally rapid DTPA clearance is an early marker for lung disease in SSc (2) and may distinguish between alveolitis and pulmonary vascular disease (3).

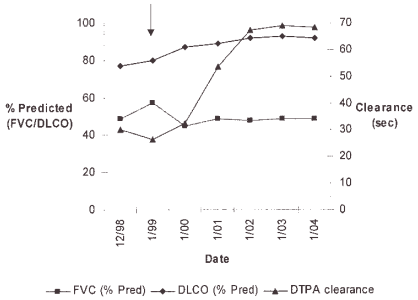

Fig. 1. Illustrates changes in FVC (% predicted), DLCO (% predicted) and DTPA clearance (sec) during treatment with ciclosporin and azathoprine. Arrow indicates commencement of ciclosporin and azathioprine.

There are no randomised trials to inform treatment for alveolitis in SSc (1). Most studies have focused on cyclophosphamide, with a retrospective cohort study suggesting improved lung function and survival in those receiving (mainly oral) cyclophosphamide (4). Others support the efficacy of IV cyclophosphamide and prednisolone for alveolitis (5-7) and while steroids alone may provide some benefit (6), most studies suggest that prednisolone alone is not adequate in the majority of cases (4,8). Our patient declined cyclophosphamide because of fears regarding ovarian toxicity and so other options were considered. Azathioprine has been utilised for idiopathic pulmonary fibrosis (9) and both ciclosporin and azathioprine have been used as maintenance therapy in pulmonary fibrosis (9). Also, by analogy with lung transplantation the combination of ciclosporin and azathioprine seemed an appropriate choice. A recent study suggests that azathioprine stabilizes lung function in SSc associated interstitial lung disease (10). A case series of 4 patients with interstitial lung disease associated with antisynthetase (Jo-1) antibodies also reported improvement with ciclosporin treatment (11). Although there are concerns about the use of ciclosporin in diffuse SSc because of the risk of renal crisis, a study of nine diffuse SSc patients treated with ciclosporin for up to 5 years found improvements in lung scores with no renal abnormalities (12). The combination of ciclosporin and azathioprine was well tolerated in our patient and led to symptomatic improvement and stabilization of her disease. We conclude that this combination may be a useful approach to evaluate further in patients with SSc associated alveolitis.

S. L. HIDER, *MRCP MSc BM BS*[1]
M. WOODHEAD, *BSc DM FRCP*[2]
P. M. TAYLOR, *FRCP FRCR*[3]
I. N. BRUCE, *MD FRCP*[1,4]

[1]arc Epidemiology Unit, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT; Departments of [2]Respiratory Medicine, [3]Radiology and [4]Rheumatology, Central Manchester and Manchester Children's University Hospitals NHS Trust, Oxford Road, Manchester M13 9WL, UK.

Pleases address correspondence and reprint requests to: Dr I.N. Bruce, arc Epidemiology Unit, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, UK
E-mail: ian.bruce@manchester.ac.uk

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