Our observations indicate that combination therapy of leflunomide and methotrexate is useful in the treatment of RA in daily practice.

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Fatal exacerbation of fibrosing alveolitis associated with systemic sclerosis in a patient treated with adalimumab

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Several cases of fatal exacerbations of fibrosing alveolitis associated with rheumatoid arthritis after infliximab treatment have recently been reported.¹ We report here a case of fatal exacerbation of pulmonary fibrosis after adalimumab treatment in a patient with polyarthritis related to systemic sclerosis (SSc).

The patient, a 74 year old woman, had been diagnosed 5 years previously with severe Raynaud's syndrome, sclerodactyly, pulmonary fibrosis, abnormal oesophageal peristalsis, and non-specific antinuclear antibodies (1/100; indirect immunofluorescence on Hep 2 cells). She also had severe distal polyarthritis affecting the wrists, metacarpophalangeal and proximal interphalangeal joints, with demineralisation but no erosion on x ray examination. She tested negative for rheumatoid factor and anti-cyclic citrullinated peptide antibodies. Successive treatments with low dose prednisone associated with methotrexate, leflunomide or azathioprine were ineffective.

In February 2004 she had a 28 joint count Disease Activity Score (DAS28) score of 7.8, a Health Assessment Questionnaire score of 2.6/3, C reactive protein (CRP) levels of 194 mg/l without any positive infectious test. Skin involvement was consistent with a limited cutaneous SSc subtype,² and Rodnan's modified skin score was 6/51. Pulmonary evaluation showed mild peripheral honeycombing with traction bronchiectasis on computed tomographic (CT) scan (fig 1A). She had a forced vital capacity (FVC) of 72% of the predicted capacity and a carbon monoxide transfer factor divided by alveolar volume of 52% of the predicted value, with normoxia at rest and no other abnormality on systemic evaluation. In view of this refractory disabling polyarthritis we proposed adalimumab treatment (40 mg, subcutaneously every other week), which was started while continuing with azathioprine (150 mg/day) treatment.

In July 2004, the articular symptoms improved slightly, with a DAS28 score of 5.1, and a CRP concentration of 10 mg/l. Systemic disease was unaffected, with FVC at 68% of

the predicted capacity and no change on pulmonary CT scan. The dose of adalimumab was increased to 40 mg/week, in association with azathioprine.

In September 2004, the patient was admitted owing to respiratory failure; dyspnoea had increased over 1 month (grade IV NYHA) with rapid exacerbation and fever for 2 days. At the time of admission, her body temperature was 39°C without haemodynamic abnormality. The skin score was unchanged. Biological tests disclosed a normal white cell count (leucocytes $7.1 \times 10^9/l$), and a CRP value of 88 mg/l. Haemocultures and bronchoalveolar lavage remained sterile, but *Chlamydia pneumoniae* antibodies (IgM and IgG) were detected and a CT scan angiography showed aggravated lesions with extensive ground glass opacities (fig 1B). Echocardiography disclosed mild impairment in the left ventricular ejection fraction (LVEF 45%) together with an increase in systolic pulmonary arterial pressure estimation (sPAP 56 mm Hg).

The patient was treated with oxygen, diuretics, azithromycin, and methylprednisolone (1 g) for 3 days followed by prednisone (1 mg/kg/day) with azathioprine. Adalimumab treatment was stopped. The fever decreased and echocardiography improved (LVEF 55% and sPAP 40 mm Hg), but the dyspnoea continued, requiring long term oxygen treatment (6 l/min, >15 h/24 h).

Pulmonary function worsened at the start of 2005, and the patient died from respiratory distress without infection in March 2005.

Anti-tumour necrosis factor α (TNF α) treatment was given because the patient had a mild systemic disease but associated severe, active, crippling, and refractory polyarthritis. *Chlamydia* infection which may have been facilitated by anti-TNF α treatment might have contributed to the initial deterioration of pulmonary function; however, it is not recognised as a contributor to the induction of the fibrotic process and, although a natural course of the disease cannot be ruled out, we strongly suspect the involvement of

Figure 1 CT scan. (A) Mild peripheral honeycombing with traction bronchiectasis; (B) aggravated lesions with extensive ground glass opacities.

anti-TNF α treatment in the deterioration of pulmonary function in our patient. TNF α overproduction is thought to occur in SSc,³ and although preliminary evaluations of the short term effects of etanercept in SSc reported no toxicity,⁴ in vitro data have suggested that TNF α has antifibrotic activity.^{5,6} Although no conclusion can be reached with case reports, it is noteworthy that our patient, like the reported patients with RA with fatal fibrosis exacerbation,¹ was concomitantly treated with azathioprine and anti-TNF. In conclusion, TNF α may trigger fibrosis in patients with underlying interstitial lung disease, possibly irrespective of the associated disease, and should therefore be used with extreme caution in such patients.

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