inadequate response. Viral upper respiratory tract infections were noted in two patients, but were of normal duration, and there were no opportunistic or other bacterial infections. There were no infusion reactions or other significant adverse events.

Marked improvement in disease activity was seen in Patient 2, who was commenced on IFX following an episode of hypertensive encephalopathy attributable to active renal vasculitis. Over the first 3 months, serum creatinine fell from 315 to 11 μmol/l, blood pressure normalized and prednisolone was weaned from 2 mg/kg/day to 0.2 mg/kg/day. The change in PR-3 antibody, ESR and CRP was from 173 μl/l, 65 mm/h, and 10.7 mg/dl at baseline, respectively, to 33 μl/l, 30 mm/h and 0.85 mg/dl by 3 months. This level of improvement was maintained and CYC was weaned off over the subsequent 9 months. Prednisolone dose at 1 yr was 0.1 mg/kg.

The other two patients had transient clinical improvements in the first 3 months after commencing IFX, but the subsequent response was equivocal. Four months after swapping Patient 1 from oral to intravenous pulsed CYC (1 mg/m²) because of gastrointestinal intolerance, IFX was commenced to control flaring of active renal disease and recurrent acute scleritis. The scleritis remitted without the need for ongoing topical steroids. The CYC was swapped for MTX (15 mg/m² subcutaneously) 6 months later when he redeveloped gastrointestinal intolerance. There was no deterioration in disease activity, and the gastrointestinal symptoms again settled. Because of unchanged abnormal urinary sediment (10–25 red blood cells per high-power field, 0.3 g protein/24 h and occasional granular casts), steroid dose (0.25 mg/kg) and raised inflammatory markers, the IFX dose was increased to 6 mg/kg and 10 mg/kg at intervals of 4 months. A repeat renal biopsy, undertaken for insidious renal deterioration, has shown persistent active glomerulonephritis, and the IFX was stopped following the recent addition of intravenous CYC. In Patient 3, radiographic resolution of the lung nodules and improvement in hearing tests were observed, but there was progressive tracheal narrowing despite increasing IFX to 10 mg/kg. There were some sustained improvement in inflammatory markers, and steroids were weaned from 2 to 0.25 mg/kg/day. IFX was subsequently stopped and rituximab was given.

The outcome of IFX use in paediatric WG does not appear to be the same as that reported in adult series [7–9], but its role as a rescue therapy has been demonstrated in one case. Further assessment of the efficacy and safety of IFX in combination therapy is required in the form of a multicentre randomized controlled trial.

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Acute progression of interstitial lung disease: a complication of etanercept particularly in the presence of rheumatoid lung and methotrexate treatment

Sir. We report two patients on etanercept who presented with severe diffuse alveolar infiltrates culminating in ground-glass change on high resolution computed tomography (HRCT) of the lung.

The first, a 64-yr-old woman with an 11-yr-history of seronegative rheumatoid arthritis (RA) had failed to achieve optimal control of her RA with multiple disease modifying anti-arthritic drugs (DMARDs) and only showed a partial response to oral methotrexate 22.5 mg/week since 2002. Etanercept was introduced at 25 mg twice a week. She developed acute breathlessness after six injections (3 weeks).

She was an ex-smoker who had stopped 10 yrs previously. She had no pre-existing rheumatoid lung disease but did have chronic obstructive pulmonary disease (COPD). Full pulmonary function tests done 5 yrs earlier showed the evidence of previous chronic obstructive airways disease, her corrected transfer factor (DLCO) corrected was 13.18 (55%) with a KCO 2.86 (62%). Chest X-ray (CXR) showed emphysema.

She was admitted with a 3-day history of increasing shortness of breath (SOB) at rest without cough. HRCT of the chest showed widespread ground-glass change throughout both lung bases, and changes of bullous emphysema.

Etanercept was discontinued. She was commenced on 40 mg oral prednisolone and broad-spectrum antibiotics. Her SOB recovered quickly but her joint symptoms flared and she was restarted on oral methotrexate 25 mg/week to good effect. Repeat HRCT scan after 4 months showed significant improvement in ground-glass changes with some minimal residual interstitial fibrotic change and bullae.

The second case, a 61-yr-old lady, with RA for 10 yrs similarly had failed multiple DMARDS. A methotrexate dose of 25 mg had been started in 1999. She had known rheumatoid lung disease, and previous pulmonary function tests showed restrictive lung disease with DLCO 2.06 (33%) and KCO 1.02 (63%). HRCT chest
scan 1 yr earlier prior to treatment showed pulmonary fibrosis suggestive of UIP, with no ground-glass change. She presented with a 2-week-history of breathlessness after 12 injections (6 weeks) of etanercept, 25 mg twice a week. There was no evidence of infection or heart failure. CXR showed new diffuse reticulonodular shadowing. CT pulmonary angiography (CTPA) confirmed widespread ground-glass change with no evidence of pulmonary embolism.

She was treated with broad spectrum intravenous antibiotics. The etanercept and methotrexate were stopped. Despite this and adding methylprednisolone 500 mg/day for 3 days and changing antibiotics, she developed worsening hypoxia and was intubated. Bronchoalveolar lavage showed no evidence of TB, bacterial or pneumocystis carinii infection.

She developed metabolic acidosis, progressive renal failure and later cardiac arrhythmias, and despite intensive treatment she died.

Both our patients had pre-existing lung disease, they had enquiry into respiratory symptoms at 3 month intervals and annual CXR prior to the commencement of etanercept and were symptomatically stable. Also, both were on methotrexate and both developed acute respiratory symptoms within 3 and 6 weeks of commencing etanercept, respectively, which culminated in accelerated interstitial lung disease. The patient with COPD presented earlier and recovered quickly with oral steroids alone after discontinuing etanercept and subsequently was able to recommence methotrexate 25 mg/week with adequate joint disease control but no recurrence of respiratory symptoms. The patient with poorer respiratory reserve developed progressive lung disease and died despite aggressive treatment.

Lung disease is a well-known complication of methotrexate, and cases of accelerated methotrexate pneumonitis are also reported within 2–3 doses of infliximab. Our patient who survived restarted methotrexate safely, hence we do not postulate this as a cause [1]. Infliximab has been reported to accelerate lung nodulosis [2, 3], and it has been reported as causing a reversible, biopsy proven, non-caseating granulomatous lung disease in RA [4]. In both our patients, lung biopsies were taken, which may have been the histological change of the respiratory disease. Four further cases of reversible non-caseating granulomatous reaction temporally related to etanercept therapy have also been reported, two of which had previous pulmonary fibrosis [5]. Our two cases demonstrate a little-known complication of etanercept, one of which was fatal. It is noticeable that the patient who died also had rheumatoid lung disease, whilst the patient with COPD survived. Previously reports from the Biologics register [6], and published reports have raised the concern of increased mortality in patients with RA and pre-existing rheumatoid lung disease on azathioprine when anti-TNF was added [7]. On the basis of these two cases caution needs to be extended to those with pre-existing lung disease, taking methotrexate when etanercept is added, particularly if the lung disease is due to rheumatoid involvement. Extra caution should be taken in patients with rheumatoid lung and poor respiratory reserve. Patients should be prompted to contact the rheumatology department if symptoms of acute breathlessness occur, especially soon after the introduction of etanercept.

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<td>• When anti-TNF agents are added, patients with pre-existing rheumatoid lung disease taking methotrexate, are at a risk of acute pulmonary disease progression.</td>
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Detection of tuberculosis by extensive screening in a patient with rheumatoid arthritis prior to anti-TNF-α therapy

SIR, TNF-α blocking agents have seen increasing use in the treatment of systemic inflammatory diseases such as rheumatoid arthritis (RA). An association of anti-TNF-α agents with the occurrence of mycobacterial infections (MTBI), with a high proportion of extrapulmonary and disseminated cases, has been noted [1, 2]. The article by Horsburgh [3] highlights the public health consequences of MTBI in the setting of anti-TNF-α therapy. It is recommended to exclude MTBI before anti-TNF-α therapy and to give prophylactic isoniazid (INH) if latent MTBI (LMTBI) is suspected [4]. The use of INH in patients > 50 yrs is associated with a considerable mortality of 2.3% [5]. In addition, the effectiveness of prophylactic INH therapy is in the range of 25–92%, depending on underlying disease, compliance and type of study [6]. Therefore, we decided to implement a more stringent pre-treatment screening protocol. This encompasses conventional radiographs of the chest in two planes and, if results were questionable, a CT scan. The tuberculin skin test (TST) was performed with two IU injected intracutaneously according to the standard procedure in Switzerland. A reading was taken 48–72 h later, an induration of ≥5 mm was considered positive. If negative, the TST was repeated after 7–10 days, with identical criteria applied for reading. If the TST was positive, and/or imaging of the chest suspicious, bronchoscopy with lavage and brushings for cultures and nucleic acid amplification tests (NAAT) for mycobacteria, and cultures and NAAT of the urine were performed.

From September 2002 until July 2004, 17 patients with the indication for anti-TNF-α therapy were screened according to this procedure. Six had further examinations, of which three were based on the chest radiograph and three on a positive TST. Among the latter, the following case of LMTBI was detected.

A 76-year-old woman with RA of 14 years duration, who had persistent erosive disease despite various disease-modifying anti-rheumatic drugs (DMARDs), qualified for anti-TNF-α...