the beclomethasone inhaler with no return of symptoms. PFT 3 months after stopping all medication had returned to normal (Table 1). Eosinophils also returned to normal within 3 weeks of stopping the drug.

Adalimumab is a fully human recombinant monoclonal anti-tumour necrosis factor-α (anti-TNF-α) antibody recently licensed for the treatment of moderate to severely active RA. Like all anti-TNF-α drugs, adalimumab has recognized side-effects, increased susceptibility to infection being the most worrying.

This is the only Committee on Safety of Medicines (CSM)-reported adverse event of asthma with adalimumab to date in the UK. Further information from Abbott Laboratories revealed that in the pivotal trials of adalimumab asthma has been reported as an adverse event in 0.3% of adalimumab-treated patients compared with 0.1% of placebo-treated patients. Neither treatment nor the pre-existence of asthma was recorded; however, no patient had to stop adalimumab.

A possible explanation of the new onset of asthma in these patients lies in the contrasting inflammatory responses in RA compared with asthma and other allergic diseases. Among T-helper cells (Th), two opposite poles of immune responses can be distinguished based on secretion of cytokines: the Th1 cytokine pattern, with predominant secretion of interferon γ (IFN-γ) and TNF-α, and induction of a cellular immune response. In contrast, the Th2 cytokine pattern has predominant secretion of interleukin (IL)-4, IL-5 and IL-13 and induction of the humoral immune response. Atopic disorders show a raised level of IgE and a Th2 cytokine response [1], whilst RA is considered to be a Th1-polarized disease [1–5].

The generation of a Th2 immune response is inhibited in the presence of Th1 cytokines and vice versa [6]. Based on reciprocal inhibition of the development of Th1 and Th2 responses, it has been suggested that Th1- and Th2-polarized diseases mutually exclude one another. We hypothesize that active RA in this case produced a Th1 cytokine response, which suppressed the clinical expression of asthma. However, once the TNF-α blocking drug was introduced, the Th1 response was suppressed, allowing the Th2-activated pathway to express itself clinically as asthma.

This hypothesis would suggest a class effect. Indeed, asthma has been reported as an adverse event to the CSM for both infliximab and etanercept. There have been two reported cases of new onset asthma with etanercept and two exacerbations of asthma, one with each of etanercept and infliximab. Additionally, there have been another 25 cases of reported bronchospasm or wheezing, although most of these have been related to anaphylaxis.

Asthma appears to be a definite but rare side-effect of anti-TNF blockade. In all the adalimumab reported cases the asthma has been mild and adalimumab has not had to be withdrawn. The details of the asthma adverse events to infliximab and etanercept are not available. In the absence of other guidelines, we followed the British Thoracic Society (BTS) guidelines for asthma [7] and added an inhaled steroid, which completely resolved the patient’s mild symptoms.

We conclude that asthma in this patient was precipitated by the anti-TNF-α drug adalimumab. Although at no stage was the asthma severe enough for the drug to be stopped, we would recommend careful observation, particularly in patients with a personal or family history of asthma or atopy, and adherence to the BTS guidelines for asthma [7] if symptoms occur.

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Fatal streptococcal toxic shock syndrome in a patient with rheumatoid arthritis treated with etanercept

Sir, We report the case of a 24-yr-old female with a 5-yr history of severe seropositive rheumatoid arthritis (RA) treated only with chloroquine and prednison. Over the last 2 yr she had been maintained on prednisone 25 mg. Her physical exam revealed Cushingoid features in addition to persistent active joint inflammation in the small joints of the hands and wrists. In view of the severity of her disease it was decided to start her on methotrexate and etanercept. She received her first dose of etanercept 25 mg subcutaneously; the next day she started to complain of nausea, vomiting and diarrhoea associated with fever. She was managed with intravenous fluid and electrolyte replacement. Two days later she presented to the emergency room with fever, hypotension (blood pressure 80/50 mmHg) and generalized leuchoery. She was managed with fluid replacement and broad spectrum antibiotics. Her condition rapidly deteriorated and she went into shock with further drop in her blood pressure, tachycardia, tachypnoea and anuria. She was intubated, mechanically ventilated and was transferred to the intensive care unit. Her blood pressure did not pick up despite full-dose inotropes and flush fluids. Her right lower extremity rapidly became mottled with sloughing of the overlying skin. She had a cardiac arrest around 12 h after her admission to the emergency room. Two blood cultures revealed streptococcus group A.

The rapid development of a streptococcal toxic shock syndrome shortly after the initiation of etanercept therapy in a
young patient with chronic RA raises the question of whether this was a coincidental occurrence or whether the etanercept caused exacerbation of an active subclinical infection. The chronic steroid therapy with 25 mg of prednisone daily should also be considered as an additional contributing factor in masking the infection. In our review of the literature only two cases of fatal sepsis associated with tumour necrosis factor alpha (TNF-α) blockers were reported [1, 2]. Baghai et al. [1] reported a case of fatal pneumococcal sepsis occurring in a 37-year-old woman with rheumatoid arthritis treated with etanercept, and Herrlinger et al. [2] reported the case of a 40-year-old woman who after six infusions of infliximab for perianal Crohn’s disease developed staphylococcal pneumonia resulting in fatal adult respiratory distress syndrome. Kroesen et al. [3] reviewed patient charts and records of the infectious disease unit for serious infections in patients with RA in the 2 yr preceding anti-TNF-α therapy and during therapy. Serious infections affected 18.3% of patients treated with infliximab or etanercept. In several cases, only a few signs or symptoms indicated the severity of developing infections and sepsis; therefore a high level of suspicion of infection is necessary in patients prior to the initiation of TNF-α blocker therapy.

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Fatal Mycobacterium peregrinum pneumonia in refractory polymyositis treated with infliximab

Sir, Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders affecting skeletal muscles and other organs. PM and DM are considered to be associated with high morbidity and mortality rates, particularly related to infectious complications, which have been described in up to 26% of patients [1]. Recently, opportunistic infections have been reported in 12–21% of PM/DM patients. Many factors have been implicated in this apparently increased frequency of infections in PM/DM, especially immunosuppressive drugs [1, 2]. We report a case of fatal Mycobacterium peregrinum pneumonia in a patient with refractory PM, which occurred shortly after institution of anti-tumour necrosis factor α (anti-TNF-α) therapy.

A 68-year-old man had PM that had evolved since December 2001. Therapy with prednisone was initiated at a dose of 1 mg/kg daily. As both clinical and biochemical status continued to deteriorate gradually, subsequent treatments were started: methotrexate, azathioprine, cyclophosphamide and cyclosporin (cumulative doses of 1080 mg, 31 500 mg, 3 g and 36 000 mg, respectively), which proved ineffective. Intravenous immunoglobulins (1 g/kg/day for 2 days monthly) for 24 months resulted in partial improvement of PM. In January 2004, the patient was admitted for generalized muscle weakness. Muscle power, gauged for eight proximal muscles by a modification of the UK Medical Research Council grading system, was 59/88 points [1]. Serum creatine kinase level was 15 000 IU/l. Pulmonary function tests showed decreased vital capacity (64% of predicted values); lung computed tomography (CT) scan was normal. Other investigations, including abdominal CT scan, gastroscopy, colonoscopy and bronchoscopy, to exclude underlying malignancy, were normal.

As PM was refractory to immunosuppressive therapy, the patient was given anti-TNF-α, as mentioned previously [3]: infliximab (5 mg/kg) at weeks 0, 2 and 6, in addition to prednisone (20 mg daily). Before initiation of infliximab, gastric aspiration product cultures for mycobacteria were performed, which proved negative.

One month after the third infliximab infusion, the patient presented with a 3-week history of fatigue, non-productive cough and progressive dyspnoea. On admission, he was febrile (38°C) and his general condition was poor. Physical examination revealed ‘Velcro’ crackles bilaterally. Laboratory findings were as follows: erythrocyte sedimentation rate 90 mm/h, C-reactive protein 142 mg/l, haemoglobin 10.2 g/dl, white blood cell count 9.5 × 10⁹/l (lymphocytes 9%, CD4 cell count 0.9 × 10⁹/l), and creatine phosphokinase 12 697 IU/l. Chest radiograph revealed diffuse bilateral lung infiltrates. Blood cultures, bacterial (Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella) and viral (cytomegalovirus, influenza viruses) serologies were negative. Bronchoscopy was normal; analysis of bronchoalveolar lavage fluid (BAL) was negative for Gram and Gomori–Grocott staining and bacterial and fungal cultures. The patient was treated with ceftriaxone (2 g daily) and ciprofloxacin (500 mg/12 h) for 2 days; however, pulmonary clinical manifestations continued to deteriorate further. Microbiological studies (Ziehl–Neelsen stain) yielded acid-fast bacilli in sputum, gastric aspiration products and BAL. The patient received combined therapy with rifampin, sizoniazid, ethambutol and pirazinamide; despite the use of mechanical ventilation, he died of respiratory failure within 9 days. Cultures of BAL and three samples of sputum and gastric aspiration products grew Mycobacterium peregrinum within 15 days.

Infections are potential complications of anti-TNF-α therapy [4–9]. In patients with rheumatoid arthritis being treated with anti-TNF-α agents, Kroesen et al. [5] have found an elevated incidence of severe infections (0.181 per anti-TNF-α therapy vs 0.008 in the 2 yr preceding anti-TNF-α therapy). In a series of patients receiving anti-TNF-α therapy, Wallis et al. [7] found the incidence rate of opportunistic infections to be as high as 313/100 000 patients; tuberculosis was the most common infection, occurring in 179/100 000 patients. Opportunistic infections due to other pathogenic microorganisms have also been observed in association with anti-TNF-α therapy: e.g. Pneumocystis carinii, Histoplasma, Aspergillus, Candida, Nocardia, Cryptococcus and non-tuberculous mycobacteria [4–9].