3 mg/kg 8-weekly was started and subsequently increased to 5 mg/kg. There was moderate improvement: although his DAS28 oscillated between 2.8 and 4.6, the patient stated that ‘he was feeling so much better!’ In autumn 2003, the patient suffered an infective episode and investigations also revealed raised prostate-specific antigen. Infliximab treatment was stopped. A diagnosis of benign prostatic hyperplasia with focal epithelial neoplasia was made. After careful review of the risk of prostate carcinoma in patients receiving immunosuppressive therapy, and considering a flare of RA and the patient’s desire to continue infliximab, treatment was restarted in 2004. In March 2005, he developed a left foot drop. In January 2006, he noticed weakness of his right leg but no sensory symptoms. On examination, it was noticed that there was wasting of his quadriceps muscles and that reflexes were brisk throughout with extensor plantar response. A computed tomography (CT) scan of the cervical and lumbar spine showed mild degenerative changes and CT scan of the head and cerebrospinal fluid examination were normal. Electromyography showed widespread denervation in the arms and legs with no fasciculation or fibrillation and normal motor and sensory conduction velocities. In March 2006, fasciculations were noted in the deltoid and scapular region and in both quadriceps. A diagnosis of ALS was made by a neurologist and treatment with riluzole was started. His disease has been progressive, with dysphagia and generalized weakness and wasting, and he is now wheelchair bound. Infliximab was stopped.

ALS is a progressive neurodegenerative disorder with selective upper and lower motor neuron loss. Information about the likely role of TNF-α in ALS is provided by the transgenic ALS superoxide dismutase 1 (G93A SOD1) mouse model [3, 4] and the mnd mouse model [5]. Detectable TNF-α mRNA and protein can be found in the brain and spinal cord of mnd mice but not in control mice; increased TNF-α immunoreactivity is also detectable in G93A SOD1 transgenic mice (starting in the presymptomatic phase) [3]. Evidence in human disease includes increased TNF-α immunoreactivity in post-mortem lumbar spinal cord sections of ALS patients [4] circulating serum TNF-α and its soluble receptor levels [9]. However, no correlation between TNF-α levels and disease severity or duration was found [9].

The results of clinical studies of TNF-α blockade in ALS are awaited. Thalidomide, an anti-TNF-α agent, was recently tested in G93A SOD1 transgenic mice, which showed improved survival, delayed disease onset and progression, and a reduction in TNF-α protein and mRNA levels in spinal cords [4]. Currently, there are two clinical trials registered in 2005 at www.ClinicalTrials.gov [6]: a pilot German safety/efficacy study of oral thalidomide in patients with ALS and a USA phase II efficacy study of oral thalidomide in the setting of disease progression. Thalidomide is a small molecule, which can readily cross the blood-brain barrier, and acts differently to anti-TNF-α monoclonal antibodies (mAbs) by inhibiting protein expression at the post-transcriptional level and by decreasing mRNA TNF-α half-life from 30 to 17 minutes [10].

Despite earlier cautious enthusiasm [2], we found no reported data on anti-TNF-α mAbs used in ALS either in animal models or in humans with ALS. The rationale for treating ALS with anti-TNF-α mAbs remains unclear. No definite data regarding the relationship between serum and CNS TNF-α levels in ALS are available and it is not known whether circulating TNF-α blockade might exhibit any effect on CNS TNF-α expression. Anti-TNF-α mAbs are macromolecules and would be expected to have negligible brain access. On the other hand, anti-TNF-α mAbs have shown protective effects in experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis [2], but in contrast, anti-TNF-α mAbs can worsen the disease in MS patients.

Treating patients who have ALS with anti-TNF-α mAbs is certainly fraught with difficulties. ALS mimics the potential complications of RA with consequent diagnostic difficulties [7, 8], and increased susceptibility to infections in ALS may be dangerously aggravated by the immunosuppression of TNF-α blockade. However, this incidental experience shows that ALS may develop and progress during TNF-α blockade treatment sufficient to ameliorate RA. Further human experience with biological anti-TNF-α agents and thalidomide may well be informative.

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Visceral leishmaniasis infection in a rheumatoid arthritis patient treated with adalimumab

Sir, Anti-tumour necrosis factor-α (TNF-α)-based therapies represent an important innovation in rheumatoid arthritis (RA) treatment, demonstrating efficacy in reducing disease activity and in retarding radiographic progression. Three different TNF-α blockers have been approved for the treatment of these conditions: infliximab, adalimumab and etanercept. TNF-α is essential for granuloma formation and maintenance, which are key components of host defences against intracellular pathogens [1]. The clinical use of TNF-α blockers has been associated with an increased risk of reactivation of granulomatous infectious diseases [2]. Visceral leishmaniasis (VL) is a disseminated protozoan infection caused by Leishmania donovani and Leishmania infantum. The acute form of the disease is almost
100% fatal if left untreated. In endemic areas, any individual showing fever, hepatosplenomegaly, pancytopenia and hypergamoglobulinaemia should be suspected for VL. Standard diagnosis includes parasite demonstration in bone marrow or splenic aspirate smears, and/or the detection of significant levels of anti-leishmanial antibodies by serological techniques [3]. In experimental VL, TNF-α plays an important role in cytokine-induced macrophage activation and tissue granuloma formation, two activities linked to control of intracellular infection caused by L. donovani [4]. VL is an extremely rare event in RA patients treated with TNF-α antagonists, and only two cases, both under infliximab treatment, have been described [5, 6]. Here, we report a case of a 69-yr-old Caucasian woman living in Genoa area (northwest Italy), who was diagnosed as affected by RA in 1976 and from that time was treated for long time with methotrexate (MTX) (7.5 mg weekly) and corticosteroids (5 mg prednisone daily). Since the patient was poorly responsive to the combination of MTX and prednisone, it was decided to introduce the anti-TNF-α treatment (adalimumab—40 mg every other week). At that time, all diagnostic tests for latent tuberculosis were negative. However, after 25 months of consecutive combination therapy with adalimumab, the patient showed intermittent daily fever (maximum 38.5°C) for a week and severe asthenia. Adalimumab and methotrexate administration were promptly stopped. Laboratory test analysis showed a C-reactive protein of 240 mg/l, an erythrocyte sedimentation rate of 100 and a pancytopenia [haemoglobin: 10 g/dl, white blood cells (WBCs): 2900 and platelets: 72.000]. During hospitalization she presented a fluctuant fever with several peaks at 39°C. Physical examination did not reveal splenomegaly or hepatomegaly. A computed tomography (CT) scan and 99mTc-HMPAO WBC scintigraphy did not reveal any infection localization. A bone marrow examination (smear and core biopsy) revealed a non-specific reactive lymphoplasmacellular infiltration with no myelodysplasia. Finally, the examination of Giemsa-stained smears from a second bone marrow aspirate detected Leishmania parasites (Fig. 1) and indirect fluorescent antibody test (IFAT) serology tested positive at the titre of 1/160 (cut-off: 1/80). A polymerase chain reaction (PCR) for the amplification of Leishmania genomic sequences in peripheral blood confirmed the diagnosis. Three patient’s serum samples stored in 2002 (2) and in 2003 (1) were available for serodiagnosis, and all tested negative at IFAT. The patient was treated intravenously with liposomal amphotericin B for a total dose of 18 mg/kg (3 mg/kg per day for 5 days, followed by 3 mg/kg on day 10). She did not develop any adverse events and 15 days after the treatment, the Leishmania PCR on blood no longer revealed parasites. The treatment with MTX was started again at the previous dosage 30 days after adalimumab and MTX were stopped. Treatment with prednisone was stable during this time. Six months after adalimumab was stopped, the patient is clinically stable and the laboratory/imaging tests did not reveal RA progression. Currently, no further clinical or biological symptoms of leishmaniasis were detected.

To our knowledge, this is the first case of VL reported in a patient treated with adalimumab. This confirms the risk of opportunistic infections and the difficulties of diagnosis in patients treated with anti-TNF-α blockers (i.e. monoclonal antibodies). Of course, this patient received several immunosuppressive drugs during the course of her disease and, taken together, might have played a predisposing role to the infection. With appropriate treatment VL was controlled [7]. Spleen and/or liver enlargement is commonly seen in adults, being reported in 70–100% of VL cases including those with HIV co-infection and during infliximab therapy [5, 6, 8, 9]. The clinical picture of our VL case was characterized by fever, asthenia and pancytopenia, but there was no hepatos- or splenomegaly. This case raises the issue of a possible atypical presentation in patients treated with adalimumab, probably due to the lack of an effective inflammatory response. The patient was living in Liguria, northwest Italy, which has long been known to be endemic for VL [10]. As widely known, patients undergoing therapy with anti-TNF-α monoclonal antibodies should be screened for a history of tuberculosis, both anamnestically and with a tuberculin test, and positive cases should be treated pre-emptively. The same cannot be recommended for VL because of the low incidence rate of this disease, although the possibility of VL should always be taken into account, at least for patients living in endemic areas.

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Successful treatment of refractory polyarticular juvenile idiopathic arthritis with rituximab

Sir, Juvenile idiopathic arthritis (JIA), being the most common chronic musculoskeletal disease of childhood, has a prevalence estimated to be 1 in 1000 children [1]. Up to 10% of these remain severely disabled in adulthood [2]. Numerous disease-modifying anti-rheumatic drugs (DMARDs) have been trialled with varying success in JIA, and therefore additional therapeutic targets have been investigated. Pro-inflammatory cytokines have been implicated in the pathogenesis of JIA especially tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6. Biological agents that directly target these cytokines such as etanercept [3], infliximab [4], anakinra [5] and tocilizumab [6] have, therefore, been used in JIA with promising results.

In addition to cytokine blockade, research arousing considerable interest in inflammatory arthritis is B-cell-targeted therapy. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been successfully used in patients with rheumatoid arthritis (RA) [7]. According to the pathogenic considerations, disease control was attempted with rituximab. Two months after stopping adalimumab, two infusions of rituximab 1 g on day 1 and day 15 were administered, with intravenous methylprednisolone 100 mg given prior. Concomitant treatment consisted of mycophenolate mofetil, hydroxychloroquine and prednisolone 7.5 mg daily. At the time of infusion, the patient was wheelchair-bound with 24 tender and 15 swollen joints and a disease activity score 28 (DAS28) of 8.32. Erythrocyte sedimentation rate (ESR) was 88 mm/h, and there were no detectable autoantibodies.

Accordingly, we investigated the safety and efficacy of rituximab in a young adult with a history of rheumatoid factor (RF) negative polyarticular JIA.

A 26-year-old woman was first diagnosed with JIA at the age of 8 yrs. Laboratory findings at presentation revealed anti-nuclear antibody positivity but absence of RF. Numerous DMARDs were initiated in an attempt to achieve symptomatic control including methotrexate, sulphasalazine, myocrisin, minocycline and ciclosporin. All of these, however, were discontinued owing to intolerable side effects or poor efficacy. Frequent flares of arthritis were controlled with high-dose corticosteroid treatment; however, the patient developed Cushing’s syndrome and osteoporotic fractures. Her course was further complicated by the need for bilateral hip replacements at the age of 21 yrs.

With limited therapeutic options, Alemtuzumab (Campath 1-H), a lymphocytic monoclonal antibody used primarily in the treatment of chronic lymphocytic leukaemia, was trialled in 1993. Despite suggestions of efficacy in a range of immune-mediated diseases, our patient did not respond to this agent. In 1999, the TNF-α antagonist etanercept was commenced, which led to a vast improvement in the signs and symptoms of disease and quality of life for 4 yrs. The development of uveitis and worsening arthritis in 2003 prompted a change to infliximab therapy. This second anti-TNF-α agent induced rapid remission of both the joint and eye manifestations of disease, although its efficacy waned after 2 yrs. It was eventually terminated after the development of multi-drug-resistant septic osteomyelitis of the mandible following dental extraction. Adalimumab was next employed, and although this third anti-TNF-α agent showed an initial biochemical response, there was no clinical benefit.

Based on pathogenetic considerations, disease control was attempted with rituximab. Two months after stopping adalimumab, two infusions of rituximab 1 g on day 1 and day 15 were administered, with intravenous methylprednisolone 100 mg given prior. Concomitant treatment consisted of mycophenolate mofetil, hydroxychloroquine and prednisolone 7.5 mg daily. At the time of infusion, the patient was wheelchair-bound with 24 tender and 15 swollen joints and a disease activity score 28 (DAS28) of 8.32. Erythrocyte sedimentation rate (ESR) was 88 mm/h, and there were no detectable autoantibodies.