Listeria monocytogenes meningitis in a patient receiving etanercept for Still's disease

Sirs,

It is well known that the reactivation of tuberculosis and development of other opportunistic infections can complicate anti-tumor necrosis factor alpha (anti TNT-α) treatment (1,2). Listeria meningitis has been described in some patients, mostly those receiving infliximab, a chimeric IgG1 monoclonal antibody (3). Here we briefly describe a case of listeria monocytogenes meningitis in a patient with adult Still's disease during etanercept treatment.

A 45-year-old man was diagnosed with Still's disease in 1986. His disease had an oligoarticular onset and took a chronic polyarticular course (4). He was treated with disease-modifying antirheumatic drugs (DMARDs) (i.e. hydroxychloroquine, methotrexate, and cyclosporin A), non-steroidal anti-inflammatory drugs, and/or low doses of oral glucocorticoids as appropriate until September 2001. At that time, despite combination therapy including methotrexate (7.5–10 mg/weekly), sulphasalazine (2 g/day) and hydroxychloroquine (200 mg/day), the patient had highly active arthritis [tender joint count (TJC) 25, swellen joint count (SJC) 6] with an erythrocyte sedimentation rate (ESR) of 80 mm/1st hr and C-reactive protein (CRP) 40 mg/l (nv ≤ 6) associated with increased disability (HAQ-DI score of 3).

After obtaining the patient's informed consent, he was given 25 mg etanercept subcutaneously twice weekly and glucocorticoids at 10/15 mg/die of prednisolone equivalent. The arthritis improved but in February 2002 the patient suffered a traumatic femoral fracture requiring surgery. Consequently, etanercept was interrupted for about 4 weeks; administration was resumed and finally interrupted on April 2, 2002 when the patient was admitted to the hospital in a confused state with headache and fever (39ºC). On admission, laboratory tests showed the following abnormalities: blood leucocyte count (WBC) 15,400/mm^3, platelet count 600,000 mm^3, CRP401 mg/l, lactate dehydrogenase (LDH) 761 U/L(nv 313-618), serum creatinine 1.8 mg/dl (nv 0.6-1.3). A cerebral computed tomography (CT-scan) was normal and an electroencephalogram (BEG) showed only some subcortical abnormalities without focal lesions. A diagnosis of meningitis was made and listeria monocytogenes was isolated in the cerebrospinal fluid. The patient received antibiotic therapy (sultamicillin, 18 g/day) for 30 days and recovered without any complications.

Our patient suffering from Still's disease was unresponsive to DMARD combination therapy and glucocorticoids. When he was given the 7 Kda IgG1 recombinant fusion protein etanercept, a highly effective TNF-α antagonist for rheumatoid arthritis (5) and other rheumatic conditions, a partial improvement was seen at weeks 12 (TJC, 25; SJC, 1; ESR, 37; CPR, 36) and 22 (TJC 17; SJC, 0; ESR, 30; CRP 28) of therapy. Unfortunately, about 6 months after beginning etanercept, meningitis caused by listeria monocytogenes made it necessary to interrupt treatment, because it is well known that the main function of TNF-α is to create host resistance to infections. There is increasing evidence that the inibition of TNF-α is associated with the development of opportunistic infections. In fact, aspergillosis, histoplasmosis, tuberculosis reactivation, moraxella catarrhalis arthritis and listeriosis (2,3,6) have been reported in some patients with rheumatoid arthritis or spondyloarthritis.

The use of dairy products was probably the source of the infection in our immunocompromised patient with underlying disease, previously treated with methotrexate and glucocorticoids. The rate of those complications is higher in patients using infliximab than in those taking etanercept (2). It is hypothesized that that discrepancy may be related to differences between the two TNF-α antagonists, differences in the duration of suppression and in the concomitant use of methotrexate in RApatients (2). The difference in the incidence of infections between infliximab and etanercept might depend either on the fact that etanercept has not yet been fully marketed yet in the countries with a high TBC incidence, or that infliximab is able to introduce complement mediated cell lysis of TNF-expressing cells and has a different binding to the TNF trimer (7).

Concerning listeriosis, at least 26 cases have been reported to the United States FDAthrough September 15, 2002, of whom 24 were receiving infusions of infliximab (2). One case reported from Italy concerned a patient with Crohn's disease. Nevertheless, since adverse events are only reported on a voluntary basis to the FDA, many cases may never be reported. Among the 26 cases reviewed by Ellerin *et al.*, meningitis was observed more than other septic complications. Other case reports have appeared on the Medline (8-11, last search February 2004).

Our report presents an additional case of meningitis due to listeria monocytogenes, which occurred in 1 out of 26 patients receiving etanercept among 87 patients with RA who were on anti TNF-α therapy. The mean (median) total exposure to etanercept was 13.6 (10) months representing 29.5 patient-years. Therefore, each patient receiving the drug had a 3.4% probability of developing the complication. In general, listeria infection can be considered an uncommon complication of TNF-α neutralizing agents, considering the high number of patients worldwide who are receiving TNF-α antagonists. Nevertheless, because listeria infection caused death in some cases during both infliximab and etanercept therapy (2), any patient receiving biological agents should avoid foods that are potential sources of listeria monocytogenes.

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Prolonged efficacy of infliximab for refractory adult-onset Still's disease

Sirs,

Adult-onset Still's disease (ASD), which was first described by Bywaters in 1971, is a rare protean disease of unpredictable evolution (1). Its treatment is poorly establish-

ed: non-steroidal anti-inflammatory drugs (NSAIDS) and corticosteroids (CS) are prescribed for most patients, and methotrexate (MTX) is recommended against refractory forms. We describe an ASD patient in whom a prolonged response was obtained with anti-tumor necrosis factor-α (TNF-α) biotherapy, in this case infliximab.

A 28-year-old woman suffering from ASD had taken CS and MTX for 10 years. The osteoarticular involvement consisted of bilateral carpal joint inflammation of the capital bone, without fusion or clear-cut ankylosis, and distal interphalangeal involvement, and was associated with a quasi-constant pseudo-urticarial skin eruption. Episodes of joint inflammation occurred every 2 to 3 years, requiring pulse CS and/or intravenous immunoglobulin injections. The patient is HLA-DR4-negative. Her plasma and intralymphocyte TNFα concentrations were low. During the last attack in 2001, the clinical picture associated debilitating inflammatory polyarthritis of the small- and medium-sized joints, fever (40°C) and aggravation of the pseudo-urticarial eruption on the trunk. Despite several CS pulses and intensification of the MTX dose, no attenuation of the manifestations was obtained.

Infliximab (3 mg/kg) was prescribed (on days 0 and 15, at 6 weeks and every 8 weeks thereafter) in combination with MTX (15 mg/week). The symptoms stabilized during the 2 weeks following the first administration, and one month later all signs had completely regressed except the skin lesions, which disappeared after the addition of dapsone. Forty-five months after starting infliximab, the patient remains totally asymptomatic, with an erythrocyte sedimentation rate of 5 mm/1st h. She continues to receive infliximab every 8 weeks. No dysimmunity or infectious complications have been observed.

TNFα receptors are expressed at the joint cartilage-pannus junction and, pertinently, the intra- articular TNFα concentration is elevated in infantile and adult rheumatoid arthritis (2). Infliximab is a chimeric monoclonal antibody that binds to TNFα with high affinity and thereby neutralizes its biological activity. Etanercept is a TNFα-receptor blocking agent; able to act at several levels, these antibodies block intra-articular receptors, decrease the *in vivo* production of other cytokines, lower the expression of endothelial cell-adhesion molecules, prevent mononuclear cell infiltration of the joints (3), and reduce the serum vascular endothelial growth factor level, which is associated with less angiogenesis (2).

The first reported cases of severe, chronic juvenile arthritis resistant to standard therapies but responding to infliximab appeared in 1997 (4); since then these initial observations have been confirmed (5, 6). Five years ago, publications based on 30 cases argued for the use of biotherapies to treat patients with ASD resistant to conventional treatments (7-10). Infliximab has been the form used most often, at concentration ranging from 3 to 5 mg/kg, infused on days 0 and 15, at 6 weeks, and then every 4-8 weeks. The largest series included only 12 patients who were primarily given etanercept. The main results were rapid efficacy with clear regression of the clinical symptoms in patients with systemic manifestations, normalization of the biologic parameters, and good safety.

However, unlike adults, children with Still's disease showed poor long-term control. The mean treatment duration in reported studies was 12-24 months (7,8). Our patient responded rapidly and completely after the second infliximab infusion associated with MTX, with excellent tolerance. We observed no side effects and no dysimmunity. Addition of dapsone led to the disappearance of skin lesions. Today, 45 months after starting infliximab, her ASD is completely controlled and she has developed no signs of relapse.

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Late onset of long-lasting fever as a sole complication of treatment with anti-TNFα

Sirs,

Several clinical trials and the experience drawn from the 5-year use of chimeric monoclonal antibody to tumor necrosis factor-α (anti-TNFα) allow the evaluation of its therapeutic value and most of its side effects (1-3). However, long-term clinical use is essential for the complete understanding of the effects of the drug. This letter concerns a patient who, after receiving anti-TNFα (Infliximab-Remicade, Schering-Plough), presented with long-lasting high fever, probably associated with the medication itself.

A 65-year-old woman with a 14-year history of rheumatoid arthritis (RA) had been treated with corticosteroids and methotrexate in the past, which were discontinued because of serious side effects. Exacerbation of RAnecessitated treatment with anti-TNFα. After a negative screening for infections (including PPD-testing, chest x-ray, and screening for common viral infections) she was given two doses of Infliximab (3 mg/kg per dose i.v.), 6 and 3 weeks before admission, without any immediate adverse effect. Twenty-one days after the second infusion, the patient presented with high fever (39.5°–41.5°C) accompanied by daily severe attacks of rigor. No relief of the symptoms was noted after the administration of *per os* antimicrobial agents (amoxycillin for 2 days and then cefaclor for 2 days).

The patient was admitted to hospital for further evaluation. Thorough investigations were negative, ruling out the possibility of tuberculosis (pulmonary and extrapulmonary) or other infection, bacterial or viral. There was also no evidence of any other disease that could present with fever, such as adult's Still disease. The high fever persisted for 13 days and was only partially relieved (by 2-3°C) by antipyrexials. On the 13th day, the fever subsided and 6 days later the patient became and remained afebrile. At present, 5 months after the episode, the patient is well although she is still suffering from RA symptoms.

A thorough consideration of this case, keeping in mind Miller's criteria (4), suggests a possible causal relationship between anti-TNFα and this febrile syndrome, i.e.:

1. The temporal association of events.
2. The lack of any other plausible etiologic explanation.
3. The spontaneous regression of fever.
4. After our failure to find a biologic etiology, we believe that the patient's fever may be attributed to either: i) the "profound control of TNFα in the periphery, which results in an enhancement of brain-derived TNFα and other cytokines" (5), or ii) a delayed hypersensitiv-