

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 TNF- 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, swollen 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 (39°C). On admission, laboratory tests showed the following abnormalities: blood leucocyte count (WBC) 15,400/mm³, platelet count 600,000/mm³, 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-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 inhibition 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-antagonists, differences in the duration of suppression and in the concomitant use of methotrexate in RA patients (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 FDA through 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 Ellerlin *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*.

G. LA MONTAGNA*, MD, Assistant Prof.

G. VALENTINI, MD, Prof. and Chief, Rheumatology Unit

Dipartimento di Internistica Clinica e Sperimentale "F. Magrassi e A. Lanzara", Unità Operativa di Reumatologia, Seconda Università di Napoli, via S. Pansini no. 5, 80131 Naples, Italy.

*To whom correspondence and reprint requests should be addressed.

References

1. KEANE J, GERSHAN S, WISE RP, *et al.*: Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2002; 346: 1098–104.
2. ELLERIN T, RUBIN RH, WEINBLATT ME: Infections and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2003; 48: 3013–22.
3. SLIFMAN NR, GERSHON SK, LEE JH, EDWARDS ET, BRAUN M: *Listeria monocytogenes* infection as a complication of treatment with tumor necrosis factor a-neutralizing agents. *Arthritis Rheum* 2003; 48: 319–24.
4. CUSH JJ, MEDSGER TA JR, CHRISTY WC, HERBERT DC, COOPERSTEIN LA: Adult-onset Still's disease. *Arthritis Rheum* 1987; 30: 186–94.
5. MORELAND LW, BAUMGARTNER SW, SCHIFF MH *et al.*: Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p-75)-Fc fusion protein. *N Engl J Med* 1997; 337: 141–7.
6. OLIVIERI I, PADULA A, ARMIGNACCO L, SABATELLA V, MANCINO M: Septic arthritis caused by moraxella catarrhalis associated with infliximab treatment in a patient with undifferentiated spondyloarthritis. *Ann Rheum Dis* 2004; 63: 105–6.
7. ANTONI C, BRAUN J: Side effects of anti-TNF therapy: Current knowledge. *Clin Exp Rheumatol* 2002; 20 (Suppl. 28): S152–7.
8. GLUCK T, LINDE H-J, SCHOLMERICH J, MULLER-LADNER U, FIEHN C, BAHLAND P: Anti-tumor necrosis factor therapy and *Listeria monocytogenes* infection: report of two cases. *Arthritis Rheum* 2002; 46: 2255–7.
9. TWEEZER-ZAKS N, SHILOACH E, SPIVAK A, RAPOPORT M, NOVIS B, LANGEVITZ P: *Listeria monocytogenes* sepsis in patients treated with anti-tumor necrosis factor-alpha. *Isr Med Assoc J* 2003; 5: 829–30.
10. JOOSTEN AA, VAN OLIFEN GH, HAGEMAN G: Meningitis due to *Listeria monocytogenes* as a complication of infliximab therapy. *Ned Tijdschr Geneesk* 2003; 147: 1470–2.
11. BOWIE VL, SNELLA KA, GOPALACHAR AS, BHARADWAJ P: *Listeria meningitis* associated with infliximab. *Ann Pharmacother* 2004; 38: 58–61.

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-