Letters to the Editor

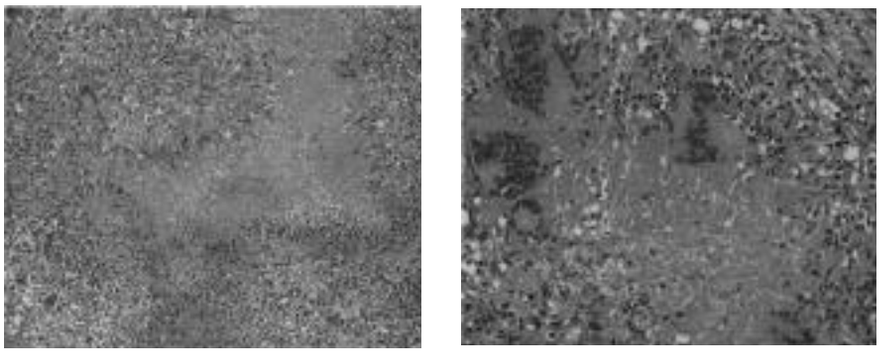
Mycobacteria tuberculosis peritonitis associated with etanercept therapy

Sirs,

The introduction of specific antagonists of tumor necrosis factor-α (TNF-α) activity represented a major advance in the treatment of rheumatoid arthritis (RA). However, TNF-α is also essential for many aspects of the normal immune response, and its inhibition may predispose patients to serious infections. Here we report the first case of tuberculous peritonitis associated with the use of etanercept, a soluble TNF-α receptor, and briefly review the role of TNF-α in the immune response to mycobacterial infections.

A 19-year-old woman with a 5-year history of juvenile-onset RA incompletely responsive to methotrexate had received etanercept 25 mg SQ twice weekly for 8 months when she developed severe, constant mid-epigastric abdominal pain without nausea, emesis, diarrhea, fevers, or other systemic symptoms. There was no known exposure to tuberculosis. She had not received glucocorticoids in the preceding year. Physical examination revealed a temperature of 37°C and a diffusely tender and distended abdomen without rebound or guarding. Bowel sounds were hypoactive. Laboratory evaluation revealed 5,800 white blood cells per uL (66% neutrophils, 8% lymphocytes, 25% monocytes, 1% basophils), and hemoglobin of 9.3 g/dl. Electrolytes, liver function, and renal function were normal, an HIV test was negative. Chest radiography revealed a pleural effusion in the left hemithorax, and computerized tomography of the abdomen was significant for omental thickening and ascites. Paracentesis yielded ascitic fluid with a cell count of 634,000 red blood cells per uL, 776 WBCs per uL (22% polys, 68% lymphs, and 10% large monocytes), and albumin 1.5 g/dl; Gram's stain was negative. Laparotomy and omentectomy were performed, and biopsy revealed caseating granulomata (Fig. 1). Anti-mycobacterial therapy (isoniazid and rifampin) was initiated, and final cultures were positive for *Mycobacteria tuberculosis.* Purified protein derivative (PPD) was positive post-operatively, with 15 mm of palpable induration at 48 hours. Methotrexate and etanercept were discontinued.

TNF-α blockade has become a standard therapy for RA. In the US, the TNF-α blockers approved for clinical use include etanercept, infliximab, and adalimumab (1, 2). In contrast to the monoclonal antibody anti-TNF-α agents, Eetanercept (Enbrel™) is a soluble TNF-α receptor that blocks TNF-α activity by competing with cell membrane receptors for the cytokine (2).



(a) (b)

Fig. 1. Photomicrographs of peritoneal tissue from this patient with *Mycobacterial tuberculosis*: (**a**) (H&E, x40) confirms the presence of a typical caseating granuloma in the peritoneum; (**b**) (H&E, x200) shows multinucleated giant cells within a granuloma from the same tissue.

Despite the dramatic clinical benefits provided by TNF-α blockade, there remain concerns that prolonged TNF-α inhibition may predispose patients to active mycobacterial infection. For example, TNF-α has been demonstrated in a murine model to be critical for an effective response to mycobacterial infection (3). Moreover, TNF-α mediates T-cell and macrophage interactions during granuloma formation, which is considered to be an essential feature of the anti-mycobacterial host defense (3-5).

In light of the animal data, it is perhaps not surprising that several cases of reactivation tuberculosis during anti-TNF-α therapy have been reported (6). Immunex, the manufacturer of etanercept, reported 13 cases of *Mycobacteria tuberculosis* associated with etanercept among 117,000 patients exposed between May 1993 and September 2001 (7). A more recent series emphasized that 52% of entanercept-associated cases of tuberculosis had evidence of extra-pulmonary infection. The median period from first dose of etanercept to the diagnosis of tuberculosis was 11.5 months (range 1 to 20 months) (8). Similarly, the apparent prevalence of active tuberculosis among RA patients receiving the anti-TNF-α monoclonal antibody infliximab was 24.4 cases per 100,000, 57% of which involved extra-pulmonary or disseminated infections, and with a median interval from the initiation of infliximab to tuberculosis diagnosis of 12 weeks (range 1-52) (6).

However, post-marketing TB reporting for etanecept and infliximab was through a voluntary mechanism and the true number of active TB cases as well as the underlying incidence in the RA population and the frequency of extrapulmonary infection remain unknown. (9)

This represents the first report of tuberculosis peritonitis associated with etanercept therapy. Although the causal relationship between TNF-α blockade and active mycobacterial disease remains unproven in humans, abundant evidence from the murine system suggests that a high index of suspicion for disseminated and extrapulmonary TB should be maintained in patients on chronic therapeutic TNF-α blockade.

A.M. MANADAN[1], *MD* J.A. BLOCK[1], *MD*
W. SEQUEIRA[1,2], *MD*

Section of Rheumatology, Rush Medical College, Chicago; [2]Division of Rheumatology, Cook County Hospital, Chicago, IL, USA. Address correspondence to: Augustine M. Manadan, MD, Section of Rheumatology, 1725 West Harrison, Suite 1017, Chicago, IL 60612, USA. E-mail: manadan@hotmail.com

References

1. CASE J: Old and new drugs used in rheumatoid arthritis: a historical perspective. *Am J Therapeutics* 2001; 8: 163-79.
2. MORELAND LW, SCHIFF MH, BAUMGARTNER SW: Etanercept therapy in RA: A randomized controlled trial. *Ann Intern Med* 1999; 130: 478.
3. FLYNN JL, GOLDSTEIN MM, CHAN J *et al.*: Tumor necrosis factor-α is required in the protective immune response against *Mycobacterium tuberculosis* in mice. *Immunity 1995*; 2: 561-72.
4. EHLERS S, BENINI J, KUTSCH S, ENDRES R, RIETSCHEL ET, PFEFFER K: Fatal granuloma necrosis without exacerbated mycobacterial growth in TNF receptor p55 gene-deficient mice intravenously infected with *Mycobacterium avium. Infect Immun* 1999; 67: 3571-9.
5. KINDLER VL, SAPPINO AP, GRAU E, PIGUET PF, VASALLI P: The inducing role of TNF in the development of bactericidal. Granulomas during BCG infection. *Cell* 1989; 56: 731-40.
6. KEANE J, GERSHON S, WISE RP *et al.*: Tuberculosis associated with Infliximab a tumor necrosis factor-α neutralizing agent. *N Engl J Med* 2001; 345 (15).
7. HOLMAN J, SABATH DF, VIVEASH D, BURGE DJ, GARRISON L,GARDINER M: Tuberculosis reports with etanercept therapy. (EULAR abstract). *Ann Rheu Dis* 2002; 61: FR10024.
8. MANADAN AM, MOHAN AK, COTE TR, SIEGEL JN, SEQUIERA W, BLOCK JA: *Arthritis Rheum* 2002; 46 (Suppl.): Ab. 356, pg. S166.
9. KENNEDY, DL, GOLDMAN SA, LILLIE RB: Spontaneous reporting in the United States. In *Pharmcoepidemiology*, 3rd ed., 2000: 10.