Etanercept for the Treatment of Human Immunodeficiency Virus–Associated Psoriatic Arthritis

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Etanercept may play an important role in modulating the inflammatory activity and progression of human immunodeficiency virus (HIV)-associated psoriasis and psoriatic arthritis. We report the case of a 45-year-old homosexual man with a CD4 cell count of less than 0.05 × 10^9/L and an HIV viral load of 4200 copies/mL (while receiving highly active antiretroviral therapy) who developed extensive psoriatic plaques, 4.5-kg weight loss, onychodystrophy, and psoriatic arthropathy with severe periarticular bone demineralization. The arthritis progressed despite the use of several disease-modifying medications, including corticosteroids, hydroxychloroquine, and minocycline. Because of uncontrolled, progressive, and disabling arthritis and resulting profound disability, he was treated with etanercept. Within 3 weeks, his psoriasis had improved dramatically and his joint inflammation had stabilized.

Psoriatic arthritis is an inflammatory disease of the joints and other connective tissues that occurs in some patients with psoriasis. Psoriatic arthritis is classified as a seronegative spondyloarthropathy, a loosely organized group of disorders that also includes ankylosing spondylitis, enteropathic arthritis, and Reiter syndrome. Among the features shared by the spondyloarthropathies is involvement of the periarticular structures in a distinctive inflammatory process called enthesopathy. This process affects tendons and ligaments at their insertions, resulting in tendinitis, dactylitis, and fasciitis. The combination of psoriasis with asymmetrical peripheral joint disease, variable involvement of the axial skeleton, nail disease, tenosynovitis, and enthesopathy is the clinical signature for the recognition of psoriatic arthritis.

The prevalence of psoriasiform skin changes in human immunodeficiency virus (HIV)–infected persons is comparable to that seen in non–HIV-infected persons (1%-2%). Psoriatic arthritis, however, appears to be more prevalent among HIV-infected individuals, and the severity of the HIV-associated psoriatic arthritis and psoriasis tends to be markedly worse than in those not infected with HIV.

Recently, etanercept, a soluble tumor necrosis factor (TNF) receptor (p75):Fc fusion protein, was approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis (RA). Preliminary studies also indicate that it is effective in the treatment of psoriatic arthritis and may offer benefit in modulating the deleterious effects of TNF in other medical conditions such as sepsis syndrome, congestive heart failure, and wasting due to malignancy or infectious organisms. However, little is known about the role of such TNF-binding inhibitors in the setting of psoriatic arthritis and HIV infection. We describe a patient with the acquired immunodeficiency syndrome (AIDS) who was treated with etanercept for the complication of rapidly progressive and debilitating psoriatic arthritis.

REPORT OF A CASE

In May 1998, a 45-year-old homosexual man with a 15-year history of HIV infection, a CD4 cell count of less than 0.05 × 10^9/L, and an HIV viral load of 4200 copies/mL (while receiving highly active antiretroviral therapy [HAART]) presented with pruritus and progressive scaling plaques involving the scalp and trunk of 1 month's duration. There was no joint inflammation. He was diagnosed as having psoriasis and was initially treated with antihistamines, topical corticosteroids, and, when his psoriasis worsened, 60 mg/d of prednisone. The psoriasis improved moderately on this regimen. Four months later, while receiving low-dose prednisone, he experienced fever, 4.5-kg weight loss, new-onset bone and joint pain, onycho-
dystrophy, and worsening skin disease. Serologic test findings for rheumatoid factor, antinuclear factors, HLA-B27, and antineutrophil antibodies were negative or normal. A dermatology consult was obtained, and ultraviolet light treatment was advised. However, the patient was not compliant with light treatments and used only topical corticosteroids. As his skin condition worsened, he was treated with hydroxychloroquine, followed later by minocycline. When, over a 2-month period, these medications proved ineffective in stabilizing his psoriasis and evolving arthritis, sulfasalazine was prescribed. He developed an exfoliative hypersensitivity reaction within 1 week, and sulfasalazine was discontinued.

In February 1999, he was hospitalized because of rapidly progressive, severe, and disabling arthritis. He was unable to walk because of pain, swelling, and stiffness in the knees and ankles, and he had difficulty feeding himself because of wrist pain, finger deformities, and stiffness. On physical examination he had severe muscle atrophy and was 11.4 kg below his ideal body weight. He also had nail pitting, onychodystrophy, swollen phalanges, and extensive psoriatic plaques all over his body, including his palms and soles (Figure 1). Flexion contractures of the right elbow and both knees were also present. His heart and lung sounds were normal, and he had no palpable lymphadenopathy or hepatosplenomegaly. Laboratory findings included the following: CD4 cell count, 0.02 x 10^9/L; viral load, 14,000 copies/mL; leukocyte count, 5.2 x 10^9/L with a normal differential; hemoglobin, 8.4 g/dL; platelet count, 525 x 10^9/L; erythrocyte sedimentation rate, 125 mm/h; and serum protein electrophoresis with hypergamma-globulinemia but no monoclonal spike. A broad panel of autoimmune serologic test findings were negative or normal. A chest x-ray film showed no infiltrates or hilar adenopathy, and infectious pathogens were not identified in multiple sets of blood cultures, by sputum, or by serologic studies for fungus, protozoa, or spirochetes. Radiographs of his hands and feet revealed psoriatic arthropathy with severe periarticular bone demineralization.

Due to rapidly progressive psoriatic arthritis and profound disability in the setting of multiple drug failures or drug reactions, etanercept was prescribed at a dose of 25 mg subcutaneously twice weekly. Within 3 weeks, his skin lesions had improved dramatically and joint inflammation...
stabilized, and the corticosteroid dose was tapered. He continued to receive physical and occupational therapy, and after 8 weeks his joint deformity (and rash) improved to the point he was able to walk with the assistance of a cane and use his hands for activities of daily living.

For the next 6 months, his leukocyte count, CD4 cell count, and HIV viral load remained stable, and his joint deformities dramatically improved, but his clinical course was complicated by recurrent polymicrobial bacterial infections. Shortly after beginning etanercept, he developed fevers due to enterococcal cellulitis, cystitis, and bacteremia and received a protracted course of antibiotics, both parenteral and oral. Two months later, his Hickman catheter exit site became erythematous and warm to the touch. Blood cultures yielded *Stenotrophomonas (Xanthomonas) maltophilia*, the catheter was removed, and he again received parenteral antibiotics. Several months later, *Pseudomonas aeruginosa* was recovered from an inflamed knee joint and from sputum at a time when he was febrile and had pulmonary infiltrates. Despite continued dramatic improvement in the patient’s psoriasis and psoriatic arthritis both clinically (Figure 2) and radiographically (Figure 3), etanercept was discontinued because of the bacterial infections.

For the next 4 months, the patient’s skin and joint problems remained relatively stable. He continued to have problems with superimposed bacterial infections and was hospitalized on 2 occasions for recalcitrant pseudomonal knee infections. During the second hospitalization, he remained febrile despite parenteral antibiotic administration and repeated knee aspirations and arthroscopically directed joint irrigation. On the 10th day of his hospitalization, he became somnolent and hypotensive and had a respiratory arrest. In accordance with the patient’s prior directives, we did not pursue resuscitative efforts, and he died. A request for autopsy was declined.

**DISCUSSION**

Psoriatic arthritis related to HIV infection is most commonly polyarticular and asymmetrical, although the simultaneous or sequential development of oligoarticular and distal interphalangeal patterns has been documented. Ap-
Figure 3. A, Soft tissue swelling involving several distal interphalangeal joints and marginal erosions of the distal interphalangeal joints of the second and fourth digits of the left hand and second digit of the right hand (arrows) and periarticular erosions involving the interphalangeal joint of the right hand, consistent with psoriatic arthritis.

Joint space narrowing of the distal interphalangeal joint of the fifth digit is also present. B, After 6 months of treatment with etanercept, the soft tissue swelling involving several distal interphalangeal joints had resolved, and distal phalangeal flexion contractures had improved.

Approximately half of these patients also have extra-articular manifestations such as dactylitis and inflammation of the tendons and ligamentous attachments to bone. Often, the clinical course is insidious, but in roughly one third of persons, it may be abrupt, with development of erosions and disabling deformities within weeks or months. Constitutional features, including fever and malaise, are rare and are usually seen only with fulminant onset and widespread joint disease, although the erythrocyte sedimentation rate and the serum complement levels are commonly elevated, reflecting activation of acute-phase reactants by cytokines. The radiologic appearance of the peripheral arthritis that characterizes psoriatic arthritis includes the distinctive asymmetrical pattern of joint involvement, the simultaneous presence of ankylosis, periosteal new bone formation, erosions and osteolysis in various joints, and the pathognomonic distal interphalangeal joint involvement.

Whether inflammation and joint destruction in a given joint are produced by RA or by psoriatic arthritis is often indistinguishable at the level of histopathology. Both entities may share certain final common pathways of tissue injury or response. Yet psoriatic arthritis, as well as the other spondyloarthropathies, is clearly distinguishable from RA in terms of mechanisms of disease. Notably, the spondyloarthropathies lack rheumatoid factor or other autoantibodies and complement consumption attributable to immune complexes and have a readily evident major histocompatibility class I pattern of genetic susceptibility.

The treatment of spondyloarthropathy in HIV-infected patients is also comparable to that for non–HIV-infected patients, with some important exceptions. The joint and tendon involvement in HIV-associated psoriatic arthritis tends to be less responsive to anti-inflammatory drugs than is psoriatic arthritis in the general population. In addition, the number of joints affected tends to increase with time. Nonetheless, nonsteroidal anti-inflammatory drugs are the first line of therapy. Phenylbutazone administered in doses of 100 mg 2 to 3 times a day is sometimes associated with a diminution in the severe enthesopathy and arthritis and is generally well tolerated except for occasional myelosuppression. Both methotrexate and azathioprine are effective but must be used cautiously; they too can cause myelosuppression and have also been associated with the abrupt development of opportunistic infection and death in individuals with AIDS. Sulfasalazine may also be useful but is associated with roughly a 30% incidence of rash among patients infected with HIV. Low-dose systemic corticosteroids are ineffective, and high doses have multiple adverse effects, including candidiasis and further immunosuppression. Anecdotally, the use of gold, oral retinoids, phototherapy, cyclosporine, and zidovudine have also helped the skin and joints of some HIV-infected individuals with psoriatic arthritis. Unfortunately, only rarely has the course of these patients' HIV disease been noted when they are treated with such medications. Information is scarce concerning the effect these medicines have on immune regulation or their pharmacokinetic interactions and metabolic consequences when combined with HAART. For example, while retinoids have long been a leading therapy in HIV-related psoriasis, their impact on the arthritic complication is less certain. Additionally, retinoids can potentiate the risk of
hypertriglyceridemia and pancreatitis when combined with several different HAART options.

Importantly, the role of HAART in modulating the clinical expression of rheumatologic disorders is still undefined. Rheumatic diseases such as Reiter syndrome, psoriatic arthritis, other spondyloarthropathies, and diffuse infiltrative lymphocytosis syndrome have all been associated with reactive expansion of CD8 cells, thus suggesting that HIV infection accelerates HLA class I restricted CD8 cell-mediated autoreactivity. In contrast, systemic lupus erythematosus, RA, and polymyositis, which are thought to be mediated by CD4 cells, remit in some patients after infection by HIV.

Evidence supporting a role for TNF- \( \alpha \) in the immunemediated inflammatory process of rheumatologic conditions continues to accumulate. Production of TNF- \( \alpha \) is elevated in the synovial fluid of patients with active RA but not in synovial fluid from patients with inactive RA. TNF- \( \alpha \) stimulates the release of other proinflammatory cytokines, including interleukin 1 (IL-1), IL-6, IL-8, and leukemia inhibitory factor and induces the release of proteases from neutrophils, fibroblasts, and chondrocytes. These enzymes, including collagenase and other neutral metalloproteinases, are likely to be responsible for joint destruction in RA. TNF- \( \alpha \) also induces the expression of endothelial adhesion molecules, leading to transmigration of leukocytes and lymphocytes into extravascular sites. Inhibition of TNF- \( \alpha \) suppresses spontaneous production of IL-1, IL-6, and granulocyte-macrophage colony-stimulating factor by RA synovial cells.

Furthermore, disease activity is markedly reduced in patients with RA placed on short-term treatment with chimeric human-mouse monoclonal antibody directed against TNF- \( \alpha \).

Importantly, infection with HIV has been associated with elevated TNF- \( \alpha \) levels, and a correlation between plasma TNF- \( \alpha \) levels and HIV viral load has also been reported. TNF- \( \alpha \) may stimulate HIV replication by activating nuclear factor \( \kappa B \), an enhancer of HIV transcription required for the establishment of chronic HIV infection. The pharmacologic inhibition of TNF- \( \alpha \) production by various agents is supported by in vitro studies. Exposing macrophages infected with HIV to thalidomide, for example, led to substantial reduction in viral replication and diminution in nuclear factor \( \kappa B \)-binding activity. Treatment with thalidomide also has been reported to inhibit the activation of HIV in peripheral blood mononuclear cells in 16 of 17 patients with AIDS, presumably through inhibition of TNF- \( \alpha \) synthesis.

The mechanism of action of etanercept in RA probably involves its ability to competitively inhibit TNF binding to cell surface TNF receptors. Modulation of the inflammatory cytokine cascade is the likely reason etanercept may also be useful in the treatment of psoriatic arthritis and may ultimately have a role in the treatment of other inflammatory conditions such as sepsis, congestive heart failure, and chronic wasting states. Although in humans and animals the administration of etanercept has been shown to prolong the half-life of TNF, it renders the TNF biologically unavailable. Less important is etanercept’s ability to bind to Fc receptors and other inflammatory cytokines in the TNF family.

Etanercept-induced adverse effects are usually mild and restricted to injection site reactions. In placebo-controlled studies, such reactions occurred in 37% of patients receiving active drug and in 10% of patients receiving placebo. The reactions consisted of mild to moderate erythema, itching, pain, or swelling and generally occurred during the first month of therapy and less frequently thereafter. They lasted an average of 3 to 5 days and only rarely required drug discontinuation. Hematologic complications are rarely associated with etanercept, thus making it a potentially useful agent for patients with HIV-associated cytopenia.

Since TNF influences cellular immunity and modulates inflammatory responses, etanercept may affect host defenses against malignancies and infections, such as Listeria or Mycobacterium infection. Yet, in only 1 clinical study were patients who received etanercept more likely to develop infection (29%) than those who received placebo (16%), and these results did not achieve statistical significance. No evidence of immunosuppression was detected through cell population changes or immunoglobulin levels. However, this study involved relatively immunocompetent patients. Etanercept’s package insert advises discontinuation of therapy in any patient who develops a serious infection.

In conclusion, etanercept rapidly and profoundly improved our patient’s psoriasis and severe, crippling psoriatic arthritis and appeared to be much more effective than the usual therapies. Etanercept and other anticytokine therapies may play an important role in modulation of the natural history of arthritis in HIV disease as well as in HIV disease itself. However, the occurrence of frequent and severe infections suggests caution and careful follow-up in prescribing this medication for HIV-infected patients. The issues of long-term immunologic effects, induction of lymphoproliferative disorders, infection, and possibly autoimmune diseases await further experience with this agent.

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REFERENCES