Case Report

Effective Etanercept Treatment for Psoriatic Arthritis Complicating Concomitant Human Immunodeficiency Virus and Hepatitis C Virus Infection

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ABSTRACT. High levels of tumor necrosis factor-α (TNF-α) are associated with hepatitis C virus (HCV) infection and all stages of human immunodeficiency virus (HIV) infection. TNF-α may have a role in both the pathogenesis and the response to treatment of these chronic viral diseases. We describe a 42-year-old HIV/HCV coinfected hemophiliac man who developed psoriasis and severe psoriatic arthritis not responding to combination treatment with methotrexate and cyclosporin A. Treatment with etanercept 25 mg twice weekly was followed by remission of the joint inflammation and improvement of the exanthem. This is the first report of anti-TNF-α treatment for rheumatic complications in a patient with both HIV and HCV infection. (J Rheumatol 2007;34:1353–5)

Key Indexing Terms:
HUMAN IMMUNODEFICIENCY VIRUS HEPATITIS C VIRUS PSORIATIC ARTHRITIS
ETANERCEPT THERAPY

Because of the essential role of tumor necrosis factor-α (TNF-α) in defence against infection, there has been much speculation about the administration of agents with TNF-α inhibitory function to patients with rheumatic diseases and concomitant chronic viral infections, such as human immunodeficiency virus (HIV) infection, hepatitis B, and hepatitis C. The first such case was reported in 2000 — patient with the acquired immunodeficiency syndrome (AIDS) treated with etanercept for debilitating psoriatic arthritis (PsA). The psoriasis and arthritis improved dramatically, but treatment had to be stopped 4 months later because of frequent polymicrobial infections[1]. Since then anti-TNF-α agents (including etanercept, infliximab, and recently adalimumab) have been administered to a few patients with rheumatic disease and either HIV or chronic hepatitis C virus (HCV) infection, with generally good responses and no serious side effects[2-7].

We describe a case of severe PsA in a 44-year-old hemophiliac man with concomitant HIV and HCV infection who had a dramatic response to etanercept treatment. This is the first report of a patient with concomitant HIV and HCV infection treated with an anti-TNF-α agent for rheumatic complications.

CASE REPORT

A 43-year-old man with hemophilia A and concomitant HCV and HIV infection was referred to our department in March 2002 because of severe psoriasis and PsA not responding to treatment. He had been treated for his bleeding episodes with non-heat treated factor concentrates since 1978 and was diagnosed with HIV in 1985 and with HCV in 1990.

In March 1999, because of persistently elevated aminotransferase levels (3 times normal), a liver biopsy was performed showing chronic active hepatitis (grade 5, stage 3, Ishak score[8]). The HCV genotype was 1b and the viral load was 7.89×1^6 IU/ml (branched DNA-2, cutoff 0.032×10^6 IU/ml). He was treated with interferon A (IFN; Roferon A; Roche) at a dose of 3,000,000 IU 3 times weekly for 1 year, with partial response (aminotransferase normalization, HCV RNA detectable). Since then the aminotransferase levels remained within the normal range and no further treatment for hepatitis C was administered.

In June 2000, soon after IFN treatment, he presented with psoriatic lesions of the elbows, knees, scalp, and trunk. There was only mild response to topical treatment, so although the CD4 count at the time was 340/mm^3 and the HIV RNA < 10,000 copies/ml, the exanthem was considered HIV-related, and highly active antiretroviral treatment (HAART) was initiated (zidovudine, lamivudine, and efavirenz). He had a very good virological response, with HIV RNA levels < 50 copies/ml, and transient improvement of the exanthem was noted, but 3 months later he presented with symmetric arthritis of the proximal interphalangeal (PIP) and knee joints. There was no response of the joint inflammation to nonsteroidal antiinflammatory drugs, so 3 months later treatment with methotrexate (MTX) 15 mg weekly was started. Still, no clinically significant improvement was noted and cyclosporin A (CSA) 150 mg daily was added to MTX treatment. Despite initial improvement, active and disabling polyarthritis soon recurred, and he was referred to our department.

Initial evaluation revealed extensive psoriatic plaques of the scalp,

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Accepted for publication February 7, 2007.

trunk, elbows, and knees as well as symmetric arthritis of the ankles, knees, wrists, PIP joints, and the left shoulder. He had difficulty walking and taking care of himself and complained of malaise and anorexia. Laboratory evaluation revealed erythrocyte sedimentation rate 80 mm/h, leukocyte count 4100/mm^3 with a normal differential, CD4 cell count 380/mm^3, CD8 cell count 880/mm^3 (HIV stage A2, CDC classification). Liver enzymes were normal. Treatment with MTX and CSA was discontinued. Treatment with etanercept 25 mg twice weekly was started. On reevaluation 1 month later, complete remission of the polyarthritis was noted and he was able to continue his daily activities.

He has been on etanercept treatment for 2 years in combination with his HAART regimen. There has been no relapse of arthritis, although he notes occasional psoriatic plaques on the elbows and knees. Liver enzymes have remained normal and the HCV RNA is 4.67×10^7 IU/ml. HIV RNA is undetectable and the CD4 cell count > 450/mm^3.

DISCUSSION

Concomitant infection with HIV and HCV is not uncommon among older hemophiliac patients who were treated with plasma products and clotting factor concentrates before blood product screening tests for both viruses were implemented[9]. In these patients HIV infection seems to accelerate the clinical and histologic course of chronic hepatitis C, while responsiveness to IFN is weaker compared to patients who are HIV-negative[9,10].

Our patient presented with psoriasis and PsA soon after completion of IFN treatment. It is well known that in patients with HCV infection IFN treatment may exacerbate PsA, while on the other hand, HIV infection itself is associated with more severe clinical manifestations of PsA compared to the disease in the non-HIV population. The role of HAART in the management of rheumatic complications of HIV infection remains undefined. However, it is probable that HAART, by controlling viral replication and thus improving the patient's immune function, may reduce the frequency and the severity of some of these complications. As well, immune function improvement allows the patient to tolerate necessary degrees of immunosuppression for rheumatic diseases not possible in the pre-HAART era[11]. It is of special interest for our case that HAART also seems to have beneficial effects in HCV/HIV coinfected patients, reducing the HCV viremia and in some cases even eliminating the virus[9].

On presentation to our department this patient had severe active polyarthritis and generalized exanthem, despite being treated with combination therapy of MTX and CSA, itself a significant immunosuppressing regimen for an already immunocompromised patient. Marked improvement in all inflammatory manifestations occurred promptly after initiation of etanercept as well as remission of the psoriatic exanthem. It is notable that several cases of psoriasis developing during anti-TNF-α therapy have been reported, raising the possibility that these agents may induce or exacerbate the disease in susceptible patients[12]. This adverse event is considered a class effect of anti-TNF-α agents. Since psoriasis is a heterogeneous skin disorder, it seems likely that certain variants of the disease, for example, palmoplantar pustular psoriasis, may have an immunologic background distinct from the typical plaque-type psoriasis resulting in a different response to TNF-α blockade. Our patient's clinical improvement has remained nearly constant during the 2-year followup, and no serious infection or other side effect has occurred. Most important, his HCV status has remained stable, while the CD4 cell count remains within the normal range and HIV RNA is undetectable.

It has already been suggested that TNF-α has a role in both the pathogenesis and the response to treatment of HCV and HIV infection. TNF-α concentrations are generally increased in HCV infection[13,14], while patients with higher levels of TNF-α are less likely to respond to IFN treatment compared to patients with lower levels. Similarly, persistence of TNF-α even when HCV RNA becomes undetectable during treatment with IFN is associated with a higher probability of relapse[15]. High TNF-α levels are also associated with all stages of HIV infection, and it seems that excessive TNF-α expression may accelerate the disease, amplify the loss of immunocompetency, and contribute to clinical manifestations of AIDS such as wasting and fever[16]. Based on the above observations and given that etanercept and other anti-TNF-α agents inhibit the binding of TNF-α to cell-surface TNF receptors, it seems likely that anti-TNF-α agents may play an important role in modulating the natural progression of HCV and HIV disease themselves[1]. A very interesting question, as formulated[2], would be whether the combination of anti-TNF-α treatment with HAART in this case had a synergistic effect on suppressing the HIV viral load.

Further clinical trials are needed to investigate, not only the longterm efficacy and side effects of etanercept and anti-TNF-α agents in general in patients with HIV and HCV infection (and even more so in HIV/HCV coinfected patients), but also the longterm immunologic effects of these agents and their contribution to the progression of these chronic viral diseases.

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