A Paradoxical Treatment for a Paradoxical Condition: Infliximab Use in Three Cases of Mycobacterial IRIS

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The management of corticosteroid refractory immune reconstitution inflammatory syndrome (IRIS) is currently unclear. Infliximab administration was associated with clinical improvement without significant adverse events in 3 patients with mycobacterial IRIS. Immunologic and virologic responses to antiretroviral therapy were unaffected. Tumor necrosis factor blockade may be beneficial for IRIS and warrants further study in clinical trials.

Keywords. immune reconstitution inflammatory syndrome; infliximab; mycobacterial infection.

Immune reconstitution inflammatory syndrome (IRIS) represents an aberrant inflammatory disorder in patients infected with human immunodeficiency virus (HIV), with paradoxical worsening of preexisting treated infections or unmasking of subclinical infections, after antiretroviral therapy (ART) initiation. It occurs in 10%–40% of patients, usually in the first few months after ART initiation. Corticosteroids represent the mainstay of therapy [1]. The management of severe steroid-unresponsive IRIS is problematic.

Infliximab is an anti-tumor necrosis factor (TNF) monoclonal antibody used commonly in the treatment of rheumatoid arthritis and inflammatory bowel disease. TNF is critical in controlling mycobacterial infections. Paucity of TNF, such as in patients on TNF inhibitors, is associated with increased incidence (up to 25 times) of tuberculosis [2]. However, excess of TNF can be detrimental by promoting inflammation [3].

Plasma levels and in vitro production of interferon (IFN)-γ and TNF by CD4+ T cells after mycobacterial antigen stimulation are often elevated in mycobacterial IRIS [4], suggesting potential roles in IRIS pathogenesis. To our knowledge, TNF inhibitors have not been used in HIV-infected patients with IRIS. Here we report 3 cases of clinical improvement temporally associated with the use of infliximab for steroid-unresponsive mycobacterial IRIS.

CASE REPORTS

Patient 1 (PT1) was a 31-year-old African American male, diagnosed with HIV infection in 2008 but declined care. He presented in January 2011 with dyspnea and weight loss and was diagnosed with Pneumocystis jiroveci pneumonia. He improved clinically with resolution of interstitial infiltrates on chest radiograph (CXR) after treatment with trimethoprim/sulfamethoxazole and prednisone.

Atazanavir 300 mg, ritonavir 100 mg, emtricitabine 200 mg, and tenofovir 300 mg daily were initiated when prednisone was tapered and trimethoprim/sulfamethoxazole reduced to prophylactic dose. Two weeks later, PT1 presented with fevers, cough, and worsening dyspnea. Chest computerized tomography (CT) showed worsening bilateral interstitial infiltrates. Initial microbiologic testing on bronchoalveolar lavage (BAL) was negative. Levofloxacin 750 mg daily was initiated for presumed community-acquired pneumonia.

Two weeks later, PT1 presented with tender right cervical lymphadenopathy. Fine needle aspiration (FNA) of the lymph node showed acid-fast bacilli (AFB). Quantiferon gold assay was negative. Azithromycin 500 mg and ethambutol 1000 mg daily were initiated for presumed unmasking Mycobacterium avium complex (MAC)-IRIS. Cultures of BAL and lymph node biopsy subsequently confirmed MAC. Despite MAC therapy, lymphadenopathy worsened, occluding the internal jugular vein (Figure 1A). Moxifloxacin 400 mg and prednisone 60 mg daily were added, and the lymph node was drained under ultrasound-guidance, leading to a reduction in lymphadenopathy. Prednisone tapering was attempted twice, but lymphadenopathy worsened on both occasions. Infliximab 5 mg/kg was administered every 2 weeks, 3 infusions in total, in an attempt to reduce lymphadenopathy. Prednisone was discontinued 2 weeks after the first dose of infliximab. Cervical lymphadenopathy diminished over the ensuing months, and PT1 went on to complete 2 years of MAC therapy.

Patient 2 (PT2) was a 41-year-old male from Honduras. He presented in December, 2011 with weight loss, right knee pain, and swelling. HIV serology was positive, and chest CT showed bilateral consolidations and a miliary pattern throughout the lungs. Empirical tuberculosis therapy (isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1000 mg, and ethambutol 800 mg daily) was initiated. Subsequently, culture of joint fluid aspirate confirmed drug-sensitive Mycobacterium tuberculosis.
Figure 1. Computerized tomography scan of the neck showing lymphadenopathy (red arrow) occluding the right internal jugular vein in Patient 1 (A). Chest radiograph demonstrating large right pleural effusion in Patient 2 (B). Over 2 L of fluid drained from chylothorax in Patient 2 (C). In vitro production of tumor necrosis factor (TNF) (D) and interferon (IFN)-γ (E) by CD4+ T-cells in response to mycobacterial antigens stimulation increased at the time of immune reconstitution inflammatory syndrome (IRIS) then reduced gradually but remained detectable 1 year after initiation of antiretroviral therapy (ART). Plasma inflammatory marker and cytokine levels in the first year of ART. Plasma C-reactive protein (CRP) (F), interleukin (IL)-6 (G), IFN-γ (H), and TNF (I) increased during the IRIS event then decreased rapidly and seemed to be temporally associated with prednisone initiation in patients 2 and 3.
PT2 responded to tuberculosis therapy with radiologic improvement.

After 6 weeks of tuberculosis therapy, tenofovir 300 mg, emtricitabine 200 mg, and efavirenz 600 mg were initiated. Two weeks later, PT2 presented with worsening right knee pain and swelling, fever, and dyspnea. Chest CT showed worsening lymphadenopathy and increased pulmonary nodules. Magnetic resonance imaging (MRI) of the right knee showed increased enhancement and an extraosseous component in the right tibia. Moxifloxacin was added for improved bone penetration, and prednisone 80 mg daily was started for presumed tuberculosis-IRIS. Synovial biopsy of the right knee was negative for AFB on smear and negative for M. tuberculosis on polymerase chain reaction (PCR) and culture. His symptoms improved with prednisone and intra-articular corticosteroids. Pyrazinamide, ethambutol, and moxifloxacin were discontinued after 12 weeks of therapy, and prednisone was reduced by 10 mg/week. PT2 presented 4 weeks later with dyspnea and cough while on prednisone 40 mg. CXR revealed new large right-sided pleural effusion (Figure 1B) from which >2 L of chylous fluid was drained (Figure 1C). Pleural fluid triglyceride level was markedly elevated (7612 mg/dL). The fluid was AFB negative on smear, and mycobacterial, fungal, and bacterial cultures were also negative. Chylothorax was thought to be secondary to intra-thoracic lymphadenopathy obstructing the thoracic duct. Prednisone 80 mg daily, octreotide 50 µg thrice daily, and a low fat diet were initiated. A single dose of infliximab 4 mg/kg was administered and the patient improved clinically over the next few weeks. Prednisone tapering was completed 2 weeks after infliximab infusion without further accumulation of pleural fluid or flare of the knee arthritis.

Patient 3 (PT3) was a 42-year-old male from Cameroon who presented in April, 2013, with weight loss, fevers, night sweats, dyspnea, cough, and tender cervical and axillary lymphadenopathy. HIV serology was positive, sputum smear showed rare AFB, and culture subsequently confirmed drug-sensitive tuberculosis. Tuberculosis therapy (rifampicin 600 mg, pyrazinamide 1500 mg, isoniazid 300 mg, ethambutol 1200 mg) was initiated and fever, dyspnea, and cough resolved.

Efavirenz 600 mg, tenofovir 300 mg, and emtricitabine 200 mg daily was initiated after 5 weeks of tuberculosis therapy. A week later, PT3 presented with painful cervical and axillary lymphadenopathy and fever. FNA of the axillary lymph node showed rare AFB; culture was negative. Prednisone 50 mg daily was initiated without improvement. Furthermore, the axillary lymph node discharged spontaneously. Pur (8 mL) aspirated under ultrasound guidance showed rare AFB; culture remained negative. Prednisone was increased to 75 mg daily without improvement. Thus, infliximab 5 mg/kg was given every 2 weeks, total of 3 infusions. The axillary node was drained 3 more times. Lymphadenopathy reduced over the ensuing months, and prednisone tapering was completed 16 weeks after the last infliximab infusion.

METHODS

Patients were participants of an NIAID institutional review board approved study (NCT00286767); an observational study evaluating predictors, incidence, and immunopathogenesis of IRIS in HIV-1 infected patients with CD4 count <100 cells/µL. All had given informed consent.

CD4 counts and HIV-RNA levels were tested at week 0, 2, 4, 8, 12, 24, 36, and 48 (Supplementary Figure 1). T-cell responses to mycobacterial antigens were assessed using flow cytometry ([5], Supplementary Material). Plasma inflammatory markers (CRP, IL-6, IFN-γ, and TNF) were measured using a multi-array electrochemiluminescence assay (Meso Scale Discovery).

RESULTS

All 3 patients had advanced immunodeficiency at ART initiation. At the time of IRIS, PT2 and PT3 had substantial increases in CD4 counts, and all 3 patients had pronounced reductions in plasma HIV-RNA levels (Supplementary Figure 1).

In vitro IFN-γ and TNF production by CD4+ T cells to mycobacterial antigen and plasma levels of C-reactive protein (CRP), IL-6, IFN-γ, and TNF (Figure 1D–J) were also elevated. Plasma CRP, IL-6, IFN-γ, and TNF decreased in PT2 and PT3, coincident with prednisone initiation. For PT1, CRP, IL-6, and IFN-γ levels decreased prior to prednisone initiation, probably in relation to MAC therapy. The reduction in inflammatory markers did not always reflect reductions in symptoms. This may be due to the localized nature of the pathologies.

HIV viremia was suppressed at week 8 (PT1 and PT2) and 24 (PT3) and was maintained at week 48. CD4 counts at week 48 were 214, 178, and 172 cells/µL for PT1, PT2, and PT3, respectively.

In vitro production of IFN-γ and TNF by CD4+ T cells to mycobacterial antigen remained detectable after infliximab therapy (Figure 1D and 1E).

DISCUSSION

Corticosteroids represent the mainstay of therapy for moderate or severe IRIS. Effective management of steroid-unresponsive IRIS has not been determined. Mycobacterial IRIS is characterized by high levels of inflammatory cytokines, including TNF, derived from both lymphoid and myeloid cells [4]. In murine tuberculosis models, adjunctive use of TNF inhibitors in combination with standard tuberculosis therapy enhanced bacterial clearance and reduced lung pathology [6].

It is common practice to discontinue TNF inhibitors in patients who develop active tuberculosis while receiving TNF inhibitors. Paradoxical deteriorations have been described, however, after discontinuation of TNF inhibitors [7–9], and improvement with resumption has been reported [10–12]. TNF inhibitors have also been used in paradoxical reactions in tuberculosis of the central nervous system in HIV uninfected patients [13, 14].

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The use of TNF blockade in HIV-tuberculosis coinfected patients may be associated with potential hazards. In our 3 patients, however, clinical improvement was observed after treatment with infliximab, enabling prednisone taper. None of our patients developed symptoms suggestive of relapse of mycobacterial disease, in agreement with previous reports in HIV-uninfected patients [10–12]. TNF inhibitors have also been evaluated in a phase 1 study of 16 HIV-infected patients with active tuberculosis (without IRIS), and no detrimental effects were identified [15].

Infliximab treatment did not adversely affect virologic control on ART. There was no evidence of abrogation of ART-associated immune restoration. CD4 count increases at week 48 were comparable to those described in the literature.

In vitro production of IFN-γ and TNF by CD4+ T cells in response to mycobacterial antigen stimulation remained detectable after infliximab therapy.

In conclusion, in 3 patients with steroid-unresponsive mycobacterial IRIS, clinical improvement was temporally associated with the administration of infliximab without obvious adverse impact on immune recovery and HIV virologic control. Though definitive causality could not be established, the efficacy and immunologic effects of TNF blockade in severe mycobacterial IRIS merits further assessment in clinical trials.

Supplementary Data
Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

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