Thalidomide Treatment for Refractory HIV-Associated Colitis: A Case Series

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Thalidomide has been used as a treatment for various human immunodeficiency virus (HIV)–associated and non–HIV-associated illnesses, generally in cases in which inflammatory disease is refractory to standard therapy. Here, we discuss the successful use of thalidomide in 3 patients with severe, idiopathic HIV-associated colitis.

Case reports. A 51-year-old, HIV-infected white man presented in 2003 with a 6-week history of diarrhea. HIV infection had been diagnosed 7 years earlier. The patient was treatment naive. His CD4 cell count was 670 cells/μL, and his viral load was 82,000 copies/mL. There was no other significant medical history—specifically, no history of gastrointestinal disease. Colonoscopy revealed colitis with scattered deep ulceration that ran the length of the colon (figure 1). Histologic examination revealed moderate inflammation with occasional crypt abscesses but no evidence of an infective etiology.

Over 4 months, symptoms persisted, with marked diarrhea and weight loss. Extensive investigations failed to elicit a cause, and no bacterial (including Bartonella species, Chlamydia trachomatis, and spirochetes), protozoal, or viral (including cytomegalovirus and adenovirus) infective pathology was found. The colitis failed to respond to treatment with high-dose steroids, azathioprine, or empirical courses of ciprofloxacin, metronidazole, valganciclovir, and clarithromycin, which were given to cover potential causes. Antiretroviral therapy with didanosine, tenofovir, and ritonavir-boosted lopinavir was initially started and later switched to efavirenz, stavudine, and lamivudine. Because of the unrelenting course of the colitis, the patient was referred for panproctocolectomy, but a therapeutic trial of thalidomide was undertaken first. Five days later, the patient was passing semisolid stools, and surgery was cancelled. After 2 weeks of therapy, the patient had gained 8 kg in weight and was passing normal solid movements once per day. He was discharged from the hospital 3 weeks after commencement of thalidomide treatment to complete a 12-week course of thalidomide (100 mg twice per day), followed by lower-dose thalidomide treatment for 1 year. The patient has subsequently been symptom free for >3 years.

Patient 2 was a 43-year-old HIV-infected man who presented with a 1-month history of watery diarrhea and weight loss in 2005. HIV had been diagnosed 15 years previously, and the patient had extensive experience with treatment. At presentation, his CD4 cell count was 77 cells/μL, and his viral load was 3413 copies/mL; at the time, his combination treatment regimen was tenofovir, emtricitabine, and ritonavir-boosted ti-
pranavir. Medical history included *Pneumocystis jiroveci* pneumonia, and since HIV diagnosis, he had experienced several self-limiting episodes of endoscopy-proven nonspecific colitis.

Sigmoidoscopy revealed inflammation and linear ulceration in the sigmoid and rectum (figure 2). Histologic examination showed active chronic inflammation. Mesalazine treatment provided no benefit, and the patient lost an additional 6 kg in weight over 2 weeks. Additional endoscopy revealed severe inflammation and exudative ulcers from the rectum to midtransverse colon. No infective process was identified, and prednisolone enemas were commenced. Extensive rectal bleeding required multiple blood transfusions, and high-dose oral steroids were added to the treatment regimen, with no improvement. A panproctocolectomy was planned, and a trial regimen of thalidomide (100 mg per day) was administered. Within a few days of treatment, the patient’s symptoms had completely resolved, and additional flexible sigmoidoscopy at day 7 demonstrated healing ulcers (figure 3). Five days later, the patient was discharged from the hospital free of symptoms. The antiretroviral regimen was changed to darunavir, ritonavir, emtricitabine–tenofovir disoproxil fumarate, and enfuvirtide. Three months later, he remained healthy, and his viral load was undetectable; his CD4 cell count was 230 cells/µL. The thalidomide regimen was stopped with gradual dose reduction over a 3-month period. In 2006, the patient had 1 additional episode of colitis, which was attributed to *Campylobacter* infection, but he has otherwise remained healthy.

Patient 3 was a 31-year-old white man who presented to the hospital in 2004 with a 2-month history of bloody diarrhea. Initial sigmoidoscopy demonstrated proctitis suggestive of inflammatory bowel disease, but treatment with mesalazine and steroid enemas was not effective. Fecal cultures yielded negative results, and no ova, cysts, or parasites were noted. One month later, a second endoscopic examination revealed multiple deep, punched ulcers, and histologic examination demonstrated ulceration with florid inflammation and intranuclear inclusion bodies (figure 4). Findings were initially thought to be consistent with cytomegalovirus (CMV) colitis, so the patient was advised to undergo an HIV test, the results of which were positive. The patient commenced valganciclovir treatment. However, on subsequent review, CMV inclusion bodies were not confirmed, and there was no biopsy evidence of any infective pathology. Immunochemistry tests for CMV and herpes simplex virus yielded negative results.

At the time of presentation with colitis, the patient’s CD4 cell count was 279 cells/µL, his HIV load was 4370 copies/mL, and the results of a CMV PCR were negative. He commenced treatment with lamivudine–zidovudine and efavirenz, followed shortly by thalidomide (50 mg per day for 1 week then 50 mg twice per day thereafter). Diarrhea had improved markedly within 1 month and had completely resolved by 2 months. An additional sigmoidoscopy was performed 4 months later and revealed healing ulcers (figure 5), and the patient’s CD4 cell count had increased to 672 cells/µL. Two months later, he was symptom free. Thalidomide therapy was stopped after a total of 6 months treatment.

**Discussion.** HIV-associated infective colitis is well described, with the major opportunistic pathogen being CMV. It may manifest as a complication of seroconversion. The diagnosis of noninfective, HIV-related colitis is also well recognized;
this diagnosis may be made once infective pathologies have been excluded and the disease remains refractory to standard therapies for inflammatory bowel disease. It may be difficult to distinguish this condition from inflammatory bowel disease, because they can be very similar histologically. Recent years have seen a resurgence in the use of thalidomide for a variety of inflammatory conditions—notably Behcet disease [7], inflammatory bowel disease [8], graft-versus-host disease, and other dermatological and rheumatological conditions [9].

During 1996–2000, several randomized, double-blind, placebo-controlled trials of thalidomide use in HIV infection were performed. Two studies by Jacobson et al. [1, 2] demonstrated a benefit of thalidomide use in HIV-infected patients with refractory oral and esophageal aphthous ulceration. Patients were treated with 200 mg of thalidomide per day for 4 weeks; the oral ulceration study demonstrated complete or partial resolution in 90% of patients (complete resolution in 55%), and 73% of patients with esophageal ulceration experienced complete resolution. In 2000, Kaplan et al. [6] studied the efficacy and safety of thalidomide use in patients with AIDS who had associated wasting. One hundred three patients were recruited and randomized to 3 groups to receive either placebo or thalidomide at 100 mg per day or 200 mg per day for 8 weeks; significant weight gain was demonstrated in both thalidomide groups. Reyes et al. [10] reported similar results in a smaller study of thalidomide (100 mg 4 times per day for 12 weeks), finding an increase in weight and higher Karnofsky score in the thalidomide group, compared with the placebo group. All 4 studies reported mild-to-moderate adverse effects (mainly rash, somnolence, and sensory peripheral neuropathy). Other case reports have described the beneficial use of thalidomide in HIV-infected patients with alopecia areata, hypertrophic genital herpes infection [3], prurigo nodularis [4], Kaposi sarcoma [10], and Castleman disease.

In the non-HIV arena, the benefit of thalidomide use is being increasingly recognized for the treatment of inflammatory bowel disease that is resistant to standard therapies. It has been used in several small studies to treat refractory disease at a variety of dosages; however, randomized, controlled trials have yet to be performed. Bariol et al. [8] described a significant improvement in symptoms and histologic findings in 11 patients with a range of inflammatory bowel pathologies who were treated for 12 weeks. Similar findings were reported by Plamondon et al. [11] in a study of 25 patients with luminal and fistulating Crohn disease.

The mechanisms underlying the immunomodulatory and anti-inflammatory actions of thalidomide remain unclear, al-
though modulation of inflammatory cytokines, particularly TNF-α, appears to be important [9]. The drug has been shown to inhibit lipopolysaccharide-induced TNF-α production in human monocytes [12], although the exact mode of action has yet to be determined. Thalidomide has also been shown to have antiangiogenic effects [9], which are thought to be mediated by suppression of vascular endothelial growth factor. This is thought to contribute to antitumor activity and has also been shown to be beneficial for cases of refractory intestinal bleeding due to Crohn disease and angiodysplasias.

Adverse reactions to thalidomide are well described, and apart from its well known potential for teratogenicity, it has also been associated with rash, somnolence, peripheral neuropathy, constipation, dizziness, neutropenia, and headache. Rare complications include hepatotoxicity and toxic epidermal necrolysis.

The optimum dosage and duration of therapy of thalidomide are unknown because of a lack of pharmacotherapeutic studies. Generally, the dose is adjusted on the basis of clinical response and tolerability, and it is gradually reduced once disease has been suppressed and a decision is made to stop therapy.

In these cases that we have described, the pathology underlying HIV-associated refractory colitis is unclear. Thalidomide has proven to be effective for treating such patients. However, it remains to be seen whether this efficacy is because the patient had undiagnosed inflammatory bowel disease or another HIV-related pathology. Large, randomized, controlled trials of treatment of both HIV-associated and non–HIV-associated colitis need to be performed to learn more about the underlying pathologies of this condition and about the safety and efficacy of treatment with thalidomide.

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References


Figure 5. Healing colonic ulceration in patient 3 after 3 months of thalidomide therapy. A color version of this figure is available in the electronic version of Clinical Infectious Diseases.