Prolonged fever after Infliximab infusion

Jennifer Katz, Michael Frank

Abstract
Pharmacologic management for ulcerative colitis (UC) has recently been expanded to include anti-tumor necrosis factor (TNF) therapy for severe disease. Infliximab, a chimeric monoclonal antibody directed against TNF α was first tested in patients with Crohn's disease. In addition to serious infections, malignancy, drug-induced lupus and other autoimmune diseases, serum sickness-like reactions, neurological disease, and infusion reactions further complicate the use of Infliximab. We report a case of prolonged fever after Infliximab infusion to treat steroid refractory UC.

INTRODUCTION
Approximately 15 percent of patients with ulcerative colitis (UC) have a severe attack requiring hospitalization for intravenous corticosteroid therapy during the course of their illness[1]. Remission rates with intravenous corticosteroid therapy, however, are only 60 percent, and patients who fail therapy often require colectomy[2]. The probability of colectomy within the first five years after diagnosis ranges from 9 percent in patients with distal colitis to 35 percent in patients with total colitis, most commonly because of failed medical therapy[3]. Patients with steroid refractory UC who wish to preserve their colon can try Infliximab or cyclosporine.

Traditionally the treatment for UC was a step-up approach that began with 5-aminosalicylates in mild to moderate UC. For patients with more severe disease, corticosteroids were used as a bridge to either a higher dose of 5-aminosalicylates or to immunomodulators, namely 6-mecaptopurine or azathioprine. Finally, when medical therapy was failing or if side effects became intolerable, surgery was also considered. Infliximab is proven to be an effective therapy to induce remission in patients with severe UC whose disease is refractory to high dose corticosteroids. In patients who were hospitalized for intravenous steroids to treat a flare of UC, therapy with Infliximab at a dose of 4-5 mg/kg resulted in colectomy avoidance in 71% of patients at 90 d[4]. Infliximab, however, is associated with multiple toxicities, namely serious infections, malignancy, drug induced lupus and other autoimmune diseases, serum sickness like reactions, neurological disease, and infusion reactions. We report on a case of prolonged fever after Infliximab.

CASE REPORT
A 61-year old woman with a 15-year history of UC who failed oral prednisone was hospitalized for parenteral steroid treatment. After no clinical response was observed, Infliximab was initiated with dramatic improvement which allowed cessation of steroids. A second
Infliximab infusion was administered after 2 wk with no observed reactions. Nine days after the second dose, the patient reported a fever to 101 degrees Fahrenheit. She complained of drenching night sweats with rigors. Her appetite remained normal, weight was stable and she had no diarrhea or abdominal pain. She denied cough, dysuria, headache, neck stiffness, joint pains or rash. A complete physical examination was unremarkable and results of laboratory testing, including complete blood count, chemistry and liver function tests, were within normal limits. The patient's C-reactive protein was elevated at 41.1 mg/L as was her erythrocyte sedimentation rate at 130 mm/h, white count was 3500 mcL, without left shift. Blood cultures, urine culture, stool culture, including clostridium difficile polymerase chain reaction assay and stool for ova and parasite were all negative for pathogens. A urinary cytomegalovirus test was negative. Computed tomography scans of the chest, abdomen and pelvis were negative except for thickening of the left colon. A repeat colonoscopy showed extensive ulceration and pseudopolyps formation in the left colon with an abrupt cut off in the splenic flexure and the proximal colon was not involved. Biopsies showed moderate inflammatory disease with no pathogens. A brain magnetic resonance imaging showed no active inflammation. Her anti-double stranded DNA and anti-histone antibody were negative. After all infectious causes were excluded, a medication-induced side effect was determined to be the most likely explanation of her persistent fevers. After 25 d the patient became afebrile. Infliximab was discontinued after her second dose and she was referred for an elective colectomy.

DISCUSSION

Infliximab is a chimeric monoclonal antibody to human tumor necrosis factor (TNF)-α. In patients with moderate to severe UC, an induction regimen, followed by maintenance infusions proved to be superior to placebo in achieving clinical response, remission and mucosal healing at 30 and 54 wk of therapy. Nonetheless, there is a high incidence of infection with anti-TNF-α agents because TNF plays a central role in the initial host response to infection. Cases of tuberculosis, serious bacterial infections, listeriosis, atypical mycobacterial infections, histoplasmosis, coccidiomycosis and pneumococcal have been reported. These agents also can effect existing viral infections like hepatitis B or C infection or human immunodeficiency virus. Anti-TNF-α therapy has also been found to cause an increased risk of malignancy, most notably lymphoma. Other potential neurological effects of anti-TNF-α medication include demyelinating syndromes, like exacerbation of or new onset of multiple sclerosis and seizures. Several studies have demonstrated that the monoclonal antibody can cause autoimmune disease, for example, drug induced lupus, vasculitis, uveitis or psoriatic skin lesions or serum sickness-like reactions manifest by myalgias, arthralgias, fever and rash. Injection and infusion reactions are the most common adverse events and limited cases of hepatotoxicity, hematological dyscrasias and even death have been reported. Concomitant immunosuppressant therapy has been shown to decrease formation of antibodies to Infliximab and reduce the likelihood of an infusion reaction, although it has also shown to increase the chance of opportunistic infections and neoplasia.

In our literature search, only one case of long-lasting high fever associated with Infliximab was found in a letter to the editor. The authors reported a case of a 65-year old woman with rheumatoid arthritis who had ceased corticosteroid and methotrexate treatment secondary to serious side effects and was treated with Infliximab. Three weeks after a second infusion, the patient developed a high fever with rigors that persisted for 13 d. A delayed hypersensitivity reaction was thought to be the cause of the febrile reaction. We have reported a patient with inflammatory bowel disease who developed 25 d of spiking fevers, starting 9 d after a second infusion of Infliximab.

REFERENCES

1. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Gut 1963; 4: 299-315
2. Järnerot G, Rolny P, Sandberg-Gertzén H. Intensive intravenous treatment of ulcerative colitis. Gastroenterology 1985; 89: 1005-1013
3. Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. Gastroenterology 1992; 103: 1444-1451
4. Järnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilen M, Ström M, Danielsson A, Verbaan H, Hellström PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005; 128: 1805-1811
5. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanss J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005; 353: 2462-2476
6. Colombel JF, Loftus EV, Tremaine WJ, Egan LJ, Harmsen WS, Schleidt CD, Zinsmeister AR, Sandborn WJ. The safety profile of infliximab in patients with Crohn’s disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004; 126: 19-31
7. Connor V. Anti-TNF therapies: a comprehensive analysis of adverse effects associated with immunosuppression. Rheumatol Int 2011; 31: 327-337
8. Toruner M, Loftus EV, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008; 134: 929-936
9. Tassiopoulos S, Benopoulou O, Mytilineou E, Andreopoulos A, Vaiopoulos G. Late onset of long-lasting fever as a sole complication of treatment with anti-TNFalpha. Clin Exp Rheumatol 2005; 23: 122-123

S- Editor Wang JL  L- Editor Hughes D  E- Editor Zhang DN