

Flare of Crohn's Disease in a Patient Receiving Chronic Tacrolimus Therapy: A Case Report and Literature Review

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We report a case of Crohn's disease (CD) of new onset in a patient being treated with tacrolimus for the prevention of renal allograft rejection. Tacrolimus is a calcineurin inhibitor used as a first-line immunosuppressive drug in organ transplant recipients to prevent allograft rejection. Recent reports also suggest a role for the drug in the treatment of CD. This case reports the onset of CD in a patient already on a potent immunosuppressive regimen. Such cases of new onset CD and CD refractory to immunosuppressive therapy support the idea that the pathogenicity of this disease is multifactorial involving multiple arms of the immune response.

INTRODUCTION

The current treatments of choice for active CD include 5-ASA compounds, immunomodulators, corticosteroids, and antibiotics. Steroid therapy, however, can be ineffective at times and resistance to this treatment has been documented (1,2). Conventional immunosuppressive therapies, such as azathioprine (AZA) and 6-mercaptopurine (6MP) have a slow

onset of action and therefore, are initially used in combination with other treatment modalities (1,3). Treatment with anti-tumor necrosis factor (TNF- α) is costly and requires intravenous infusions and is ineffective in a subset of patients. Tacrolimus and cyclosporine A (CsA) are drugs currently used to prevent allograft rejection following organ transplantation. Small uncontrolled studies of these agents have shown favorable results in the treatment of CD and ulcerative colitis (UC) (1–5). In addition, a recent placebo-controlled trial of tacrolimus in fistulizing CD demonstrated fistula response but little fistula closure (6). We report here a case of new-onset CD while the patient was receiving tacrolimus for prevention of renal allograft rejection.

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Figure 1. Endoscopic photograph of the transverse colon showing patchy erythema, edema and serpiginous shallow ulcers.

CASE REPORT

A 54-year-old white male, with no family history of inflammatory bowel disease (IBD) was admitted to Beth Israel Medical Center with a two-week history of progressively worsening abdominal pain, diarrhea, and vomiting. The diarrhea was described as 15–20 watery, nonbloody stools per day associated with diffuse crampy abdominal pain and fever to 103°F. There was no recent travel or antibiotic use, except for chronic trimethoprim/sulfamethoxazole therapy. There had been a 25-pound weight loss over the past year. His past medical history was remarkable for end-stage renal disease secondary to interstitial nephritis diagnosed in 1990. He underwent renal transplantation in 1993. Allograft rejection developed requiring long-term steroid treatment, and he eventually received a second kidney transplant in 1996. The patient was maintained on oral tacrolimus 3 mg twice daily, prednisone 5 mg daily, and trimethoprim/sulfamethoxazole three times per week following the transplant. Physical examination revealed a thin male in no acute distress. The patient was tachycardic to 102 bpm and afebrile. Abdominal examination revealed a soft abdomen with

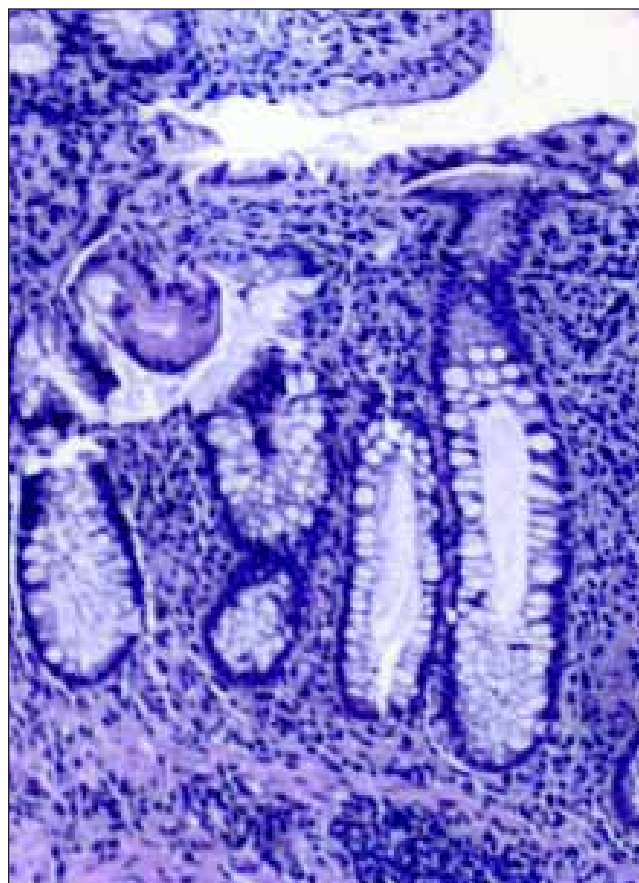


Figure 2. Photomicrograph of colonic mucosal tissue at the hepatic flexure using H&E stain, 40× magnification, showing chronic inflammatory changes in the intestinal wall with lymphocyte infiltration of the lamina propria, polymorphonuclear leukocytes infiltration into the crypts.

hyperactive bowel sounds, and right lower quadrant tenderness with voluntary guarding. Rectal examination revealed brown stool, which tested negative for occult blood. Stool studies were positive for leukocytes and routine stool cultures, ova and parasites, and *Clostridium difficile* toxin assay were negative. Laboratory testing revealed a white blood cell count of 8,900/mm³, hematocrit of 38.2%, and platelet count of 210,000/mm³. Metabolic profile and biochemical liver test results were all within normal limits. An erythrocyte sedimentation rate was 82 mm/h and C-reactive protein was 25.2 mg/dL. Serum trough levels of tacrolimus prior to admission were 9 ng/mL which is in therapeutic range (5–10 ng/mL).

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On hospital day one, the patient was placed on a full liquid diet and started on oral ciprofloxacin 500 mg twice daily and oral metronidazole 250 mg three times daily and mesalamine 800 mg orally three times daily. Prednisone was increased to 20 mg by mouth daily and computed tomography (CT) scan of the abdomen with contrast revealed no acute intra-abdominal process. Colonoscopy showed patchy erythema, edema, and serpiginous shallow ulcers (Figure 1) with intervening areas of normal appearing mucosa (skip lesions) throughout the colon except for the rectum. Multiple mucosal biopsies obtained from the hepatic flexure and transverse colon revealed severe chronic active inflammation (Figure 2).

The patient's symptoms gradually improved, including resolution of diarrhea. The prednisone dose was increased to 40 mg daily, mesalamine was continued, antibiotics were discontinued, and the patient was started on a regular diet and discharged home. Throughout the entire hospital course, the patient was maintained on his regular dosage of tacrolimus.

DISCUSSION

Crohn's disease is an inflammatory bowel disease characterized by an inappropriate immune response in genetically susceptible individuals (7), and is probably triggered by an environmental factor. Under normal conditions the intestinal mucosa exists in a state of physiologic inflammation in which homeostasis is maintained by immune tolerance to self and nonpathogenic antigens (7). Antigens in susceptible hosts trigger an inappropriate mucosal immune response that leads to chronic mucosal inflammation and the elaboration of proinflammatory mediators that overwhelm the usual defenses of the intestine, disrupting and injuring the intestinal epithelium. The precise etiology and pathogenesis of CD is not completely understood, and therefore this disease remains difficult to treat and maintain in remission.

Conventional medical therapy of CD has been directed at suppressing the immune response. Therapies such as corticosteroids have a broad effect on multiple arms of the immune response, and newer biologic agents have more focused mechanisms of action.

Among the new therapies aimed at specific points along the inflammatory cascade is the potent immuno-

modulator, tacrolimus. This immunosuppressive agent specifically suppresses the production and release of lymphokines such as interleukin-2 (IL-2) from T cells (8). Tacrolimus suppresses the transcription of the IL-2 gene (8-10). Since IL-2 dependent T-helper 1 (Th-1) activation may underlie the pathogenesis of intestinal inflammation in CD, suppression of IL-2 and the Th-1 pathway may be the mechanism of action of tacrolimus in IBD.

The molecular structure of tacrolimus has features in common with macrolides but is different than cyclosporine A (CsA), which has a similar biologic effect (2). Tacrolimus is approximately 100 times more potent than CsA *in-vitro*, in its suppression of T-cell lymphokine production (2). Tacrolimus in clinical trials of renal transplant rejection is superior to CsA in prevention of primary rejection. Tacrolimus may be more effective than CsA in IBD although clinical trials of IBD have not compared these two agents directly.

We reviewed the literature describing the use of tacrolimus in the treatment of IBD between 1998 and 2005 regarding CD (1,4,12), both CD and UC (5), and UC alone (2) (Table 1). Ierardi, et al (1) conducted a prospective, uncontrolled study of oral tacrolimus therapy in patients with CD refractory to steroid treatment. Thirteen patients were treated with long-term oral tacrolimus. The median dose was 0.1–0.2 mg/kg/day and was adjusted to achieve trough levels of 5–10 ng/mL, while mesalamine was continued concomitantly. The median treatment time was 27.3 months with a goal intended to resolve both acute attacks and maintain remission. The Crohn's disease activity index score (CDAI) (13) and the IBD life-quality questionnaire (IBDQ) (14) were used to evaluate resolution of acute disease and remission. Only one of 13 patients dropped out of the study secondary to adverse events; three of six patients experienced complete closure of fistulas; there was a marked decrease in hospitalizations during the study; supplementation with low-dose oral steroids was required in five patients; and two patients underwent surgery. The CDAI score significantly decreased after six months in 11 patients; in nine patients after one year; and in two after seven years. Also, the IBDQ score significantly

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Table 1
Tacrolimus in IBD Reference Summary

Reference	Study Type	Patients (n)	CD/UC/Both	Treatment	Outcome
Ierardi, et al (1)	Prospective	13	CD	Oral tacrolimus	<ul style="list-style-type: none"> • Decrease in hospitalizations • Complete closure of fistulas in 3/6 patients • Low-dose steroids in 5 patients
Lowry, et al (4)	Retrospective	11	CD	Oral tacrolimus, AZA or 6MP	<ul style="list-style-type: none"> • Complete response in 7 patients • Partial response in 4 patients
Ierardi, et al (13)	Case report	2	CD	Oral tacrolimus	<ul style="list-style-type: none"> • Complete healing of perianal fistula • Improvement of perianal fistula
Fellermann, et al (5)	Prospective	11	Both	IV then oral tacrolimus + mesalamine	<ul style="list-style-type: none"> • Rapid remission in 7/11 patients • Moderate improvement in 2/11 • Rectovaginal fistula closure 1/11 • Early colectomy in 1/11 • Late colectomy in 1/11
Matsushashi, et al (2)	Case report	1	UC	IV tacrolimus then oral + steroids	<ul style="list-style-type: none"> • Remission induced with tacrolimus therapy • Steroid dose tapered off
Sandborn, et al (6)	Randomized Double blind Placebo-controlled	48	CD	Oral tacrolimus versus placebo	<ul style="list-style-type: none"> • 43% of tacrolimus-treated patients had fistula improvement • 8% of placebo-treated patients had fistula improvement • 10% of tacrolimus-treated patients had fistula remission

CD = Crohn's Disease; UC = Ulcerative Colitis; AZA = Azathioprine; 6MP = 6-mercaptopurine; IV = Intravenous

increased over the same periods. This study suggests both a short- and long-term benefit of tacrolimus therapy in CD when conventional therapies fail.

Few studies to date have evaluated the use of tacrolimus in fistulizing CD. Lowry, et al (4) investigated the use of oral tacrolimus in combination with AZA or 6-MP in patients with treatment-refractory CD with perianal fistulae in a retrospective, uncontrolled study. A chart review was undertaken of all patients who received oral tacrolimus with CD and perianal fis-

tulae seen at the Mayo Clinic from 1996-1998. Clinical response was categorized as: complete, partial, or none. Eleven patients were treated with tacrolimus for a mean duration of 22 weeks. AZA or 6-MP was continued in combination with tacrolimus and started simultaneously in four patients. All patients clinically improved, seven had a complete response and four were partial responders. The mean time to improvement was 2.4 weeks, while mean time to complete response was 12.2 weeks. Ten of the 11 patients had

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adverse reactions, including nausea, paresthesias, tremor, and nephrotoxicity. The nephrotoxic side effect was dose related. Patients receiving lower doses did not experience this side effect and there was no apparent therapeutic advantage to administering higher doses of tacrolimus. Combination treatment with oral tacrolimus and AZA or 6MP shows efficacy in the treatment of CD associated perianal fistulae.

Sandborn, et al, studied 48 patients with CD and draining perianal or enterocutaneous fistulae who were randomized to treatment with oral tacrolimus or placebo for ten weeks (6). The study was a randomized, double-blind, placebo-controlled, multicenter clinical trial that measured fistula improvement and closure for at least four weeks as a primary outcome. Forty-three percent of tacrolimus-treated patients had fistula improvement compared with eight percent of placebo-treated patients ($p = 0.004$). Ten percent of tacrolimus-treated patients had fistula closure compared with eight percent of placebo-treated patients ($p = 0.86$). Adverse events associated with tacrolimus, including headache, increased serum creatinine level, insomnia, leg cramps, paresthesias, and tremor, were managed with dose reduction.

Ierardi, et al (12) described two patients with CD affected by severe perianal fistulae resistant to conventional therapies, that ultimately responded to treatment with oral tacrolimus. The successful use of tacrolimus in complicated CD seen in these two patients, as well as other studies suggests that this agent should be investigated further as a primary therapy to control active disease rather than as a "bridge" to other treatments.

A pilot study conducted by Fellermann, et al (5) assessed the efficacy and safety of tacrolimus (as an alternative to CsA) in 11 patients with steroid refractory disease (six UC, two indeterminate colitis, two CD, and one pouchitis) and with CDAI >150 . Tacrolimus was administered intravenously for 7–10 days to all patients at a dose of 0.01–0.02 mg/kg/day, followed by 0.1–0.2 mg/kg orally twice daily. AZA and mesalamine were given concomitantly. Seven patients achieved remission rapidly, and in two patients disease activity was decreased from severe to moderate. Moreover, rectovaginal fistula closure occurred in a case of CD and an improvement in pou-

chitis was achieved. Steroids were tapered to low-dose in all nine responders during oral tacrolimus therapy and a mean remission time of 9.2 months was maintained in five patients.

Lastly, a case report by Matsushashi, et al (2) showed the efficacy of tacrolimus in bringing about remission in a 73-year-old female that had UC refractory to IV steroids, CsA, and AZA.

It appears trough levels ranging from 5–10 ng/mL are adequate for the successful treatment of IBD (1, 4), however, dose ranging studies to determine efficacy have not been done. Serious side effects occur when patients are maintained on high doses of tacrolimus, achieving whole blood concentrations of 10–20 ng/mL (4). Many side effects are dose dependent, however, with no additional therapeutic advantage attributed to higher dose therapy. Patients clinically improved when maintained at a mean trough level of 9.4 ng/mL (4).

Our patient has been maintained on tacrolimus since 1996 for renal allograft rescue at serum trough levels of 5–10 ng/mL. The clinical onset of CD experienced by this patient while on a therapeutic dose of tacrolimus brings into question the efficacy of this drug as a maintenance agent. However, new-onset IBD has been reported following solid organ transplants on immunosuppressive therapy. One case series by Riley, et al, describes 14 patients who developed IBD after solid organ transplantation (12 liver, 2 kidney) despite immunosuppression (15). Four of the 12 patients who underwent liver transplantation had a pretransplant diagnosis of autoimmune hepatitis; two had primary sclerosing cholangitis (PSC); four had non-A, non-B, non-C hepatitis (NANBNC); one had giant cell hepatitis; and one had biliary atresia. They were maintained on either tacrolimus therapy alone ($n = 6$), a combination of tacrolimus and prednisone ($n = 4$), CsA ($n = 1$) or CsA and prednisone ($n = 1$). It is possible that the history of autoimmune disease or PSC in these patients may have been a manifestation of unrecognized IBD. This is especially true of the patients with PSC who had no evidence of IBD prior to immunosuppressive therapy. In one study by Perdigoto, et al (16) 17 of 105 (16%) patients with autoimmune hepatitis, treated with steroids, were found to have previously undiagnosed ulcerative colitis and five of 12 (42%) had features

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consistent with PSC on cholangiograms. There was no history of autoimmune disease in the two patients that underwent kidney transplants. One patient had Polycystic Kidney Disease and the other had obstructive uropathy. These patients were never maintained on tacrolimus and were treated with prednisone and CsA, making our patient the first reported renal allograft recipient to develop IBD on tacrolimus therapy. Biopsies of these patients revealed UC in nine patients and CD in five. Therefore, while immunosuppressive therapy is standard in the treatment of moderate to severe IBD, these agents may actually be associated with new-onset disease in certain patients. These cases support the notion that the immune pathogenesis of IBD is multifactorial and the immune mechanisms of disease may differ among patients. Since each sub-type of IBD may be driven by different subsets of immune effector cells and distinct mechanisms of inflammation, these patients may benefit from different therapy. Hence, new onset IBD can develop after solid organ transplantation, despite use of immunosuppressive therapy with tacrolimus (15,17). Studying these patients may help explain why immunosuppression is not uniformly effective for IBD and provide clues to the inflammatory determinants of this disease.

Our patient represents the first reported case of CD developing while on chronic tacrolimus therapy suggesting that in certain patients the aberrant immune response resulting in CD can bypass T-cell specific immunosuppression. Therefore, despite recent case reports and pilot studies showing tacrolimus to be a promising new treatment modality in IBD, a randomized, double-blind, placebo-controlled trial is needed to further investigate the efficacy and safety of this immunosuppressant. Such studies may also identify the specific subset of IBD patients most responsive to tacrolimus. There has already been one multicenter double-blind controlled trial using tacrolimus (6), however this study specifically looked at patients with fistulizing CD and did not investigate mucosal healing in CD or UC patients, nor did it explore tacrolimus as a long-term therapeutic agent. Perhaps tacrolimus may be most effective as an adjunct or "bridge" to long-term maintenance therapy with AZA or 6MP (4), but studies defining its role as primary therapy and in remission maintenance are needed. ■

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