CASE REPORT

Oral Tacrolimus for Megacolon in Patients with Severe Ulcerative Colitis

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Abstract

Toxic megacolon is an infrequent but life-threatening complication that occurs most commonly in patients with severe ulcerative colitis. Intravenous steroids are often recommended for patients with toxic megacolon secondary to ulcerative colitis. However, steroid dependency may mask the presence of intra-abdominal sepsis and is associated with refractoriness, during which cytomegalovirus reactivation may occur. In this report, we present two rare cases of megacolon accompanying pancolonic severe ulcerative colitis that were successfully treated with oral tacrolimus, including one steroid-naïve patient. In cases of ulcerative colitis with megacolon, treatment with oral tacrolimus is recommended, thereby avoiding steroid dependency and improving the long-term prognosis.

Key words: ulcerative colitis, toxic megacolon, tacrolimus, top-down

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Introduction

Toxic megacolon is an infrequent but lethal complication of inflammatory bowel disease (IBD) (1). Toxic megacolon is more commonly observed in patients with ulcerative colitis (UC); the frequency of toxic megacolon complicating UC is reported to be 1.6-8.0% (2). Many (76%) patients undergo surgery, with a mortality rate of 16% (3). Due to the high mortality rate, the timing of surgery is one of the most important considerations for treatment. Generally, colectomy is recommended after 48-72 hours if persistent colonic distension is observed (1). Tacrolimus, a calcineurin inhibitor, inhibits interleukin-2 production and T lymphocyte activation (4). Since calcineurin inhibitors have a rapid onset of action and are highly effective in patients with refractory UC, they are approved as alternative treatment agents for refractory UC under the national health insurance system in Japan (5). Since differences in the onset of action of various agents are thought to influence the achievement and maintenance of disease remission, early intervention with tacrolimus may improve the long-term prognosis of patients with UC (6). In this paper, we report two cases of severe UC with megacolon that were successfully treated with tacrolimus, including a steroid-naïve patient. To our knowledge, this is the first reported case report to describe the successful use of top-down therapy with tacrolimus for megacolon in patients with UC.

Case Reports

Case 1

A 58-year-old man with a month-long history of bloody diarrhea was diagnosed with UC. Despite receiving initial treatment with mesalazine (4.0 g/day), he exhibited exacerbation of symptoms in the form of bloody diarrhea and fever. Therefore, he was referred to our hospital. On admission, the patient complained of bloody stools up to 23 times per day. His vital signs were as follows: blood pressure 100/60 mmHg, heart rate 120 bpm, respiratory rate 20 breaths per minute, and body temperature 39.5°C. Physical examination revealed abdominal distension, tenderness, and muscle spasm. Laboratory tests showed a white blood cell count of 20,000/μL, platelet count of 50,000/μL, and C-reactive protein level of 10 mg/dL. An abdominal computed tomography scan revealed marked thickening of the colonic wall and intra-abdominal fluid collection. Due to the refractory nature of the patient’s condition, oral tacrolimus was initiated at a dose of 0.1 mg/kg/day. Over the next few days, the patient’s symptoms improved, and the dose of tacrolimus was gradually increased to 0.2 mg/kg/day. The patient was discharged after 2 weeks of treatment, with complete resolution of symptoms and improvement in physical examination findings.
pressure, 132/74 mmHg; temperature, 39.0°C; and heart rate, 100 beats per minute (bpm). On a physical examination, his abdomen was markedly distended with normoactive bowel sounds, although no tenderness was noted. The initial laboratory studies were remarkable for an elevated C-reactive protein (CRP) level of 32.07 mg/dL and a decreased serum albumin level of 2.8 g/dL, while the white blood cell count was normal. In addition, the patient displayed no evidence of cytomegalovirus (CMV) antigens (C7-HRP) in the serum, and stool cultures revealed no pathogenic organisms. The abdominal X-ray findings were compatible with those of megacolon (a large bowel diameter up to 96 mm) (Fig. 1A). However, an abdominal computed tomography (CT) scan showed no signs of perforation.

Since the physical examination demonstrated no signs of peritonitis, and the patient did not elect to undergo surgical resection, treatment with oral tacrolimus was started at a dose of 0.1 mg/kg per day, without concomitant steroids, in addition to mesalazine, after the patient provided his full informed consent. The optimal target tacrolimus blood concentration (10-15 ng/mL) was achieved seven days after treatment initiation. Following the commencement of oral tacrolimus treatment, the CRP level gradually decreased to 0.97 mg/dL, and Lichtier’s clinical activity index (CAI) fell from 12 (the day prior to the initiation of tacrolimus) to 3 after 28 days of treatment (Fig. 1B). Colonoscopy performed five weeks after treatment showed a grossly denuded mucosa and multiple pseudopolyps in the transverse colon, with findings suggestive of an improvement in mucosal healing (Fig. 1C). The patient was discharged 98 days after admission and has remained in remission for more than 12 months under a maintenance regimen of azathioprine (50 mg daily) and infliximab (300 mg every 8 weeks) (Fig. 1D).

**Case 2**

A 58-year-old woman with a month-long history of diarrhea was transferred to our hospital with a diagnosis of steroid-resistant UC, as more than two weeks of intravenous steroid treatment (prednisolone, 30-50 mg/day) had failed to induce remission. Upon admission, the patient complained of acute abdominal pain, stool frequency of around 5 times per day, and a temperature of 38.5°C. On examination, she was found to have tenderness on the right lower quadrant. Laboratory findings revealed a white blood cell count of 12,000 cells/μL, a C-reactive protein level of 20.5 mg/dL, and an erythrocyte sedimentation rate of 50 mm/h. A colonoscopy revealed extensive ulcerations in the transverse colon, with findings suggestive of active inflammation. Treatment with oral tacrolimus was initiated at a dose of 0.2 mg/kg per day, and the patient was discharged 4 weeks after admission with a plan for continued maintenance treatment with infliximab (300 mg every 8 weeks).
of bloody stools up to 17 times per day with severe abdominal pain. Her vital signs were as follows: blood pressure, 110/62 mmHg; temperature, 37.1°C; and heart rate, 62 bpm. On a physical examination, her abdomen was slightly distended with severe tenderness and mild rigidity. The Lichtier’s CAI value was 20. The initial laboratory studies were remarkable for an elevated CRP level of 18.29 mg/dL and a decreased serum albumin level of 2.3 g/dL, while the white blood cell count was normal. Blood cultures, bowel pathogen tests and a CMV antigenemia analysis were negative. An abdominal X-ray showed colonic dilatation, predominantly in the transverse colon, measuring 65 mm (Fig. 2A).

Since the patient’s UC was refractory to steroids, treatment with oral tacrolimus was started at a dose of 0.1 mg/kg per day, while the dose of prednisolone was gradually tapered and ganciclovir (500 mg twice daily) was administered, although the test for CMV antigenemia was negative. The optimal target tacrolimus blood concentration was achieved two days after treatment initiation. The CRP level rapidly normalized seven days after treatment. Lichtier’s CAI fell to 4 after 14 days of treatment (Fig. 2B). The patient was discharged 27 days after admission and has remained in remission for more than five months under maintenance therapy with azathioprine (50 mg daily).

**Discussion**

The definition of toxic megacolon is non-destructive dilatation of the colon in association with systemic manifestations. Megacolon is defined as dilation of the colon (5-6 cm or more) on an X-ray examination, with manifestations of systemic toxicity, including the presence of at least two of the following: tachycardia >100 bpm, pyrexia >38.6°C, leukocytosis >10,500 per μL or hypoalbuminemia <3.0 g/dL (7). Since the mortality rate of toxic megacolon associated with UC has been reported to be 16-27% (1, 3), colectomy is recommended after 48-72 hours in cases of persistent colonic distention. However, the mortality rate has recently decreased as a result of various factors, including early recognition of the condition and the prompt institution of medical therapy (8-10). In this report, Case 1 was diagnosed with toxic megacolon and Case 2 was diagnosed with nontoxic megacolon associated with severe UC.

The calcineurin inhibitor, tacrolimus, has been shown to be safe and effective as salvage therapy for steroid-refractory UC. Both oral and intravenous tacrolimus have been reported to be effective. With regard to the use of rapid induction therapy with tacrolimus, the administration of intravenous tacrolimus may be more useful than that of oral tacrolimus. However, to date, few reports have described the efficacy and safety of intravenous tacrolimus in patients with refractory UC (11, 12). In a prospective multicenter study, we found that rapid induction therapy with oral tacrolimus (started at a dose of 0.1 mg/kg daily without food) achieved a high trough level (10-15 ng/mL) in more than 90% of patients and significantly suppressed the CAI beginning two days after treatment (13). Therefore, the administration of top-down or accelerated step-up therapy with tacrolimus may improve the prognosis of refractory UC, similar to that observed with infliximab in patients with Crohn’s disease (6). In Case 1, the patient had steroid-naive UC, and top-down therapy with tacrolimus resulted in a marked improvement. Regarding CMV reactivation, it is often difficult to make a diagnosis of complicating CMV infection, as serum testing for CMV can remain negative even though the patient’s clinical course and colonoscopic findings suggest CMV infection (14). Moreover, CMV infection is associated with refractory UC and may precipitate toxic megacolon, and corticosteroids have little or no positive effect on the induction of mucosal healing (15). Therefore, in Case 2, tacrolimus and ganciclovir were first administered, after which the steroid treatment was gradually tapered. Taken together, these results suggest that tacrolimus should be...
strongly recommended for the treatment of megacolon in patients with UC. In addition, treatment with tacrolimus avoids the risk of steroid dependency, which may mask the presence of intra-abdominal sepsis and prevent mucosal healing. Similar to cyclosporine A, tacrolimus is known to be associated with many adverse effects, including infection, renal dysfunction, hypertension and neurological toxicity (6). The most commonly reported adverse effects are tremors, paresthesia, and headaches. Generally, these effects are mild and reversible. In the present two cases, Case 1 developed a systemic *Candida albicans* infection, which was easily resolved with the administration of intravenous micafungin sodium and a reduction in the dose of tacrolimus. After stopping the tacrolimus therapy, infliximab was added to the patient’s regimen in order to maintain remission. In conclusion, we herein reported the successful use of rapid induction therapy with oral tacrolimus for the treatment of megacolon in patients with severe UC. Since prompt intervention with potent medical therapy is crucial in the management of toxic megacolon, and early surgery may be necessary in patients who do not respond to medical therapy, we conclude that rapid induction therapy with oral tacrolimus may be promising as a non-surgical treatment of toxic megacolon. Currently, there are not enough reports to recommend the use of oral tacrolimus therapy in patients with severe UC, as observed in these cases. Hence, further studies of well-defined groups of patients with severe UC are required.

The authors state that they have no Conflict of Interest (COI).

References


