

Case Series

Tacrolimus Therapy for Three Patients with Elderly-Onset Ulcerative Colitis: Report of Three Cases

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Keywords

Tacrolimus · Elderly-onset ulcerative colitis · Remission induction

Abstract

In recent years, cases of elderly-onset ulcerative colitis (UC) have been increasing in number and are currently reported to account for 10–15% of all cases of UC. Although the treatment of UC is essentially similar between older and younger patients, evidence of the therapeutic efficacy of tacrolimus in elderly-onset UC patients is still limited. Herein, we report our attempt to induce remission using tacrolimus in three patients with elderly-onset UC. A 75-year-old Japanese woman, a 71-year-old Japanese man and a 76-year-old Japanese woman with severe elderly-onset UC of the pancolitis type were treated with tacrolimus. Although all three patients showed response to the drug, the eventual outcome was poor in the first patient, who developed toxic megacolon, underwent surgery, and suffered from recurrent infections and hemorrhage after the surgery. However, clinical remission was successfully achieved in the second and third patient. Tacrolimus shows some indication of effectiveness in the treatment of elderly-onset UC. However, in elderly-onset UC patients, it is necessary to keep in mind the higher risk of adverse effects of medical therapy and postoperative complications because of the high comorbidity rates. Moreover, in situations where surgery needs to be considered, it is important to ensure appropriate timing of the surgery.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the bowel of unknown etiology that predominantly affects the large intestine. The number of patients with UC has steadily increased in Japan and was estimated to be approximately 166,000 in 2013. The disease most commonly affects young adults in their 20s, but can also occur in elderly persons. Along with the aging of the society and the increasing incidence of UC, cases of elderly-onset UC (onset of UC at the age of 60 years or over) are also increasing in number and are currently reported to account for 10–15% of all cases of UC [1, 2]. Although the treatment of UC is essentially similar between older and younger patients [2, 3], the management of elderly-onset UC is complex because of problems with misdiagnosis, treatment of comorbid diseases, multiple drug interactions, impaired mobility and cognition, and difficult social and financial issues [4]. There are no reported cases of remission having been achieved using tacrolimus among patients with severe elderly-onset UC; therefore, evidence on the efficacy and safety of tacrolimus in patients with elderly-onset UC is still scarce. Herein, we report three patients with elderly-onset UC in whom we attempted to induce remission using tacrolimus.

Case Reports

Case 1

A 75-year-old Japanese woman visited a local hospital with a 3-month history of loose stools and a 2-week history of bloody stools, abdominal pain and fever. She was diagnosed as having infectious enteritis and started on treatment with oral antibiotics. However, the symptoms persisted, and she was admitted to a hospital. Even after hospital admission, the fever persisted at approximately 38°C; the patient had diarrhea 8 times a day, and the bloody stools also persisted. Sigmoidoscopy revealed multiple deep ulcers in the bowel segment extending from the rectum to the sigmoid colon, and the patient was transferred to our hospital for more detailed examination and treatment. At the time of her transfer to our hospital, the laboratory test results were as follows: white blood cell (WBC) count 5,770/ μ l, hemoglobin (Hb) 8.5 g/dl, serum albumin (Alb) 1.7 g/dl, serum C-reactive protein (CRP) 10.93 mg/dl, and erythrocyte sedimentation rate (ESR) 43 mm/h. The stool was negative for *Clostridium difficile*. Sigmoidoscopy revealed deep hemorrhagic ulcers and mucosal defects throughout the bowel segment extending from the rectum to the sigmoid colon. The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was 11 (fig. 1a). Computed tomography (CT) revealed hypertrophy of the bowel wall extending from the rectum to the transverse colon. Based on these findings, the patient was diagnosed as having severe UC of the pancolitis type. Because of the possibility of the disease becoming fulminant, treatment was initiated with intravenous prednisolone (PSL) at 1 mg/kg/day, tacrolimus at 0.1 mg/kg/day, and 5-aminosalicylic acid (5-ASA). The doses of tacrolimus were based on tacrolimus trough blood levels in an attempt to maintain troughs of 10–15 ng/ml in the first 2 weeks and of 5–10 ng/ml after 2 weeks. Although the patient tested negative for cytomegalovirus (CMV) antigenemia, ganciclovir administration was initiated concomitantly because CMV infection was suspected based on the endoscopic findings. Lichtiger's Clinical Activity Index (CAI) decreased from 17 to 9 within 2 weeks of initiation of this treatment. On hospital day 13, sigmoidoscopy revealed re-epithelialization of the ulcers, and the UCEIS had decreased to 7 (fig. 1b). However, the patient developed fever again on hospital day 18, and CT on hospital day 20 revealed toxic megacolon. Total colectomy was performed, along with creation of a

rectal mucous fistula and end ileostomy, on hospital day 22. The postoperative course was unfavorable. Along with repeated episodes of hemorrhage and infections, the patient also developed *Pneumocystis* pneumonia 1 month after surgery. She died of hemorrhagic shock 4 months after surgery.

Case 2

A 71-year-old Japanese man had bloody diarrhea 30 times a day for 4 days and visited a local hospital. Abdominal CT revealed marked edema of the entire colon, and sigmoidoscopy revealed mucosal edema and redness as well as hemorrhagic lesions. Under the suspected diagnosis of UC, treatment with 5-ASA and oral PSL at 1 mg/kg/day was initiated, along with total parenteral nutrition. However, as the symptoms did not improve, the patient was transferred to our hospital 1 month after the onset of symptoms. The results of the blood tests on admission were as follows: WBC count 10,500/μl, serum CRP 2.85 mg/dl and ESR 58 mm/h; the test result for CMV antigenemia was positive. Stool was negative for *C. difficile*. Sigmoidoscopy revealed continuous and circumferential spontaneous hemorrhage, mucosal redness and edema as well as mucosal defects, and the UCEIS was 11 (fig. 2a). The patient was diagnosed as having severe UC of the pancolitis type. The PSL and 5-ASA were continued, and tacrolimus was initiated at a dose of 0.05 mg/kg/day. The doses of tacrolimus were based on tacrolimus trough blood levels as in case 1. Furthermore, administration of ganciclovir was initiated, as well as of trimethoprim/sulfamethoxazole, which was administered concomitantly to prevent *Pneumocystis* pneumonia. By 2 weeks after the initiation of tacrolimus, the CAI had decreased from 12 to 4. The PSL dose was gradually tapered, and azathioprine was initiated at a dose of 50 mg; the patient was discharged on hospital day 35. Colonoscopy performed 3 months after the initiation of tacrolimus revealed an apparent trend toward improvement, and the UCEIS was 7 (fig. 2b).

Case 3

A 76-year-old Japanese woman visited a local hospital with a 2-week history of diarrhea. Laboratory examination revealed increased levels of inflammatory response markers, and CT revealed hypertrophy of the bowel wall extending from the ascending to the transverse colon. As colonoscopy showed an extensive mucosal defect extending only from the ascending to the transverse colon, the patient was diagnosed as having UC of the right-sided colitis type. Treatment was initiated with 5-ASA and oral PSL at 1 mg/kg/day, and the diarrhea showed a tendency to resolve. However, while the PSL dose was being tapered, the serum CRP levels increased again; the patient had diarrhea 7 times a day, and bloody stools appeared. The patient was transferred to our hospital 2 months after symptom onset. The results of the blood tests on admission to our hospital were as follows: WBC count 4,760/μl, Hb 14.0 g/dl, CRP 6.13 mg/dl, Alb 2.3 g/dl and ESR 8 mm/h, and a positive test result for CMV antigenemia. Her stool was negative for *C. difficile*. Colonoscopy revealed ulcers and mucosal defects throughout the bowel segment extending from the cecum to the transverse colon, and the UCEIS was 10. However, the mucosa of the left half of the colon was normal (fig. 3a). As histology was consistent with the diagnosis of UC, the patient was diagnosed as having severe elderly-onset UC of the right-sided colitis type. She was judged to have PSL-dependent UC. Tacrolimus was initiated at the dose of 0.1 mg/kg/day, while PSL was gradually tapered and eventually discontinued. The doses of tacrolimus were based on tacrolimus trough blood levels as in case 1. As the patient tested positive for CMV antigenemia, ganciclovir administration was also initiated concomitantly. The CAI decreased from 15 to 4 within 2 weeks of initiation of tacrolimus treatment, and the UCEIS, which 3 weeks after the

initiation of treatment had been 7, showed a trend toward improvement (fig. 3b). Azathioprine was initiated at a dose of 25 mg/day. The patient was discharged on hospital day 28.

Discussion

In patients with elderly-onset UC, the rate of comorbidity is high [3], and it is necessary to keep in mind the higher risk of adverse effects of medical therapy and postoperative complications [2, 5]. In case 1 reported above, although the clinical findings 1 week after the initiation of tacrolimus treatment and the colonoscopic findings 2 weeks after the initiation of treatment suggested that the patient was responding to the therapy, the patient developed toxic megacolon 3 weeks after the initiation of tacrolimus. Toxic megacolon may be caused by destruction of the myenteric plexus, use of anticholinergic and narcotic drugs, long-term use of steroids [6], *C. difficile* infection [7], and CMV infection [8]. In this patient, however, the test for *C. difficile* infection was negative, and the clinical condition deteriorated after sigmoidoscopy. The deterioration might have been related to the impact of endoscopy, use of several doses of butylscopolamine as an analgesic drug, or CMV infection, because the patient tested positive for CMV antigenemia after surgery.

The poor postoperative prognostic factors in patients with elderly-onset UC include male gender, a preoperative Alb level <2.8 g/dl, and emergency surgery [9, 10]. In a previous study of patients aged ≥60 years who underwent emergency surgery, 46.7% died postoperatively [11]. Moreover, it has been reported that a history of steroid therapy influences the risk of postoperative complications [12], while elective colectomy seemed to be associated with improved survival relative to medical therapy among patients with advanced UC aged ≥50 years [13]. However, the association between tacrolimus treatment and the risk of postoperative complications remains unknown. Case 1 suffered from repeated episodes of infections and hemorrhage postoperatively. This poor outcome may have been associated with the emergency surgery, the poor nutritional status due to UC, and/or the use of several immunosuppressants, such as steroids and tacrolimus.

Although the European Crohn's and Colitis Organisation (ECCO) Statement recommends the use of cotrimoxazole for the prevention of *Pneumocystis* pneumonia in patients receiving triple immunomodulator therapy including a calcineurin inhibitor or anti-tumor necrosis factor, no consensus has been reached yet on the appropriate prophylaxis for patients receiving double immunomodulator therapy [14]. Since case 1, who received two drugs (a steroid and tacrolimus), developed *Pneumocystis* pneumonia after surgery, concomitant use of the trimethoprim/sulfamethoxazole combination seems to be preferable in patients, especially older patients, receiving these two drugs.

Conclusion

Tacrolimus shows some indication of effectiveness for the treatment of elderly-onset UC. However, more extensive study is required to determine the utility and safety of this therapy in this vulnerable population. Since tacrolimus is sometimes used in combination with steroids and azathioprine, measures against susceptibility to opportunistic infections are necessary, especially in this subset of patients. Moreover, in situations where surgery should be considered, it is important not to miss the appropriate time for the surgery.

Statement of Ethics

This study was approved by the Etiological Study Ethical Review Board of Saitama Medical Center, Jichi Medical University, Saitama. Written informed consent was obtained from cases 2 and 3 and from a bereaved relative of case 1 for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Disclosure Statement

The authors have no conflict of interest to declare. This study received no funding.

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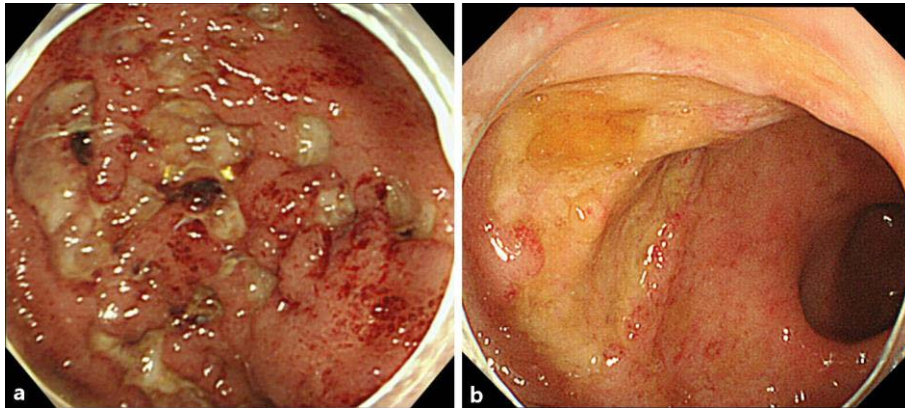


Fig. 1. Sigmoidoscopic findings in case 1. **a** Sigmoidoscopic findings on admission showed deep hemorrhagic ulcers, punched-out lesions and mucosal defects in the rectum. **b** Sigmoidoscopic findings on hospital day 13 showed that the ulcers in the rectum were re-epithelialized.

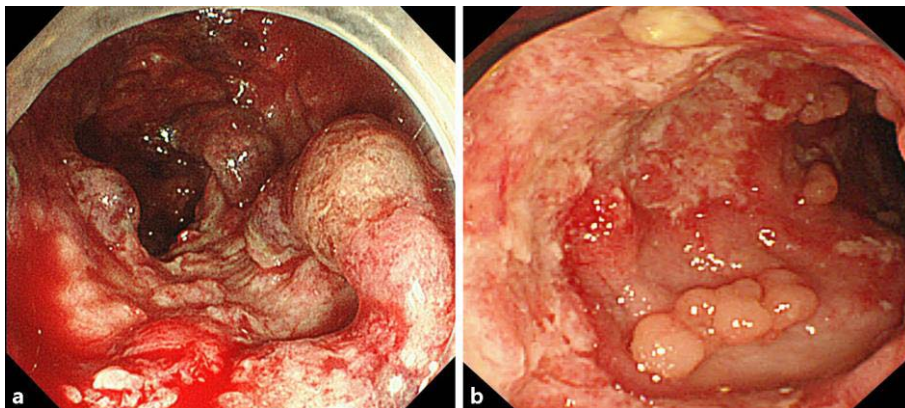


Fig. 2. Sigmoidoscopic findings in case 2. **a** Sigmoidoscopic findings on admission showed circumferential ulcers, spontaneous hemorrhages and mucosal defects in the sigmoid colon. **b** Sigmoidoscopic findings after 3 months of treatment with tacrolimus revealed that the ulcers in the sigmoid colon were re-epithelialized, showing an apparent trend toward improvement. However, active inflammation persisted.

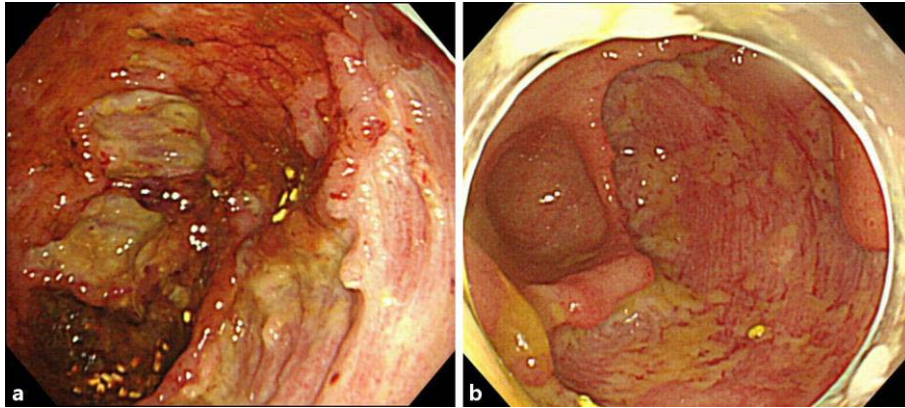


Fig. 3. Colonoscopic findings in case 3. **a** Colonoscopic findings on admission showed ulcers and mucosal defects in the cecum. **b** Colonoscopic findings after 3 weeks of treatment with tacrolimus showed that the ulcers in the cecum were re-epithelialized.