Rescue Therapy with Tacrolimus for a Patient with Severe Ulcerative Colitis Refractory to Combination Leuko-cytapheresis and High-Dose Corticosteroid Therapy

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Abstract

A 19-year-old man complaining of severe diarrhea and hematochezia was admitted to our hospital. Endoscopic findings and laboratory data revealed that he had ulcerative colitis (UC). Despite combination therapy with high-dose corticosteroids and intensive granulocytapheresis, his condition did not improve. Therefore, we initiated tacrolimus therapy. Intravenous administration of tacrolimus with a trough level of 10 to 15 ng/ml relieved his abdominal symptoms within 1 week. The patient experienced no UC relapse 1 year after treatment with oral tacrolimus. Tacrolimus is a promising therapy for patients with UC refractory to the combination of high-dose corticosteroids and leukocytapheresis.

Key words: ulcerative colitis, tacrolimus, leukocytapheresis

(Introduction) Tacrolimus is a macrolide antibiotic isolated from Streptomyces tsukubanesis that has immunomodulatory properties; it is efficacious and widely used for the prevention of allograft rejection in patients undergoing liver transplantation (1). Although its action is similar to that of cyclosporin (CyA), the immunosuppressive effect is 10 to 20 times greater in vivo than that of CyA and its intestinal absorption is more reliable, even in the presence of gastrointestinal disease (2). Therefore, much attention has been directed to tacrolimus for patients with inflammatory bowel disease (IBD) that are refractory to conventional therapy. In several uncontrolled studies, tacrolimus improved fistulizing Crohn’s disease (CD) and steroid-refractory ulcerative colitis (UC) (3, 4). A recent randomized control study demonstrated the efficacy and safety of oral tacrolimus for inducing remission of refractory UC (5). Here, we report a patient with severe UC which was refractory to combination high-dose corticosteroids and leukocytapheresis therapy and was successfully treated with tacrolimus.

Case Report

A 19-year-old man with no medical history was admitted to our hospital because of high fever and frequent bloody diarrhea. Physical examination revealed localized tenderness at the left lower abdomen and increased bowel sounds. His temperature was 38°C. The following pathologic laboratory findings were noted: white blood cell count 11600/mm³, C-reactive protein (CRP) 14 mg/dl, and serum albumin 2.9 g/dl (Table 1). Repeated blood cultures and testing for parasitic and bacterial bowel pathogens were negative. Colonoscopy revealed dull colonic mucosa and an erythematous pattern with a granular texture and gross pitting, and a blurred vascular pattern. Computed tomography showed increased wall thickness throughout the entire colon and increased vascularity within the bowel walls. The patient was diagnosed with severe total type UC. Under this diagnosis, daily therapy with 50 mg of prednisolone (PSL), along with 3000 mg mesalamine was started. Despite this...
therapy, the patient’s condition worsened. We then initiated treatment with 60 mg PSL and methylprednisolone pulse therapy (1000 mg for 3 days). His condition improved 2 weeks after initiating this therapy. When the dose of PSL was tapered to 50 mg per day, however, his condition deteriorated again. He became increasingly anemic and hypoalbuminemic, and both blood in the stool and bowel movements increased. We thought that additional mesalamine enema might worsen the patient’s symptoms and therefore did not perform it. Next, we started intensive granulocytapheresis (G-CAP) twice a week as additional therapy. Although we performed combination therapy with PSL and G-CAP six times, his condition did not improve. Colonoscopy revealed deep longitudinal ulcerations with mucosal erythema and edema at the sigmoid colon (Fig. 1). At this time, cytomegalovirus (CMV) antigenemia was negative. Histology and polymerase chain reaction method to detect CMV in a colonic biopsy specimen revealed no existence of concomitant CMV infection. We considered that it would be necessary to use immunosuppressive therapies with a strong and rapid onset of action for this patient because he was refractory to intensive G-CAP and high-dose corticosteroid therapy.

After informed consent was obtained from the patient and his family, tacrolimus was given by continuous intravenous infusion to adjust the serum trough levels of tacrolimus from 10 to 15 ng/ml. One week after initiating intravenous administration of tacrolimus, his abdominal pain disappeared and CRP became negative (Fig. 2). We then switched to oral administration of tacrolimus with the same trough level. Eight weeks after initiating the oral tacrolimus therapy, the administration of PSL was tapered off and the patient’s condition was completely improved. Colonoscopy revealed regenerating epithelium at the sites of previous ulcerative lesions (Fig. 3). During this therapy, the patient did not experience any serious side effects other than tremor. We tapered the dose of tacrolimus to achieve a trough level of 5 to 10 ng/ml and he remained in remission 3 months later. One year later, the patient is still in remission without any side effects and the laboratory data show no signs of active inflammation.

**Discussion**

This is a case report of a 19-year-old Japanese patient with severe UC that was successfully treated by intravenous and oral administration of tacrolimus. The initial therapy for patients with moderate or severe UC is a combination of oral mesalamine and corticosteroids. Recently, the therapeutic effect of G-CAP for active UC was reported in Japan. G-CAP is a new therapy in which granulocytes and monocytes are selectively absorbed by a G-1 Adacolumn. Naganuma et al reported that G-CAP therapy is a promising option for patients with moderate UC that are refractory to conventional therapy, with regard to reducing and avoiding PSL re-administration, but that five sessions of G-CAP is not very effective for patients with severe UC (6). In this case, we intensively performed G-CAP twice per week to reduce the colonic inflammation, because the patient did not respond to high-dose PSL administration. This combination therapy, however, was not effective for this patient. In addition, endoscopic findings revealed deep longitudinal ulcer, which was suggestive of impaired mucosal healing. We therefore started intravenous administration of tacrolimus, for expecting rapid onset of action and letting this patient go into remission as soon as possible, because azathioprine may be ineffective in this active phase for its delayed onset of action.

Generally, intravenous administration of CyA is effective as a rescue therapy for patients with severe UC. The rapid
efficacy of CyA to avoid emergency colectomy is approximately 50% to 80% in UC, but 35% to 67% of patients eventually undergo surgery (7-10). In addition, maintenance of remission with CyA requires high doses that are frequently associated with significant side effects such as gingival hyperplasia, hypertrichosis, hypertension, diabetes, nephrotoxicity, and neurotoxicity (11).

Another major disadvantage of CyA is the necessity to administer it intravenously to achieve sufficient, stable levels due to its variable intestinal absorption. The original oil-based oral formulation of CyA is characterized by high intra- and inter-patient’s pharmacokinetic variability and poor bioavailability in patients with diarrhea, thereby preventing the stable blood levels of CyA (12).

Tacrolimus, however, is well-absorbed orally, compared to intravenous administration, even in severe colitis (4, 13). Moreover, recent evidence from transplant patients suggests that tacrolimus is superior to CyA with respect to immunosuppressive potency and has a lower incidence of side effects (14, 15). Based on these findings, we selected tacrolimus for this patient.

Tacrolimus has immunosuppressive properties similar to CyA, but is approximately 100 times more potent than CyA (16). Tacrolimus interacts with the calmodulin-dependent serine/threonine phosphatase calcineurin by binding of the immunophilin FKBP12. The main action is an abrogation of the translocation process of the nuclear factor of activated T-cells. This leads to a decrease in interleukin-2 levels, which in turn reduces the activation and proliferation of T cells (17). As for the therapeutic effects of tacrolimus in patients with IBD, some published case reports and uncontrolled studies suggest that tacrolimus therapy is beneficial in patients with steroid-resistant IBD or perianal fistulating CD (3, 4, 18, 19). A recent randomized study demonstrated dose-dependent efficacy and safety of oral tacrolimus for remission-induction therapy of refractory UC (5). Of refractory UC patients, that had been treated with a high trough concentration of tacrolimus (10~15 ng/ml), 68.4% had an improved disease activity index score with a reduction of more than four points within 2 weeks. Moreover, 20% of patients with refractory UC treated with such a high trough level of tacrolimus went into remission. These results suggest that the optimal treatment range, in terms of efficacy, for the induction of remission is 10 to 15 ng/ml. Therefore, we started tacrolimus therapy with aiming the trough level of 10~15 ng/ml, which resulted in the rapid improvement of the present patient’s condition. In this case, although the patient has continued tacrolimus therapy for nearly 2 years, he has not experienced any serious side effects. He has been maintained in clinical remission with a trough level of tacrolimus of 5 to 10 ng/ml. There are currently only a few reports on the long-term efficacy and safety of tacrolimus as a maintenance treatment for patients with UC (18). In this regard, further clinical trials are needed to evaluate whether tacrolimus is an optimal drug for maintenance therapy for patients with UC (19, 20).

In conclusion, we report a patient with UC refractory to combination of corticosteroid and intensive G-CAP therapy, that was successfully treated with tacrolimus. Controlled trials comparing tacrolimus with CyA in patients with UC are not yet available, and it is therefore difficult at present to conclude which drug is superior. Tacrolimus, however, is an alternative option for patients with UC that are refractory to conventional therapy.

This work was supported by a Grant-in-Aid for Scientific Research (C) from the Ministry of Culture and Science of Japan (18590677).
References