We were able to induce and maintain remission with camostat mesilate, a serine protease inhibitor, in two patients with ulcerative colitis, to whom salicylazosulfapyridine could not be administered due to previous side effects. The enzymatic activity of proteases from granulocyte, pancreatic juice and bacteria is possibly harmful to the inflammed colonic mucosa. Camostat mesilate can be expected to have an anti-inflammatory effect on the damaged mucosa of inflammatory bowel disease.

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**Key words:** salicylazosulfapyridine, inflammatory bowel disease

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**Introduction**

Ulcerative colitis is a chronic disorder of unknown etiology characterized by inflammation of the colonic mucosa. In the treatment of mild to moderate colitis, salicylazosulfapyridine (SASP) is widely used; adverse reactions, however, are occasionally encountered. Protease inhibitors are thought to be possible therapeutic agents since their action is exerted on mucosal inflammation. We recently administered camostat mesilate, a serine protease inhibitor, to two patients with active colitis, whose symptoms resulted in subsidence.

**Case Report**

**Case 1**

In 1987, a 43-year-old male was hospitalized with more than ten episodes of bloody diarrhea and lower abdominal pain daily. Five years previously, at the age of 37, he was first diagnosed as having ulcerative colitis and received medication of SASP for one year; SASP was then discontinued because of severe nausea.

On examination he was undernourished and exhausted but afebrile. There was marked tenderness in the left lower abdomen and hyperactive bowel sounds. Bacteriological examination of feces showed no pathological finding. Erythrocyte sedimentation rate was 20 mm/hr. Other laboratory data of hematology and biochemistry were all within normal range. Barium enema (Fig. la), colonoscopy (Fig. 1b) and histological examination of colonic biopsy specimens (Fig. 1c) showed active colitis involving the total colon.

The treatment for the patient began with total parenteral nutrition (TPN), berberine chloride of an anti-diarrheal drug and tranexamic acid of a hemostatic drug. He declined medication of SASP because of the adverse reaction in the previous treatment. During the first 2 weeks of this hospitalization, bloody diarrhea and abdominal pain were somewhat relieved. In the 3rd week, however, bloody diarrhea was exacerbated. Then, oral administration of camostat mesilate in a daily dose of 600 mg was supplemented, which resulted in a gradual clinical improvement. The patient gave consent to this original medical treatment. He no longer complained of abdominal pain or hematochezia in the 5th week. Hence, a low-residue diet was started and all medicines but camostat mesilate were discontinued. After 2 months of hospitalization, repeated stool examinations were negative for occult blood, and barium enema (Fig. 2a) and colonoscopic examination (Fig. 2b) showed normal findings. His diet was returned to normal. The sole treatment with camostat mesilate was continued after discharge. He thereby remained in total remission at least for 20 months with visits to the outpatient department.

**Case 2**

In 1990, a 36-year-old male who had been followed up at the outpatient department was hospitalized because of bloody diarrhea with lower abdominal pain two to four
Fig. 1. Examinations before treatment in case 1. Barium enema (a) shows a diffusely granular appearance of the total colon mucosa and loss of haustra in the transverse and descending colon. Endoscopic view of the transverse colon (b) shows extensive ulceration with contact bleeding. Histological finding of the mucosa (c) reveals superficial ulceration and a crypt abscess (HE stain, ×100).

Fig. 2. Barium enema (a) and endoscopic view of the transverse colon (b) in case 1 after treatment.
Fig. 3. Examinations before treatment in case 2. Barium enema (a) shows a diffusely granular mucosa and loss of haustra in the total colon. Endoscopic view of the descending colon (b) shows granular and hyperaemic mucosa with small shallow ulcers. Histological findings of the mucosa (c) shows a distorted crypt architecture and a crypt abscess (HE stain, ×100).

Fig. 4. Barium enema (a) and endoscopic view of the descending colon (b) in case 2 after treatment.
times a day.

Two years earlier, the diagnosis of active ulcerative colitis was first made and he was given SASP in a daily dose of 3.0 g with a good response. At that time, however, levels of GOT, GPT and alkaline phosphatase became moderately elevated, but returned to normal immediately after SASP was discontinued.

The patient was afebrile and physical examination was unremarkable except for mild tenderness in the lower abdomen. Stool cultures yielded no enteric pathogens. The white-blood-cell count was 14,800 /μl/ml with a slight left shift of the granulocytic series. Other hematological and biochemical examinations were within normal limits. Barium enema (Fig. 3a), colonoscopy (Fig. 3b) and histological examination of colonic biopsy specimens (Fig. 3c) showed active colitis involving the total colon.

The patient was treated with parenteral nutrition, a low-residue diet and oral administration of camostat mesilate in a daily dose of 600 mg with informed consent. No other medicine for treatment of ulcerative colitis was used. His symptom of colitis disappeared in a week and occult blood test returned to negative at three weeks after admission. Then, he started to take a normal diet. The follow-up examinations of barium enema (Fig. 4a) and colonoscopy (Fig. 4b) revealed marked recovery of colitis. He has continuously received medication of camostat mesilate after discharge, and thus remission has been maintained for 24 months.

Discussion

We were able to induce total remission with oral administration of camostat mesilate in our two patients with mild (in case 2) and moderate (in case 1), total ulcerative colitis, for whom SASP could not be of use due to side effects. After their discharge, remission was maintained by the sole treatment with camostat mesilate during the periods of at least 24 months and 20 months, respectively.

In the course of inducing remission, we administered parenteral nutrition and/or a low-residue diet for bowel rest in combination with camostat mesilate therapy. Even though colitis symptoms were relieved to some extent by the state of bowel rest, there was no evidence that nutritional therapy led the patients with ulcerative colitis to total remission (1). It was noteworthy that, in case 1, the initial hospital course was unsatisfactory despite TPN therapy until camostat mesilate was administered.

Although the etiology of ulcerative colitis is unknown, the activity of proteases from granulocyte, pancreatic juice and bacteria in colon is respected as a factor exacerbating inflammation in involved mucosal tissue. Bohe et al (2, 3) hypothesized a local protease-anti-protease imbalance in the pathogenesis of active ulcerative colitis, on the basis of the increasing levels of pancreatic elastase, anionic trypsin and granulocytic elastase in fecal extracts and the decreasing level of alpha2-macroglobulin in plasma from patients with this disease. They therefore suggested the possible favorable effect of an appropriate protease inhibitor on inflammatory mucosa.

Camostat mesilate, which has been commonly used for treatment of chronic pancreatitis in Japan (4), inhibits serine proteases, such as trypsin, plasmin, thrombin, kallikrein (5). No serious side effect has been reported even in long-term medication. On the other hand, while the pathogenesis of active ulcerative colitis appeared to be relevant to platelet activating factor (PAF) locally synthesized (6), an in vitro study (7) has indicated that camostat mesilate inhibits elastase release from PAF-stimulated granulocytes. Since this drug can be expected to have an anti-inflammatory effect on the intestine as well as on the pancreas, camostat mesilate may be worthwhile as a therapeutic attempt in patients with inflammatory bowel disease (IBD).

Other protease inhibitors such as ulinastatin and gabexate mesilate also have the possibility as therapeutic agents for IBD. Yagita et al (8) investigated the clinical effect of ulinastatin and prednisolone injected into superior or inferior mesenteric artery of patients with severe IBD with good response. Tada et al (9) reported that six out of eight cases of active ulcerative colitis unresponsive to SASP or and steroid therapy were improved by a concomitant use of ulinastatin. In the present patients, total remission was induced and maintained by oral administration of camostat mesilate, not in combination with SASP or steroid therapy. We believe that the favorable responses of these patients provide us a clue for establishing new therapy of IBD. Furthermore, we need to accumulate clinical experience with camostat mesilate in colitis patients, and to ascertain the effects of this drug in experimental colitis animals.

References

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