Abstract  Background: Toxic megacolon is a life-threatening complication most commonly observed in patients with ulcerative colitis or Crohn’s disease that is characterized by total or segmental nonobstructive colonic dilatation of at least 6 cm on plain abdominal films associated with systemic toxicity.  

Case report: We report an unusual case of fulminant steroid-refractory ulcerative colitis complicated by toxic megacolon treated successfully with the immunosuppressant tacrolimus.  

Conclusion: Tacrolimus administration induced clinical remission and bridged the time interval, until the standard immunosuppressant azathioprine could maintain clinical remission, thereby avoiding eminent emergency colectomy.

Keywords Tacrolimus · Ulcerative colitis · Toxic megacolon · Azathioprine · Steroid refractory

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) usually characterized by intermittent acute flare-ups of active disease followed by phases of quiescent disease or only limited disease activity. Although the condition can be controlled in the majority of patients by classical treatment regimens consisting of systemic and topical steroids and 5-acetylsalicylic acid derivatives, a subset of patients does not respond to the conventional treatment with steroids or 5-acetylsalicylic acid derivatives and has a more aggressive course of disease, with rapid progression of symptoms and signs of systemic toxicity finally leading to toxic megacolon. Toxic megacolon is a life-threatening complication of IBD not restricted to UC but may also complicate Crohn’s disease, ischemic and infectious colitis, diverticulitis, volvulus, and obstructive colon cancer [1]. Conventional immunosuppressants such as azathioprine, 6-mercaptopurine, and methotrexate are not helpful in this subset of patients because of their slow onset of action. The immunosuppressants cyclosporine A and tacrolimus are potent calcineurin inhibitors and exert similar effects on the immune system, resulting in the inhibition of T-cell activation. Both immunosuppressants are approved and are widely used for the prophylaxis of organ rejection in patients receiving allogenic liver or kidney transplants [2, 3]. Both drugs are also used to prevent rejection in patients receiving allogenic heart and small bowel transplants. Although neither drug is approved for the treatment of IBD, they have been used for active UC and for active and fistulizing Crohn’s disease [4, 5, 6, 7, 8, 9, 10, 11, 12].

Although the efficacy of cyclosporine A as “rescue” medication in severe steroid-refractory acute UC is well established, its therapeutic potential may be limited by severe drug-induced side effects [4, 5, 6, 7, 8, 9]. Frequent side effects include paresthesia (26%), hypertri-
chosis (13%), arterial hypertension (11%), tremor (7%), nausea (6%), nephrotoxicity (6%), hepatotoxicity (3%), gingival hypertrophy (2%), and neurotoxicity (1%) [8]. Limited clinical experience suggests that tacrolimus is beneficial in patients with severe steroid-refractory IBD [10, 11, 12]. The experience with tacrolimus in transplant patients provides some evidence that tacrolimus is superior to cyclosporine A with respect to its immunosuppressive potency and frequency of side effects [2, 3]. Our own experience with tacrolimus in the management of patients undergoing liver, kidney, or small bowel transplantation as well as the published evidence on the use of tacrolimus in IBD patients mentioned above led us to choose tacrolimus to treat a patient with fulminant steroid-refractory UC complicated by a toxic megacolon. This individual treatment approach was initiated to avoid eminent emergency colectomy and to gain time for elective surgery or maintenance therapy with long-acting immunosuppressants such as azathioprine and 6-mercaptopurine. As it turned out, tacrolimus successfully avoided colectomy at all. The patient achieved a rapid remission that has now been maintained for more than 18 month under a maintenance therapy with azathioprine (2.5 mg/kg daily).

Case report

A 31-year old woman with a 5-year history of UC was admitted to a local hospital on 2 February 2001 because of severe bloody diarrhea. Three weeks before admission she had diarrhea that became bloody and frequent. Before admission she was on maintenance treatment of mesalamine at 500 mg three times per day. In 1996 she had one severe attack that was treated successfully with prednisolone. Six months before admission she had delivered a healthy baby by normal vaginal delivery. Her paternal uncle also had UC and her paternal cousin type 1 diabetes. Her medical history was otherwise unremarkable.

She was considered to have a severe attack of UC and was treated with intravenous prednisolone 100 mg per day, oral mesalamine 3 g per day, intravenous ciprofloxazine 200 mg twice per day, and intravenous fluid replacement. Total parenteral nutrition was initiated when she did not improve. Oral azathioprine 1 mg/kg body weight per day (suboptimal dose) was added. Despite this treatment her condition deteriorated, she became increasingly anemic and hypoalbuminemic, and the bloody bowel movements increased.

When she was referred to our hospital 3 weeks later she had 23 bloody stools a day, abdominal pain, fecal urgency, and crampy abdominal pain. She was pale. Her temperature was 38.9°C, heart rate 130/min, blood pressure 120/60 mmHg, and respiration rate 28/min. Abdominal examination revealed diffuse abdominal distension and tenderness without signs of local or general peritonitis. The following pathological laboratory findings were noted: white blood cell count of 11.2×10⁹/l (normal 3.4–10), hemoglobin 7.6 g/dl (normal 12.5–15.5), C-reactive protein 231 mg/l (normal <6 mg/l), and serum albumin 2.4 g/dl (normal: 3.5 – 4.5 g/dl). Repeated blood cultures and testing for parasitic and bacterial bowel pathogens were negative. Acute viral infection, especially acute cytomegaly infection was excluded by serological and polymerase chain reaction testing. Autoantibodies, including rheumatoid factor, antinuclear, anti-smooth muscle, anti-ribonucleoprotein, and anti-neutrophil cytoplasmic antibodies, were all negative. Plain abdominal radiographs showed toxic dilatation of the transverse and descending colon reaching diameters of 7 cm in the transverse colon (Fig. 1a). Sonographic features of the colon were consistent with a severe pancolitis with simultaneous terminal ileocecal involvement, accentuated wall stratification, loss of haustral markings, signs of aperistalsis, increased vascularization within bowel walls, and colonic diameters up to 7 cm. Emergency colectomy was contemplated.

After the patient’s fully informed consent had been obtained, tacrolimus was given at 0.01 mg/kg per day by continuous intravenous infusion for 4 days followed by oral administration of tacrolimus (0.1 mg/kg bodyweight per day in two divided doses). We aimed for a whole-blood tacrolimus level of 10–12 µg/l in the first 4 days and approx. 5 µg/l thereafter. Prednisolone 100 mg per day, azathioprine 2.5 mg/kg per day, mesalamine 4.5 g per day, broad-spectrum antibiotics, ciprofloxazine 500 mg twice per day, and metronidazole 400 mg twice per day were given concomitantly orally. The occurrence of bloody stools rapidly decreased and ceased 3 days after initiation of tacrolimus therapy. The clinical