Transplant International

Transplant International ISSN 0934-0874

CASE REPORT

Two cases of severe *de novo* colitis in kidney transplant recipients after conversion to prolonged-release tacrolimus

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Keywords
colitis, immunosuppression, kidney transplantation, tacrolimus.

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Received: 10 September 2009
Revision requested: 1 October 2009
Accepted: 2 November 2009
Published online: 1 December 2009

doi:10.1111/j.1432-2277.2009.01009.x

Summary

Diarrhea is a frequent complication in patients after solid organ transplantation. We describe two cases of severe new onset colitis in kidney transplant recipients that developed shortly after the introduction of the therapy with prolonged-release formulation of tacrolimus replacing standard twice daily formulation of tacrolimus in one case and cyclosporine A in the second case. Both patients developed severe, intermittent bloody diarrhea with abdominal pain, weight loss, dehydration and worsening graft function that required immediate hospitalization. The symptoms did not diminish after dose reduction or withdrawal of mycophenolic acid derivatives. After excluding bacterial, viral, fungal, and parasite infections, colonoscopy with colonic biopsy was performed in both patients, which revealed features typical of colitis. Both patients received mesalazine until the symptoms stopped. In one of the patients, standard formulation of tacrolimus was immediately reintroduced. The second patient was given everolimus in an acute phase of diarrhea. Although the two cases presented in this report cannot fully support a causal relationship between the prolonged-release tacrolimus and colitis, they should increase awareness among transplant physicians and prompt more close monitoring of such potential side effects as a part of the pharmacovigilance plan for a new formulation of the well-established immunosuppressive drug.

Introduction

Gastrointestinal (GI) adverse events are common after solid organ transplantation, occurring in 20–50% of kidney transplant recipients [1–5]. Their clinical course may range from mild, manifesting as nausea, abdominal discomfort or loss of appetite, to more severe, diagnosed with vomiting, diarrhea, abdominal pain, weight loss, and cachexia [5]. Among the GI complaints in organ transplant recipients, diarrhea is one of the most frequently encountered event, has a marked negative impact on quality of life, and may result in a risk of graft dysfunction, discontinuation of immunosuppressive therapy, and mortality [4,6]. Among the most common causes of GI complications are infections and medication-associated side effects. The scale of GI problems in transplant recipients is increasing mostly because of more frequent use of potent immunosuppressive agents and broad-spectrum antibiotics [4]. The diarrhea may occur in patients treated with different immunosuppressive regimen, but appears more frequent in the patients treated with tacrolimus than in those with cyclosporin A [7,8] as well as with mycophenolate mofetil (MMF) [9]. So far, there have been only a few reports on new onset colitis that developed under various immunosuppressive regimens [10,11]. Here we describe two cases of severe new onset colitis in kidney transplant recipients that developed shortly after the start of therapy with once-daily

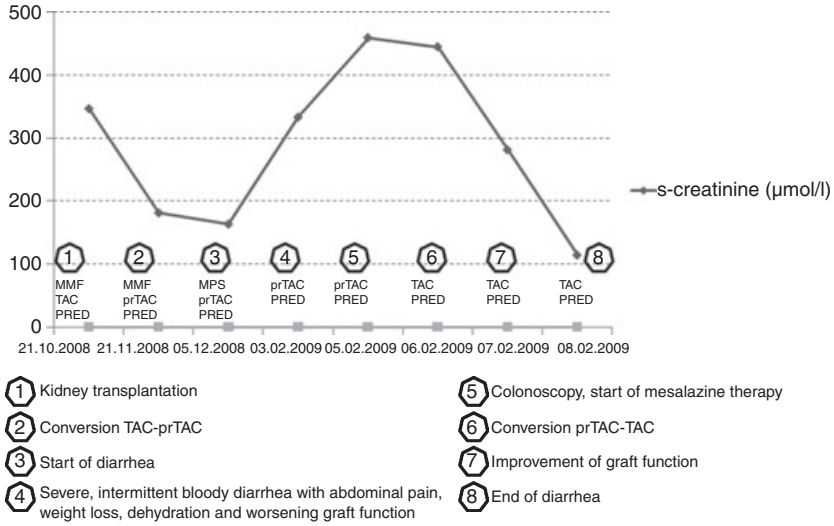

Figure 1 Case 1: Clinical course, serum creatinine, and immunosuppressive therapy.

prolonged-release formulation of tacrolimus (prTAC) that replaced standard twice-daily formulation of tacrolimus or cyclosporin A.

Case 1

A 43-year-old man with end-stage kidney disease resulting from the polycystic kidney disease received a kidney transplant from a deceased donor after 10 months of uncomplicated chronic hemodialysis therapy (Fig. 1). His primary immunosuppression regimen consisted of steroids, MMF (CellCept®; Roche Pharma AG, Grenzach Wyhlen, Germany), and tacrolimus (Prograf®; Astellas Pharma Europe B.V., Leiderdorp, the Netherlands) twice daily. The through levels of tacrolimus were monitored twice weekly, and from day 5–30 post-transplantation, levels were maintained within a range of 10–13 ng/ml and later in the range of 7–10 ng/ml. The patient was discharged from the hospital 14 days after surgery, and during the first scheduled visit in the outpatient department, standard TAC twice-daily formulation was changed to once-daily extended-release formulation of tacrolimus (Advagraf®; Astellas Pharma Europe B.V.). Two weeks after the conversion, the patient developed recurrent episodes of diarrhea (≥3 stools/day with a daily stool bulk exceeding 150 ml). The dose of MMF was immediately reduced to 250 mg twice/day, and shortly thereafter, MMF was converted to mycophenolate sodium (MPS, Myfortic®; Novartis Pharma GmbH, Nuernberg, Germany) (180 mg twice daily). As the diarrhea did not subside, the treatment with MPS was discontinued. The medical therapy 3 months post-transplantation included prednisone 7.5 mg/day, prTAC 5 mg once daily, ranitidine (150 mg daily), allopurinol 100 mg/day and

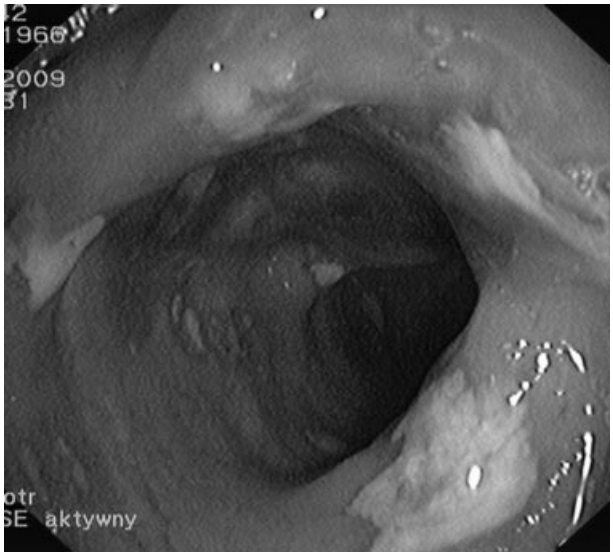

Figure 2 Case 1: Colonoscopic image.

extended-release verapamil 120 mg/day. Several days later, the patient had to be immediately hospitalized because of severe, intermittent bloody diarrhea with abdominal pain, weight loss (14 kg in 2 months), dehydration, and worsening graft function (serum creatinine increased from 183.2 µmol/l to 328.3 µmol/l). The laboratory investigations revealed also anemia (hemoglobin 9 g/dl) and high C-reactive protein level of 228 mg/l, and the pancreatic and liver enzymes were in normal range. The through blood level of tacrolimus transiently increased to 16 ng/ml, most probably as a result of diarrhea. Stool cultures showed negative results for routine bacteriological (*Salmonella*, *Shigella*, *Yersinia*, *Escherichia*

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coli 0157, *Campylobacter* species), parasitic, and fungal examinations. Stool specimens for *Clostridium difficile* toxin A and B by enzyme-linked immunosorbent assay (ELISA) also tested negative. Cytomegalovirus (CMV) infection was excluded by negative CMV-DNA in both serum and colonic biopsy specimen. The colonoscopy revealed superficial ulcers covered by easy flushable fibrin both in the descending and sigmoid colon and anus flat (Fig. 2). The colorectal mucosa was swollen and granular with the loss of vascular pattern. During the colonoscopy, endoscope was inserted only to splenic flexure because of high risk of perforation. Colonic biopsies demonstrated mild lymphoplasmacytic cell infiltration of the mucosa and single ulcerations with intravascular thrombosis of the small vessels (Fig. 3). There were no typical features of intestinal CMV infection as well as mycosis. Immunohistochemistry revealed positive CVD3, CD34 and weak positive CD20 staining in the vascular epithelium.

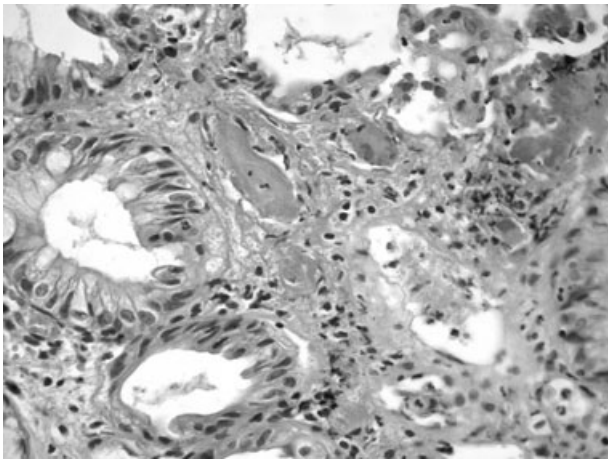

Figure 3 Case 1: Colonic biopsy.

The immunosuppressive regimen was immediately changed, i.e. tacrolimus once daily was converted to TAC twice daily, the dose of steroids was increased (30 mg/day of prednisone in tapering doses) and mesalazine (500 mg t.i.d.) was initiated. The therapy led to a rapid improvement in graft function (serum creatinine decreased to 115.0 μmol/l) and GI complaints. The treatment with mesalazine was continued for up to 3 months and then withdrawn. For the next 6 months, the patient was without any GI side effects, was treated with prednisone (5 mg/day) and TAC (1.5 mg twice daily, with blood level of about 5 ng/ml) and his serum creatinine was stable around 115 μmol/l.

Case 2

A 50-year-old man, 7 years after kidney transplantation due to kidney failure in the course of the chronic glomerular disease, was admitted to our hospital because of abdominal cramps, intermittent bloody diarrhea, general weakness, and deterioration of graft function (Fig. 4). The symptoms had begun 2 months earlier, 2 weeks after a change of an immunosuppressive regimen. The patient had been previously treated for more than 6 years with prednisone 10 mg/day, cyclosporine A (100 mg b.i.d., with a mean C0 blood level of 100 ng/ml), and MMF 750 mg b.i.d. The immunosuppressive regimen was modified and cyclosporine A was replaced by the prolonged-release TAC

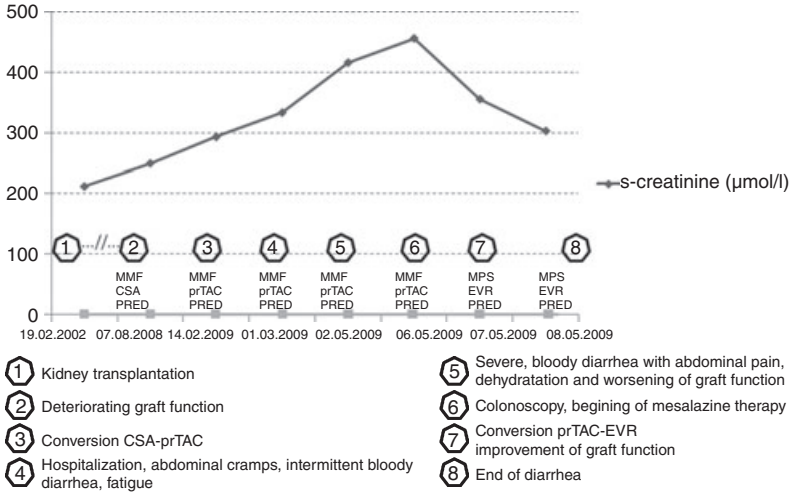

Figure 4 Case 2: Clinical course, serum creatinine, and immunosuppressive therapy.

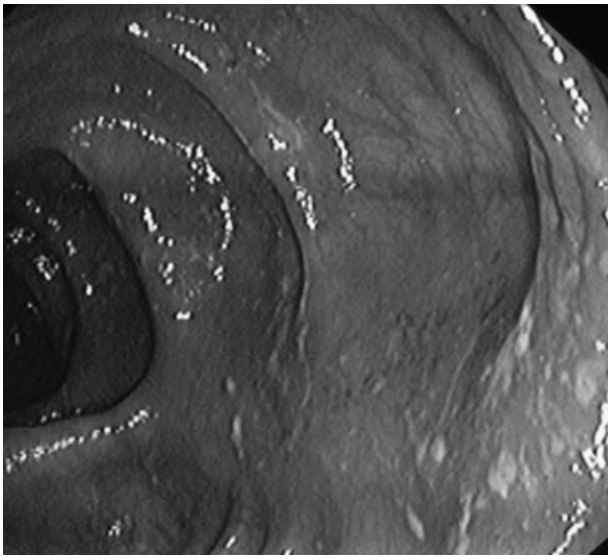

Figure 5 Case 2: Colonoscopic image.

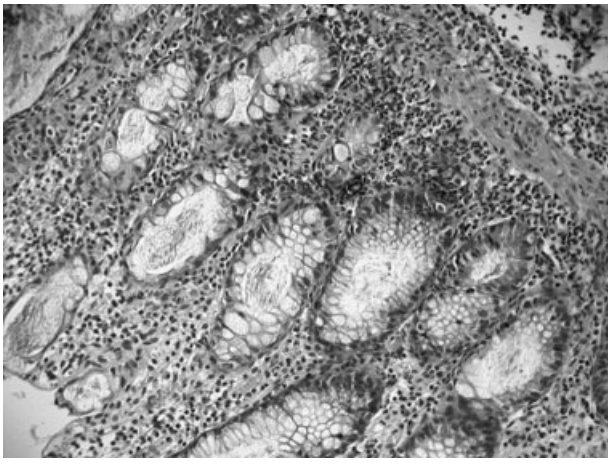

Figure 6 Case 2: Colonic biopsy.

mainly because of a slow but consistent worsening of graft function (serum creatinine rose from 230 μmol/l to 348 μmol/l during the last 9 months). After admission to a hospital, the laboratory tests showed serum creatinine 421 μmol/l, anemia (hemoglobin 6.9 g/dl), and elevated C-reactive protein (98 mg/l). Pancreatic and liver enzymes were within normal range. Blood level of tacrolimus was 5.5 ng/ml. Bacterial, parasitic, fungal or viral infections were excluded in the same way as outlined in Case 1. The colonoscopy performed after excluding the infections as a cause of diarrhea revealed edematous, granular mucosa with multiple superficial small erosions, aphtous ulcersand loss of the normal vascular pattern in descending, transverse, and ascending colon and the cecum (Fig. 5). The sigmoid colon and anus colonic mucosa showed no pathological changes. Colonic biopsies, which were taken from the colonic mucosa with pathologic appearance, disclosed edematous colorectal mucosa with severe lymphoplasmacytic and acidophilic granulocyte infiltration of lamina propria of the mucosa, crypts, and epithelium. Superficial epithelium in the colorectal mucosa was partially not visible. Microscopic view suggested aphtous colorectal inflammation with increased concentration of acidophilic granulocytes (Fig. 6).

After the colonoscopy, everolimus was replaced with prTAC, the dose of prednisone was kept stable at 10 mg/day and MMF was replaced with MPS 360 mg b.i.d., and treatment with mesalazine (2×1 g) was started. Under that treatment, the patient's symptoms resolved quickly, and the graft function partially improved (serum creatinine 309 μmol/l).

Discussion

We describe two cases of patients at different times after kidney transplantation, who developed severe diarrhea caused by colitis shortly after a conversion from a calcineurin inhibitor (standard twice-daily formulation of tacrolimus or cyclosporin A) to a new form of prolonged-release tacrolimus.

Diarrhea is a frequent complication after organ transplantation, but is mostly of mild to moderate intensity [12]. In most cases, diarrhea is caused by infections or pharmacological treatment including immunosuppressive drugs [4,12]. The role of the latter remains controversial as a recent analysis from 16 transplantation centers in Belgium questioned a dominant position of immunosuppressive therapy-associated severe diarrhea in renal transplant patients [12]. The same study also provided practical recommendations for the diagnosis of diarrhea, which we strictly followed in our patients, excluding carefully in the first stage bacterial, viral, fungal, and parasite infections [12].

The colonoscopy findings presented in this report are infrequent in renal transplant patients as the cases of new onset inflammatory bowel disease (IBD) on immunosuppressive therapy have been rarely reported mostly in patients after liver transplantation [10,11]. Sarkio *et al.* [3] found in the retrospective study that severe GI complications affected 10% of 1515 kidney transplant recipients, and half of them occurred during the first year of post-transplantation. Twenty-three percent of patients had colonic involvement, mainly diverticulitis or perforations, but colitis was diagnosed in only three cases [3]. The major risk factors for developing GI problems were the polycystic kidney disease and delayed graft function. The relationships between immunosuppressive therapy

and *de novo* post-transplant colitis were not straightforward, and among immunosuppressive agents, only MMF was found to promote the development of post-transplant enterocolitis and Crohn's disease-like pattern of colitis [13].

In our transplantation center, during the short period of time, we observed two cases of severe diarrhea caused by *de novo* colitis, first in a patient early after renal transplantation, and the second several years after transplantation. Both patients had no history of GI complaints. Interestingly, in both cases, the colitis developed shortly after the introduction of prolonged-release tacrolimus into the immunosuppressive regimen. In the first case, prTAC was given instead of a standard twice-daily TAC formulation but in the second, it replaced another calcineurin inhibitor cyclosporine A. In both patients, the GI symptoms seemed not to be related to other immunosuppressive drugs like steroids or MMF/MPS; however, in case 2, we cannot exclude the possibility that the conversion of cyclosporine to tacrolimus (prTAC) could result in the increase in plasma mycophenolic acid levels thereby causing GI side-effects [14]. Unfortunately, we routinely monitored mycophenolic acid plasma concentration in our patients at that time.

As a result of the increased risk of diverticulitis, the adult polycystic kidney disease is one of the main risk factors of GI complications after transplantation [3]. Although the first of our patients had polycystic kidney disease as primary cause of ESRD, the colonoscopy performed routinely before transplantation did not reveal any abnormalities in the colon that strengthens our concept that the most likely causal factor for the development of colitis in our patients was the introduction of prolonged-release tacrolimus. The concept is further supported by the fact that the symptoms of bowel disease subsided in both patients after the discontinuation of prTAC and in one of the patients did not relapse even after the immediate reintroduction of the standard TAC administered twice daily plus steroids with complete withdrawal of mesalazine. However, in the second case, the relationship between prTAC and colitis was not so straightforward because after the episode of diarrhea, we decided to discontinue a calcineurin inhibitor and replace it with a regimen consisting of everolimus, mycophenolate sodium, and prednisone.

The effect of tacrolimus on the development of diarrhea remains unclear; however, some trials show increased incidence of diarrhea in tacrolimus-treated patients. It was postulated that it could have been due to a prokinetic effect of TAC on the intestinal tract [4]. Moreover, the observation among the patients after liver transplantation suggested that tacrolimus may specifically promote the development of *de novo* IBD [8]. Despite that, enterocolitis as the cause of diarrhea has been described mostly in patients on immunosuppressive regimens containing MMF [9,13].

Prolonged-release tacrolimus is a new formulation that has been recently approved in Europe and therefore experience with its clinical use is limited in large part to clinical trials. The recent review that summarized the clinical development of prTAC revealed that the overall incidence of treatment-emergent adverse effects with both TAC and prTAC were similar including the almost identical rate of diarrhea, which was the most common problem found in over 40% of the patients on therapy with each drug [15]. In a study of 70 liver transplant recipients observed for 2 years, after the conversion from TAC to prTAC, the treatment was discontinued in 13 patients including only one case of diarrhea [16]. In a group of 70 stable kidney transplant recipients, none of eight patients who discontinued the treatment for 2 years after the conversion from TAC to prTAC did so because of diarrhea [17]. To our knowledge, there have been no reports of new onset colitis in patients after conversion to prolonged-release tacrolimus from twice-daily standard TAC formulation or cyclosporin A. The reason why prTAC could cause colitis with severe diarrhea remains unknown. We also cannot definitely prove that it had anything to do with the different pharmacokinetic properties of prTAC; however, it is worth mentioning that one of the effective ways of reducing the toxicity of other immunosuppressive drugs (e.g. MMF) including GI toxicity is to divide their daily oral dose into more frequent doses [18].

We cannot also exclude the possibility that the increased blood level of tacrolimus in case 1 could be partially responsible as Asano *et al.* [19] described a case of severe diarrhea in a renal transplant patient in association with a high blood level of tacrolimus. However, it is of note that in their patient, TAC blood level was much higher than in our case (28.7 vs. 16 ng/ml).

There were also occasional reports on the use of tacrolimus (standard formulation) as a rescue therapy for severe ulcerative colitis refractory to corticosteroids in nontransplant patients [20].

These two case reports cannot fully support the causal relationship between the prolonged-release tacrolimus and colitis, but should increase awareness among transplant physicians of such a possible complication.

Both patients had to be treated with mesalazine that may have obscured the possible relationship of prTAC with colitis but such severe course of colitis prompt us to initiate the therapy that was in full agreement with the current recommendations [21]. However, the diarrhea did not relapse after the discontinuation of mesalazine.

We therefore conclude that the rapid resolution of GI complications after changing of immunosuppression

regimen with discontinuation of prTAC in our patients might indicate that the dose manipulation, reduction of total dose, and/or dose splitting (e.g. the dosing from once to twice daily) of certain immunosuppressive drugs, including tacrolimus, could be a reasonable strategy in managing or even for prevention of GI toxicity, including colitis-associated severe diarrhea in organ-transplant recipients.

Authorship

IK: designed and performed the study, analyzed the data, and wrote the manuscript. MB: performed the study, analyzed the data, and wrote the paper. PD performed the study and contributed to the writing of the paper. MWD: assessed colonic biopsies and wrote the manuscript. MN: designed the study, analyzed the data, and wrote the paper.

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