

Improvement in Severe Mycophenolic Acid-associated Gastrointestinal Symptoms after Changing Enteric-coated Mycophenolate Sodium to Mizoribine in Renal Transplant Recipients: Two Case Reports

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Abstract

Clinical results point to a better gastrointestinal tolerability with enteric-coated mycophenolate sodium as compared to mycophenolate mofetil. However, some transplant recipients who are treated with enteric-coated mycophenolate sodium still experience gastrointestinal symptoms. We herein present two cases of renal transplant recipients with severe gastrointestinal symptoms who were switched from enteric-coated mycophenolate sodium to mizoribine, and the symptom reversal effects were evaluated using the Gastrointestinal Symptom Rating Scale. The results of this study showed a significant improvement in severe gastrointestinal symptoms in renal transplant recipients after converting from enteric-coated mycophenolate sodium to mizoribine.

Key words: renal transplantation, immunosuppression regimens, Gastrointestinal Symptom Rating Scale (GSRS)

(Intern Med 55: 2005-2010, 2016)

(DOI: 10.2169/internalmedicine.55.5968)

Introduction

Mycophenolic acid is the cornerstone in maintenance immunosuppression regimens after renal transplantation due to its beneficial effects in preventing both acute rejection and chronic allograft nephropathy.

Mycophenolic acid is available as mycophenolate mofetil or as enteric-coated sodium, both providing mycophenolic acid as the active ingredient. Gastrointestinal symptoms such as diarrhea, abdominal pain or dyspepsia frequently occur in renal graft recipients treated with mycophenolate mofetil (1), who thus require dose reductions to reduce side effects and thereby increase the risk of rejection episodes and graft loss (2, 3).

Enteric-coated mycophenolate sodium has improved the gastrointestinal tolerability profile because mycophenolic acid release with this formulation is delayed until it reaches the small intestine. Previous studies have shown that the mycophenolic acid dosage is better maintained with enteric-

coated mycophenolate sodium than mycophenolate mofetil, with fewer gastrointestinal symptoms in recipients receiving enteric-coated mycophenolate sodium (4, 5). The benefits of changing renal transplant recipients who develop gastrointestinal symptoms while on mycophenolate mofetil therapy to enteric-coated mycophenolate sodium were recently established in many studies (6, 7). However, our experience reveals that patients who have been treated with enteric-coated mycophenolate sodium may still experience gastrointestinal symptoms.

As another immunosuppression regimen, mizoribine blocks inosine 5-monophosphate dehydrogenase in the same manner as mycophenolate mofetil. It was shown that there were fewer gastrointestinal symptoms with mizoribine compared to mycophenolate mofetil (8, 9). To the best of our knowledge, comparisons between enteric-coated mycophenolate sodium and mizoribine, or converting from enteric-coated mycophenolate sodium to mizoribine, have not yet been investigated in renal transplant recipients.

We herein report two successful cases where the out-

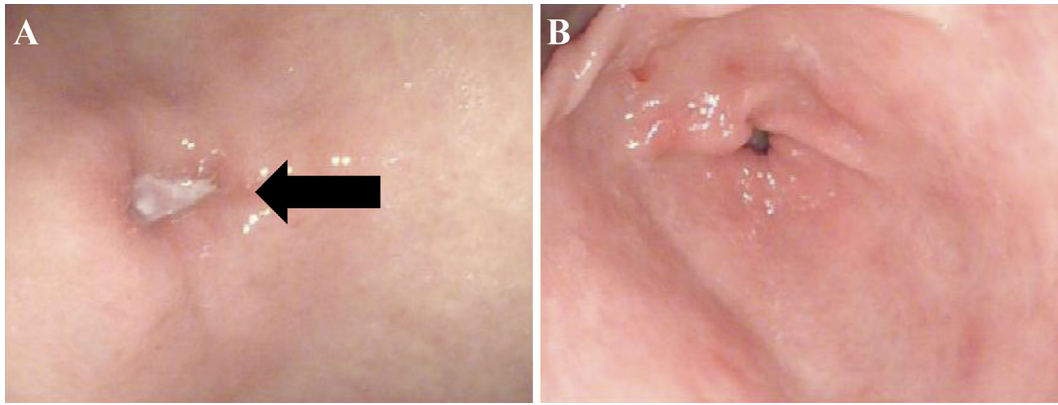


Figure 1. (A) A gastroscopic examination in March 2013. Gastroscopy revealed an active stage 1 gastric ulcer in the gastric antrum (black arrow) and edema of the gastric mucosa; (B) Gastroscopic examination in May 2013. Gastroscopy revealed that the gastric ulcer had completely healed.

comes were an improvement in gastrointestinal symptoms after changing from enteric-coated mycophenolate sodium to mizoribine in renal transplant recipients. One case was a renal transplant involving a cardiac death donor while the other was a living-donor renal transplant. The Gastrointestinal Symptom Rating Scale (GSRS), a 15-item instrument designed to assess common gastrointestinal symptoms, was used to evaluate the symptom reversal effects (10, 11). The different effects of enteric-coated mycophenolate sodium and mizoribine are unknown. However, the results of this report indicated that the renal function was maintained within a normal range and no severe side effects were observed after switching from enteric-coated mycophenolate sodium to mizoribine in either case.

Case Reports

Case 1

A 31-year-old woman with end-stage renal failure due to acute nephritic syndrome underwent renal transplantation from a cardiac death donor in January 2013 after 14 months of hemodialysis. Immunosuppressive therapy was initiated with tacrolimus (5 mg/d), mycophenolate mofetil (1,500 mg/d), and prednisolone (50 mg/d). The trough tacrolimus levels ranged from 10 to 15 ng/mL, and she had a stable graft function.

Two days after renal transplantation, the patient complained of abdominal bloating (GSRS 4) and mycophenolate mofetil was switched to enteric-coated mycophenolate sodium (1,080 mg/d). Her abdominal bloating improved a day after the treatment change, although she developed indigestion (GSRS 3) that resolved spontaneously after a few days.

In early March 2013, the patient complained of abdominal pain of an unknown cause (GSRS 5). Because abdominal pain may be associated with gastric acid, the patient was administered omeprazole (20 mg, twice a day). While the abdominal pain improved a day later, she still experienced minor abdominal discomfort for several days (GSRS 2).

Due to severe abdominal pain (GSRS 6) in late March 2013, the patient underwent a gastroscopic examination where a gastric ulcer (0.7 cm) was found (Fig. 1A). The histologic evaluation revealed active chronic inflammation of the mucosa, hyperplasia of gastric foveolar epithelial cells, and focal degeneration. Two days after gastroscopy, the enteric-coated mycophenolate sodium dosage was reduced to 720 mg/d due to an exacerbation in her condition (GSRS 7) and no observed improvement in her abdominal pain.

Enteric-coated mycophenolate sodium therapy was discontinued and the immunosuppressive regimen was modified to tacrolimus (5 mg/d), mizoribine (100 mg/d), and prednisolone (10 mg/d) in early April 2013 during the patient's admission. Abdominal pain resolved (GSRS 1) the next day, and on the second gastroscopic examination in May 2013 (Fig. 2), the gastric ulcer was found to have completely healed (Fig. 1B). A second histologic evaluation revealed mild chronic inflammation of the mucosa.

After follow-up, the patient's serum creatinine level remained stable between 0.67 and 0.78 mg/dL, and no further gastrointestinal symptoms were observed.

Case 2

A 45-year-old man diagnosed with chronic kidney disease started maintenance hemodialysis in May 2009. The patient underwent a living-donor renal transplantation in May 2010 after 12 months of hemodialysis. Immunosuppressive therapy consisted of cyclosporin A (350 mg/d), mycophenolate mofetil (1,500 mg/d), and prednisolone (50 mg/d), with trough cyclosporin A levels ranging from 250 to 350 ng/mL. Acute rejection was not observed postoperatively, and the patient's serum creatinine level remained at 1.33 mg/dL.

At the 43-month follow-up, the patient was noted to have had severe diarrhea in early December 2013 (GSRS 5). After changing mycophenolate mofetil to enteric-coated mycophenolate sodium (1,080 mg/d), diarrhea improved (GSRS 3) in late December 2013. However, due to a subsequent sudden deterioration in diarrhea (GSRS 6), the patient's treatment was changed from enteric-coated mycophenolate

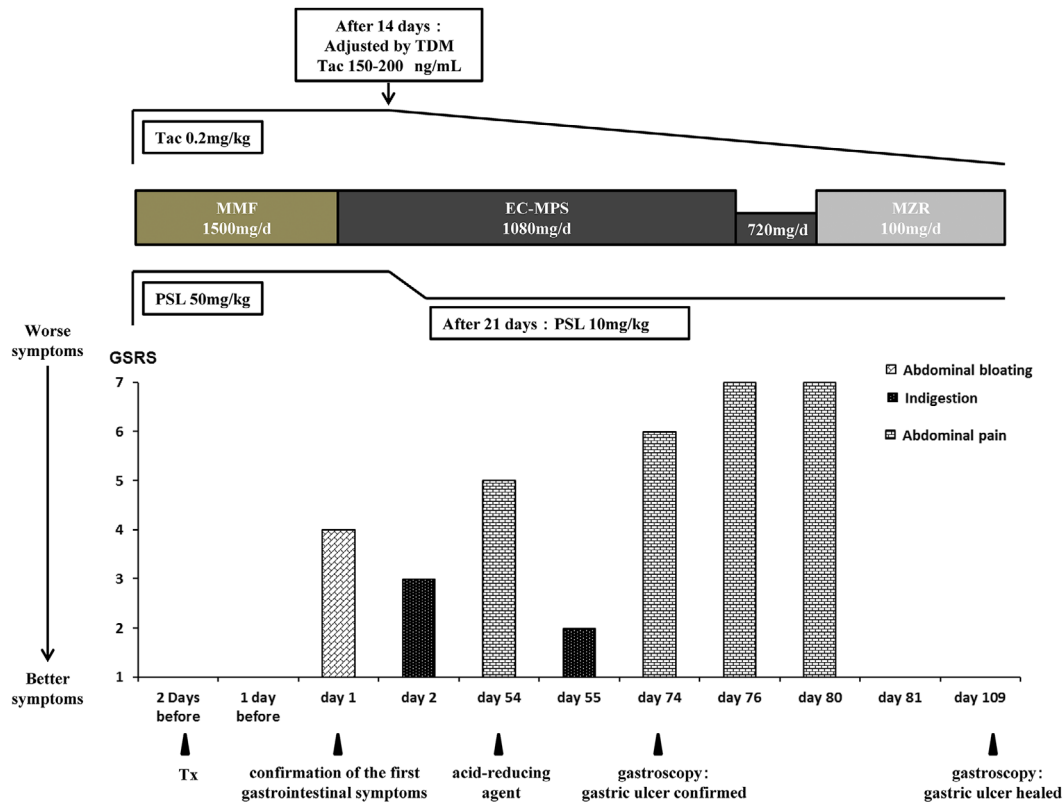


Figure 2. Clinical course of Case 1 after renal transplantation. EC-MPS: enteric-coated mycophenolate sodium, Tac: tacrolimus, MMF: mycophenolate mofetil, MZR: mizoribine, PSL: prednisolone, TDM: therapeutic drug monitoring, Tx: transplant

sodium to mizoribine (100 mg/d) in March 2014, with diarrhea improving the following week (GSRS 2).

During the next three months, the patient was followed up at a local hospital. As the local hospital did not stock mizoribine, his treatment was switched back to enteric-coated mycophenolate sodium (1,080 mg/d) according to the judgment of the doctor at the local hospital in early June 2014.

Within the next few days, the patient developed severe diarrhea (GSRS 6) again and was admitted to our hospital. After admission, enteric-coated mycophenolate sodium was switched back to mizoribine (100 mg/d) and diarrhea resolved (GSRS 1) in late June 2014 (Fig. 3).

After follow-up, the patient has maintained a stable graft function with a serum creatinine value between 1.11 and 1.33 mg/dL, and neither diarrhea nor other gastrointestinal symptoms have been observed.

Discussion

It is becoming clear that the gastrointestinal toxicity of mycophenolic acid is related to events surrounding drug absorption and metabolism. Two potential molecular targets that may cause gastrointestinal symptoms of toxicity are N-(2-hydroxyethyl) morpholine and acyl-mycophenolic acid glucuronide.

Both molecules are metabolites of mycophenolic acid. N-(2-Hydroxyethyl) morpholine is a metabolic product of my-

cophenolate mofetil and has been shown to manifest local irritating properties. Acyl-mycophenolic acid glucuronide is an active metabolite of both mycophenolate mofetil and enteric-coated mycophenolate sodium. The *in situ* production and exposure of this metabolite in the intestinal wall may induce toxic damage via protein adduct formation.

If local intestinal toxicity is important in determining the tolerance of mycophenolic acid treatment, then strategies that alter the location of mycophenolic acid delivery to the intestines may be beneficial. These strategies may include the use of formulations such as enteric-coated mycophenolate sodium that stagger mycophenolic acid release in the gut (12, 13).

Previous studies have shown that the mycophenolic acid dosage is better maintained with enteric-coated mycophenolate sodium than mycophenolate mofetil, with fewer and less severe gastrointestinal symptoms in patients receiving enteric-coated mycophenolate sodium (4, 5). Nevertheless, the gastrointestinal symptoms in patients receiving enteric-coated mycophenolate sodium totaled 35.5% (4) and 27.4% (5) in these studies. Numerous studies have confirmed that changing mycophenolate mofetil to enteric-coated mycophenolate sodium improved the gastrointestinal symptoms in renal transplant recipients (6, 7). However, 15.3% (6) and 50% (7) of the patients had no improvement (no change or exacerbated) in the gastrointestinal symptoms after changing mycophenolate mofetil to enteric-coated my-

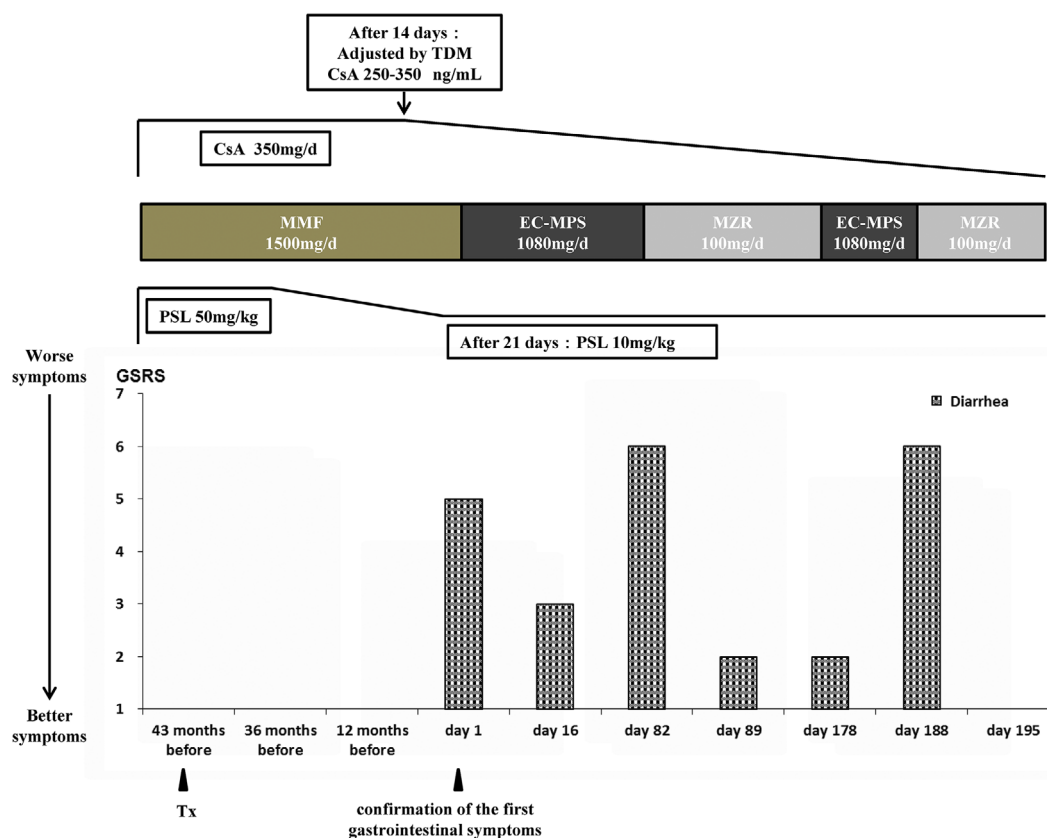


Figure 3. Clinical course of Case 2 after renal transplantation. CsA: Cyclosporin A, EC-MPS: enteric-coated mycophenolate sodium, MMF: mycophenolate mofetil, MZR: mizoribine, PSL: prednisolone, TDM: therapeutic drug monitoring, Tx: transplant

cophenolate sodium in these studies.

In addition, it remains controversial as to whether, in comparison to mycophenolate mofetil, the gastrointestinal side effects are reduced with enteric-coated mycophenolate sodium (14). In a recent clinical trial, no clinically important difference between mycophenolate mofetil and enteric-coated mycophenolate sodium was observed regarding side effects and efficacy (15). These results suggest that although enteric-coated mycophenolate sodium delays the release of the mycophenolic acid, some mycophenolic acid is likely to be released and metabolized to acyl-mycophenolic acid glucuronide, which may induce gastrointestinal symptoms.

In comparison to mycophenolic acid, mizoribine was more rapidly absorbed and its levels declined more rapidly after oral ingestion. Within 24 hours, 85% of the administered dose was excreted in the urine and 1.0% in the bile. An inverse isotope dilution analysis showed that unchanged ^{14}C -mizoribine accounted for more than 99% of the radioactivity in the plasma one hour after dosing, and 85% of mizoribine excreted in the urine within 24 hours after administration was unchanged (16).

As discussed previously, it is clear that the absorption and metabolism of mizoribine is different from mycophenolic acid (mycophenolate mofetil or enteric-coated mycophenolate sodium), and that it is likely to be beneficial for gastrointestinal symptoms.

Due to the influence of medical insurance and other factors, enteric-coated mycophenolate sodium has been used only recently in China. It is often used in conversion treatment for the maintenance of renal transplant recipients receiving mycophenolate mofetil who develop gastrointestinal symptoms. However, numerous studies have confirmed that patients who have been treated with enteric-coated mycophenolate sodium may still experience gastrointestinal symptoms, and our experience has been the same.

In this report, we presented two cases of renal transplant recipients who underwent renal transplantation from a cardiac death donor and a living-donor, respectively. After transplantation, both of the two cases showed typical gastrointestinal symptoms upon receiving mycophenolic acid (mycophenolate mofetil or enteric-coated mycophenolate sodium).

The first patient developed a wide range of gastrointestinal symptoms such as abdominal bloating, indigestion, and severe abdominal pain over a few months. After changing mycophenolate mofetil to enteric-coated mycophenolate sodium, the patient presented with abdominal pain multiple times, even though he was administered an acid-reducing agent or the enteric-coated mycophenolate sodium dosage was reduced. In addition, a gastric ulcer was found on the first gastroscopic examination.

After replacing enteric-coated mycophenolate sodium with

mizoribine, the abdominal pain resolved immediately, and the gastric ulcer was found to have completely healed on the second gastroscopic examination. According to these results, we speculate that the abdominal pain associated with symptoms of the gastric ulcer was likely to have been induced by enteric-coated mycophenolate sodium.

On the other hand, the second patient experienced late (more than 3 years), severe diarrhea after transplantation. Since he did not show any improvement in his gastrointestinal symptoms after switching from mycophenolate mofetil to enteric-coated mycophenolate sodium, we therefore considered replacing enteric-coated mycophenolate sodium with mizoribine. After replacing enteric-coated mycophenolate sodium with mizoribine, diarrhea resolved immediately.

In addition, we also observed in case 2 a patient who showed improvement in his gastrointestinal symptoms, but suffered from recurrence of the symptoms after mizoribine was switched back to enteric-coated mycophenolate sodium. According to the reasons mentioned above, this was an indirect indication that diarrhea in this patient could be associated with enteric-coated mycophenolate sodium.

The results of both cases showed improvements in the gastrointestinal symptoms as a result of changing enteric-coated mycophenolate sodium to mizoribine according to the GSRS, which we used to evaluate the gastrointestinal symptoms reversal effects.

Mizoribine has been approved in Japan for induction and maintenance immunosuppressive therapy after renal transplantation. Although it has also been released in South Korea and China, it has not seen wide acceptance throughout the world due to its less immunosuppressive potency, despite its fewer adverse events (17). Recently, a meta-analysis compared the efficacy and safety of mizoribine with mycophenolate mofetil as immunosuppressive therapy in Asian transplant recipients. The safety profile was assessed by monitoring the occurrence of adverse events such as gastrointestinal symptoms, leukopenia, hepatic dysfunction, viral infections, and hyperuricemia. On the whole, except for hyperuricemia, the mizoribine group had a significantly lower incidence of adverse events compared to that of the mycophenolate mofetil group, and no heterogeneity was detected (18).

Therefore, in this report we also monitored the serum uric acid level once a month after switching to mizoribine. In case 1, after switching to mizoribine, the serum uric acid level was normal and ranged from 231 to 284 $\mu\text{mol/L}$, and we did not observe an increased in the serum uric acid level or hyperuricemia. In case 2, after switching to mizoribine, the serum uric acid level remained at 350 $\mu\text{mol/L}$. Similar to case 1, we did not observe an elevated serum uric acid level or hyperuricemia.

On the other hand, strategies to prevent cytomegalovirus (CMV) infection have significantly reduced CMV disease; as a result all renal transplant patients are treated prophylactically with valganciclovir (900 mg per day) for 3 months in our hospital. Anti-CMV IgG and anti-CMV IgM titers were

assessed 6 months after transplantation and as clinically indicated, such as when other adverse events were detected. The results showed anti-CMV IgG positivity with concurrent anti-CMV IgM negativity, which was consistent with the results before transplantation in cases 1 and 2. We did not observe CMV infection in either case.

In addition, we did not observe other adverse events such as leukopenia, hepatic dysfunction, or other active infections in either case. We therefore considered that the gastrointestinal symptoms in both cases were likely to have been induced by noninfectious causes associated with mycophenolic acid therapy (mycophenolate mofetil or enteric-coated mycophenolate sodium).

In conclusion, our experience suggested that renal transplant recipients with severe mycophenolic acid-associated gastrointestinal symptoms may benefit from changing enteric-coated mycophenolate sodium to mizoribine as it improves the gastrointestinal symptoms and the GSRS. This could help improve the clinical outcomes of renal transplant recipients, translating to greater patient benefits.

The authors state that they have no Conflict of Interest (COI).

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