Rapid resolution of persistent mycophenolate mofetil-induced diarrhoea with a single dose of infliximab

Souad Bouhbouh and Maarten B. Rookmaaker

Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence and offprint requests to: Maarten B. Rookmaaker; E-mail: M.Rookmaaker@umcutrecht.nl

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Background

Diarrhoea is a common complication seen in renal transplant recipients. Post-transplantation diarrhoea may result from infectious agents, drug-specific effects or metabolic conditions. Although infections are the major cause of diarrhoea after transplantation, almost a quarter of the cases are related to medication. Approximately 50% of the drug-induced diarrhoea is caused by mycophenolate mofetil (MMF) [1]. MMF is a commonly used immunosuppressive agent that can induce ulcerating colitis [2,3]. MMF-induced ulcerating colitis is a diagnosis by exclusion. The pathological diagnosis is difficult because of the similarities with other causes of diarrhoea such as inflammatory bowel disease [4]. Although MMF-induced colitis usually resolves after dose reduction or cessation of MMF, persistent cases have been reported [5]. We present a case in which MMF-induced ulcerating colitis persisted after withdrawal of MMF but was successfully treated with tumour necrosis factor-alpha (TNF-α) inhibition.

Case report

A 65-year-old female patient presented with a 1-week history of watery non-bloody diarrhoea, with weight loss and abdominal cramps. She passed ∼10 stools a day. Her medical history comprised a kidney transplantation 6 years earlier because of end-stage renal failure due to autosomal dominant polycystic kidney disease. The medication comprised tacrolimus 4 mg b.i.d. with MMF 500 mg b.i.d. and had not been changed recently. Physical examination revealed a temperature of 37.2°C, a blood pressure of 129/70 mmHg and a heart rate of 72 b.p.m. The abdomen was tender, with vivid bowel sounds. No enlarged lymph nodes were found. Laboratory investigation showed a leucocyte count of $9.9 \times 10^9$/L, a C-reactive protein (CRP) of 66 mg/L and a serum creatinine level of 82 μmol/L. Stool cultures and examination for parasites were repeatedly negative. Cytomegalovirus (CMV) was excluded by quantitative polymerase chain reaction in plasma.

With the working hypothesis MMF-induced colitis, MMF was switched to prednisone 30 mg per os once daily. Because diarrhoea persisted for 2 weeks after withdrawal of MMF, a colonoscopy was performed that showed linear ulceration throughout the colon (Figure 1A). The terminal ileum showed no abnormalities. Histological examination revealed extensive ulceration with severe transmural mixed-cellular infiltration without granulomata (Figure 1B). Immunohistochemical staining for CMV was negative.

Because of a possible causative role, tacrolimus was also withdrawn, and 25 mg prednisolone was given intravenously b.i.d. as the sole immunosuppressive agent. As the clinical condition did not improve in the next 2 weeks, a second colonoscopy was performed, which showed no improvement.

Because of persistent non-infectious colitis 8 weeks after discontinuing MMF and 2-week high-dose steroid treatment, we decided to treat our patient with infliximab (5 mg/kg). Within 72 h, after a single infusion of infliximab, the stool frequency dropped from 10 to 4 times a day. Her appetite increased, and the abdominal cramps diminished. The CRP decreased to 3 mg/L, whereas serum creatinine remained unchanged (81 μmol/L). The prednisolone dose was tapered, and the patient was discharged 14 days later. The immunosuppressive regimen was finally changed to azathioprine 2 mg/kg once daily and prednisone 10 mg once daily.

Discussion

MMF is a pro-drug that is metabolized in the liver into the active compound mycophenolic acid (MPA). MPA is a reversible inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme in purine synthesis in lymphocytes. By inhibiting the proliferation of lymphocytes, MPA exerts its immunosuppressive action [6]. However, MPA also decreases the proliferation of enterocytes. MPA is further degraded by the liver to acyl glucuronide (AC) which stimulates mononuclear cells to release TNF-α. TNF-α plays a central role in the pathogenesis of mucosal inflammation. TNF-α causes disruption of the epithelial barrier, induces apoptosis and secretion of chemokines in
epithelial cells, activates endothelial cells and inflamma-
tory cells, and stimulates the production of matrix metal-
loproteinases [7–9]. This TNF-α-mediated inflammatory
damage combined with reduced intestinal regeneration is
the proposed mechanism of MMF-induced colitis.

In most cases, MMF dose reduction or withdrawal is suf-
icient to reverse the ulcerative colitis. However, in our case,
the diarrhoea persisted despite discontinuing MMF and even
after anti-inflammatory treatment using high-dose prednis-
one. Because the role of TNF-α in MMF-induced colitis
and the histopathologic resemblance of MMF-induced colitis
to Crohn’s colitis, we decided to treat our patient with inflix-
imab. Infliximab is a chimeric IgG1 monoclonal antibody
which neutralizes the biological activity of TNF-α effector cells [9,10].

The rapid clinical response to infliximab suggests that
TNF-α plays a crucial role in both the initiation and the main-
tenance of MMF-induced colitis.

After resolution of the MMF-induced ulcerating colitis,
the patient was switched to azathioprine. It should be noted

that the role of MMF as a preferred immunosuppressive
agent to azathioprine in renal transplantation has recently
been questioned by Cravedi et al. [11]. Indeed, the benefits
of MMF over azathioprine have not been proven convinc-
ingly, especially in the light of higher cost and the un-
favourable adverse event profile of the former drug.

Although our working hypothesis was MMF-induced
colitis, we cannot completely rule out Crohn’s disease.
However, it is uncommon for Crohn’s disease to start at
age 65, without involvement of the small bowel and with-
out granulomata in repeated biopsies. Furthermore, the oc-
currence of Crohn’s disease despite immunosuppressive
therapy and lack of clinical response to treatment with
high-dose steroids are also atypical, favouring the diagno-
sis MMF-induced colitis.

To our knowledge, we here present the first case of per-
sistent MMF-induced colitis that is successfully treated
with infliximab. The rapid resolution of the diarrhoea in
response to infliximab suggests that TNF-α is not only in-
volved in the initiation but also in the maintenance of
MMF-induced colitis. It should be stressed that infliximab
is an expensive drug that potentially has serious side ef-
fects, and our observation is limited to only one case.
However, infliximab might be an interesting new ther-
apeutic option for the treatment of persistent MMF-induced
colitis.

References

3. Maes BD, Dalle I, Geboes K et al. Erosive enterocolitis in mycope-
nolate mofetil-treated renal-transplant recipients with persistent
afebrile diarrhea. Transplantation 2003; 75: 665–672
4. Selbst MK, Ahrens WA, Robert ME et al. Spectrum of histologic
changes in colonic biopsies in patients treated with mycophenolate
5. Mohsin N, Jha A, Kallankara S et al. Rapid resolution of mycope-
nolate associated diarrhea with a small dose of octreotide: a case re-
port. Transplant Proc 2003; 35: 2754
6. Allison AC, Eugui EM. The design and development of an immuno-
suppressive drug, mycophenolate mofetil. Springer Semin Immunopathol
1993; 14: 353–380
7. Wieland E, Shipkova M, Schellhaas U et al. Induction of cytokine
release by the acyl glucuronide of mycophenolic acid: a link to side
effects? Clin Biochem 2000; 33: 107–113
8. Shipkova M, Armstrong VW, Oellerich M et al. Acyl glucuronide
drug metabolites: toxicological and analytical implications. Ther
Drug Monit 2003; 25: 1–16
9. van den Brande JM, Braat H, van den Brink GR et al. Infliximab but
not etanercept induces apoptosis in lamina propria T-lymphocytes
from patients with Crohn’s disease. Gastroenterology 2003; 124:
1774–1785
10. ten Hove T, van Montfrans C, Peppelenbosch MP et al. Infliximab
treatment induces apoptosis of lamina propria T lymphocytes in
azathioprine in organ transplantation. Am J Transplant 2009; 9:
2856–2857

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