

# Mycophenolate Induced Diarrhoea

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## Abstract

Mycophenolate (MMF) has arisen as an important addition in the immunosuppression armamentarium. GI disturbances (diarrhea) and bone marrow suppression are its main side effects requiring dose reduction or even withdrawal. The mechanism of diarrhoea is unknown, although some theories have been postulated. We evaluated three of our patients on MMF who came to us with chronic diarrhoea. Their evaluation consisted of CBC, stool routine examination, stool culture, endoscopy and biopsy. Histopathologic examination in all three cases showed villous atrophy. All of them improved with discontinuation of MMF and addition of folic acid suggesting that diarrhoea was related to MMF. Since this complication is seen in only a few cases, we can hypothesize that it may be due to lower levels of the enzyme inosine monophosphate dehydrogenase (IMPDH) - the site of action of MMF.

## Introduction

The discovery of Mycophenolate<sup>4</sup> (MMF) has proved to be a useful addition in the immunosuppression armamentarium. GI disturbances<sup>2</sup> (dyspepsia, diarrhea) and bone marrow suppression are its main side effects, requiring dose reduction or even withdrawal.

Mycophenolate inhibits the enzyme inosine monophosphate dehydrogenase<sup>9</sup> (IMPDH) and prevents the conversion of inosine monophosphate into guanosine monophosphate, decreases purine synthesis and arrests the cell cycle (Figure 1). Most cells in the body, except the 'T' cells, 'B' cells and GI cells, then use the salvage pathway to complete the cell cycle. Having arrested the production / proliferation of T and B cells in this way, mycophenolate confers immunosuppression. Similarly, proliferation of GI cells is also affected causing a decrease in villi formation, and thereby a decrease in absorption.

In order to understand the mechanism of diarrhoea in mycophenolate treated subjects, we evaluated three patients on mycophenolate who presented to us with chronic diarrhoea. Their evaluation included a complete blood count (CBC), stool routine examination, stool culture and sensitivity, CMV IgM antibody, endoscopy and biopsy.

### Case 1

A 36 year old male, recipient of a live related renal transplant (June 2004), was on triple immunosuppression – Cyclosporine A, MMF and prednisolone. His post-transplant creatinine was 1.1 mg%. He was admitted in May 2007 with a history of diarrhoea for three to four months. He had pallor, cheilosis, drop in hemoglobin from 13 g% to 10 g%. His stool routine was normal; stool culture was negative and CMV IgM was negative. Oesophagogastroduodenoscopy (OGD) was normal. Small intestine biopsy was taken, which on histopathologic examination (HPE) showed marked villous atrophy (Figure 2) and a decrease in villi to crypt ratio. Figure 3 shows normal appearing villi for comparison. MMF was stopped, he was treated with folic acid and GI symptoms improved in a month's time.

### Case 2

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A 45 year old male who underwent a live related renal transplant in August 2006 and was on triple immunosuppression with Tacrolimus, MMF and Prednisolone. His post-transplant creatinine was 1.0 mg%. Two months post transplant he started having intermittent loose stools. He developed persistent diarrhoea six months post transplant and MMF was changed to Mycophenolate Sodium<sup>8</sup>, but there were no significant improvement in symptoms. He had oral ulcers, weight loss of two kilograms in one month, pallor, glossitis, macrocytic anemia. He was negative for CMV IgM and had a normal OGD. Small intestine biopsy on HPE showed villous atrophy. MMF was stopped and in its place Azathioprine was instituted. He was supplemented with vitamin B12 and folic acid. Diarrhoea was better and his hemoglobin improved.

### Case 3

A 35 year old female, class IV lupus nephritis with creatinine of 0.8 mg% was on MMF and prednisolone for fifteen months. She had history of loose stools since one year and lethargy, anemia, loss of weight. She was admitted with us with pulmonary sepsis and persistent diarrhoea. Sepsis improved and in the meantime her stool routine examination, stool culture, CMV IgM and PP65 were negative. OGD and colonoscopy were normal; HPE of duodenal biopsy was suggestive of marked villous atrophy. MMF was stopped. She was treated with folic acid. Diarrhoea improved within one month.

## Discussion

The mechanism of mycophenolate induced diarrhoea is unknown, however, a few theories have been postulated –

1. Mycophenolate inhibits the enzyme IMPDH<sup>(9)</sup> (Figure 1), which decreases denovo purine synthesis affecting GI epithelial cell replication (since most GI cells do not use the salvage pathway for replication). This leads to villous atrophy<sup>5,6</sup>, malabsorption and diarrhoea.
2. Mycophenolate gets metabolized to acyl glucuronides<sup>7</sup>, which in turn trigger the immune system leading to hypersensitivity, inflammation and autoimmune reactions in the gut, presenting as enterocolitis<sup>(3)</sup> simulating an inflammatory bowel disease.

We feel that the first theory is more likely since the biopsies showed villous atrophy rather than inflammatory changes. Withdrawal of Mycophenolate resulted in resolution of diarrhoea in all the three cases.

Not all patients on Mycophenolate develop diarrhoea, and only a few are actually affected. These patients have been found to have low levels of the enzyme Inosine Monophosphate Dehydrogenase (IMPDH)<sup>1</sup> – the enzyme inhibited by Mycophenolate (Figure 1). It is likely that in those subjects in whom levels of IMPDH are already low, Mycophenolate causes a critical decrease in levels, making GI cells unable to replicate at all leading to villous atrophy. In subjects having normal levels of IMPDH, the decrease in its level due to IMPDH inhibition may not be critical enough to cause a complete arrest of the GI cell replicative process, and they may have just enough villi necessary for adequate absorption.

We can thus hypothesize that those patients who develop diarrhea after Mycophenolate have lower levels of the enzyme IMPDH to start with and may require lower doses of the drug to maintain adequate immunosuppression. Indeed, in our experience, reduction in the dose of Mycophenolate in kidney transplant recipients who developed diarrhea has not precipitated any rejection episode.

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