BRIEF ARTICLES

Use of mycophenolate mofetil in inflammatory bowel disease

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Abstract

AIM: To assess the efficacy and safety of mycophenolate mofetil (MMF) prospectively in inflammatory bowel disease (IBD) patients intolerant or refractory to conventional medical therapy.

METHODS: Crohn's disease (CD) or ulcerative colitis/IBD unclassified (UC/IBDU) patients intolerant or refractory to conventional medical therapy received MMF (500-2000 mg *bid*). Clinical response was assessed by the Harvey Bradshaw index (HBI) or colitis activity index (CAI) after 2, 6 and 12 mo of therapy, as were steroid usage and adverse effects.

RESULTS: Fourteen patients (9 CD/5 UC/IBDU; 8M/6F; mean age 50.4 years, range 28-67 years) were treated and prospectively assessed for their response to oral MMF. Of the 11 patients who were not in remission on commencing MMF, 7/11 (63.6%) achieved remission by 8 wk. All 3 patients in remission on commencing MMF maintained their remission. Ten patients were still on MMF at 6 mo with 9/14 (64.3%) in remission, while of 12 patients followed for 12 mo, 8 were in remission without dose escalation (66.7%). Three patients were withdrawn from the MMF due to drug intolerance. There were no serious adverse events attributed due to the medication.

CONCLUSION: MMF demonstrated efficacy in the management of difficult IBD. MMF appeared safe, well tolerated and efficacious for both short and long-term therapy, without the need for dose escalation. Further evaluation of MMF comparing it to conventional immunosuppressants is required.

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INTRODUCTION

The natural history of both forms of the inflammatory bowel diseases (IBDs), Crohn's disease (CD) and ulcerative colitis (UC), is characterized by a lifelong course of remissions and relapses and a proportion of these patients are steroid refractory or develop steroid dependence requiring maintenance immunosuppression. The most commonly used immunomodulatory medications are azathioprine (AZA), or its metabolite 6-mercaptopurine (6MP). Approximately 10% of patients, however, will be intolerant of these drugs, resulting in their withdrawal and the need for an alternative immunomodulator[1]. Up to 50% of CD and 20% of UC patients will also develop a severe acute episode of their disease requiring hospitalization[2] and almost half of these patients will require rescue therapy or surgery[2,3]. In severe steroid refractory UC, remission may be achieved through the use of cyclosporine or infliximab, but despite continued maintenance therapy for these patients with AZA/6MP, over 65% will relapse by 12 mo and 30% will require colectomy[4]. Thus, despite the advent of new biological agents, used in combination with AZA/6MP, efficacy is not universal so the need for other immunomodulatory medications remains imperative.

Mycophenolate mofetil (MMF) is a powerful

immunosuppressant primarily indicated for prevention of solid organ transplantation rejection. It is an anti-metabolite with pharmacodynamic properties similar to AZA. MMF appears to be very safe and efficacious for this indication and is used as a first-line anti-rejection drug in many transplant centers. More recently, however, this immunosuppresant has been employed in the management of difficult IBD cases[5,6]. Its efficacy has primarily been assessed in small, uncontrolled case series with only a few small randomized trials[7-9]. They indicate that MMF may be effective in IBD, but its role is controversial. The problem arises primarily from observations that despite clinical remission and response achieved early in the course of treatment, a large proportion of patients ultimately flare and require biological agents or surgery. There is also a suggestion that the MMF dose needs to be increased over time in order to maintain an effect and some studies also suggest non-superiority of MMF to conventional immunosuppressants such as AZA[10,11].

Most of the early studies on MMF were undertaken in patients with chronic active CD who failed, or were intolerant to, AZA, and demonstrated good efficacy[7,9]. These findings, however, were not supported by later studies, with either a low response or high relapse rate[5,8,12]. The rate of treatment discontinuation due to side effects was also high[6,12,13] and studies comparing MMF to AZA yielded conflicting and inconsistent results[7,10]. In one study MMF was identified to be more likely to be effective in AZA intolerant, rather than refractory patients, and was not inferior to AZA in the management of UC for the induction or maintenance of remission at 6 mo[11]. Another study with longer term outcomes evaluating MMF in a cohort of AZA resistant/intolerant patients, however, observed that although MMF was initially effective, relapses were common[14].

This study presents our experience in the use of MMF in the treatment of IBD patients in the short and long term. We prospectively assessed the efficacy of MMF in both the induction and maintenance of remission in patients who were intolerant of AZA/6MP and had previously failed courses of either methotrexate (MTX), antibiotics and/or infliximab. We particularly examined the need for dose escalation over time in patients who initially responded to the MMF as this has been a criticism of its long-term efficacy.

MATERIALS AND METHODS

All subjects were patients at the Centre for Inflammatory Bowel Diseases, Fremantle Hospital, which is a specialist IBD unit in a 450 bed tertiary institution that services the southern metropolitan region of Perth, Australia. Patients with IBD were classified as CD or ulcerative colitis/IBD unclassified (UC/IBDU) according to the "Montreal Classification" (a modification of the Vienna Classification). The diagnosis of IBD had to be definite, and was made in accordance with previously established criteria based upon clinical, endoscopic, histopathological

and radiological findings. The diagnoses of CD or UC/IBDU were exclusive of infective enterocolitis (excluded by stool microscopy and culture, bacterial and amoebic serology, acid-fast staining of biopsies and mycobacterial cultures), Behcet's disease and microscopic colitis. Patient demographics, disease status, infusion number, response and remission rates and adverse effects were recorded.

All patients were treated between Jan 2003 and July 2008. Patients treated with MMF received between 500 mg and 2000 mg twice a day with the dose optimized to maintain the white cell count (WCC) between 4 and 6×10^9/L, neutrophil count $> 2.0 \times 10^9$/L and lymphocyte count at or just below the normal range of 1.1×10^9/L without side effects. A clinical response to the MMF in CD patients was determined by a reduction in the Harvey Bradshaw index (HBI) of greater than or equal to 3, with a remission defined as a HBI less than 5 off steroids. A clinical response to the MMF in the UC/IBDU patients was defined as a reduction of 4 or more points in the colitis activity index (CAI) and remission was considered to be CAI of less than or equal to 4 off steroids. The response and remission rates after 8 wk of therapy and long-term response to treatment with MMF were assessed.

Serious adverse effects (SAE) were analyzed. Serious adverse effects are defined as any adverse drug experience occurring that results in death, life-threatening adverse event, persistent or significant disability/incapacity, required in-patient hospitalization, or prolonged hospitalization or congenital anomaly or birth defect.

RESULTS

The primary indications for treatment were either steroid refractoriness, or dependence, and allergy, or intolerance, to AZA/6MP therapy. Patients were steroid dependant if they were unable to be withdrawn from steroids without a disease flare and patients were steroid refractory if they continued to suffer active inflammation whilst on steroids of 20 mg or greater per day. All patients with active disease were considered for treatment with MMF only after demonstrating failure of disease control or steroid dependency. Two CD and 1 UC/IBDU patients were in clinical remission at the time of commencing the MMF. One of these patients suffered from severe psoriasis in addition to her CD and was changed to MMF in consultation with the dermatologists in an attempt to control both the psoriasis and the CD. The second patient had undergone 3 terminal ileal resections with recurrent severe ileal inflammation occurring within 1 to 2 years after each surgery, but was allergic to AZA/6MP, while MTX and infliximab were ineffective. The third patient required 6MP to maintain remission, but was intolerant of this medication due to severe alopecia.

Patient Demographics
Fourteen patients (9 male, 5 female) were treated with MMF during the study period (Table 1). The ages at time of commencing the MMF ranged from 28-67 years (mean age 50.4 ± 12.9 years). Nine patients suffered from CD

Table 1 Demographics of the IBD patients using the Montreal classification

	CD patients $n = 9$	UC/IBDU patients $n = 5$
Gender: male	57.1% (8/14)	57.1% (8/14)
Age at diagnosis		
Mean ± SE (range)	38.6 ± 13.3 yr (19-54)	44.0 ± 12.7 yr (30-63)
A1- ≤ 16	0% (0/9)	0% (0/5)
A2-17-40	44.4% (4/9)	40% (2/5)
A3- > 40	55.6% (5/9)	60% (3/5)
Disease duration		
Mean (range)	10.4 yr (1-26)	9.8 yr (1-28)
Crohn's disease		
L1-terminal ileum	22.2% (2/9)	
L2-colon	33.3% (3/9)	
L3-ileocolonic	44.4% (4/9)	
L4-upper GI	11.1% (1/9)	
P-perianal	22.2% (2/9)	
B1-inflammatory	44.4% (4/9)	
B2-stricturing	33.3% (3/9)	
B3-perforating	22.2% (2/9)	
Ulcerative colitis/IBDU		
E1-proctitis		20% (1/5)
E2-left sided		40% (2/5)
E3-extensive		40% (2/5)
Raised CRP	55.6% (5/9)	80.0% (4/5)

Table 2 Medications taken by study patients at time of the commencement of MMF therapy

	CD patients $n = 9$	UC/IBDU patients $n = 5$
5-ASA		
Current	88.9% (8/9)	100% (5/5)
Steroids		
Current	55.5% (5/9)	100% (5/5)
Intolerant	22.2% (2/9)	0%
AZA/6MP		
Intolerant	88.8% (8/9)	100% (5/5)
Methotrexate		
Ineffective	33.3% (3/9)	N/A
Intolerant	11.1% (1/9)	
Refused	33.3% (3/9)	
Antibiotics		
Ineffective	33.3% (3/9)	N/A
Intolerant	11.1% (1/9)	
Infliximab		
Current	0%	0%
Ineffective	44.4% (4/9)	40% (2/5)
Intolerant	22.2% (2/9)	0%

N/A: Not applicable.

Table 3 Response and remission rates at 8 wk and CRP levels with MMF therapy

	CD patients $n = 9$	UC/IBDU patients $n = 5$
Remission	66.7% (6/9)	80% (4/5)
Response	66.7% (6/9)	80% (4/5)
Intolerant	22.2% (2/9)	20% (1/5)
Ineffective	11.1% (1/9)	0% (0/5)
Raised CRP		
In responders	0% (0/6)	0% (4/5)
In non responders	33.3% (1/3)	100% (1/1)

and 5 had UC/IBDU. Of the CD patients, 77.8% (7/9) suffered from colonic inflammation, 22.2% (2/9) had ileal involvement alone, 11.1% (1/9) had jejunal CD, and 22.2% (2/9) suffered from perianal disease. Of the UC/IBDU patients, 2 had extensive colitis, while 2 suffered left-sided colitis and 1 patient had proctitis. The age of diagnosis was lower in the CD patients (mean 38.6 ± 13.3 years, range 19-54 years) compared to the UC/IBDU patients (mean 44.0 ± 12.7 years, range 30-63 years), but this was not statistically significant. Both the CD and UC/IBDU patient groups had similar disease duration at the time of the MMF therapy (mean 10.4 years and 9.8 years respectively). Four (44.5%) of the CD patients had previously undergone at least one surgery (1 subtotal colectomy, 2 small bowel resections and 1 total colectomy and ileal surgery). C-reactive protein (CRP) levels were also elevated in 5 of the 9 CD patients and 4 of 5 UC/IBDU patients prior to commencement of the MMF.

Current and previous medical therapy

Conventional therapies had been tried in all patients (Table 2). Surgical options had been discussed in detail and were considered to be either medically inappropriate at that stage, or were declined by the patient. Of the 9 CD patients, 88.9% (8/9) were on 5-aminosalicylic acid (5ASA) and 77.8% (7/9) were dependent on, or intolerant to, oral steroids. Antibiotic therapy with metronidazole and ciprofloxacin had been tried and was unsuccessful in 44.4% (4/9) of CD patients. All but 1 (88.9%) of the CD patients were allergic or intolerant to the use of AZA/6MP (drug fevers, severe vomiting requiring hospitalization, severe alopecia and hepatotoxicity). MTX was ineffective in 33.3% (3/9) with 44.4% (4/9) intolerant to, or refusing to take, this medication. Infliximab was ineffective and not continued

in 44.4% (4/9) and 22.2% (2/9) were intolerant to its use (anaphylaxis and serum sickness).

Of the UC/IBDU patients, all were currently on both 5ASA and oral steroid therapy. All of these patients were intolerant to AZA/6MP therapy, while infliximab had been tried and was ineffective in 2 patients.

Efficacy at 8 wk

After 8 wk of MMF therapy, 63.6% (7/11) of patients (3 CD and 4 UC/IBDU) who were not in remission at commencement of MMF responded and went into remission, while 71.4% (10/14) went into remission or maintained clinical remission (Tables 3 and 4) as determined either by the HBI or CAI. The 2 patients who had AZA/6MP ceased and MMF commenced due to concurrent severe psoriasis and severe alopecia, maintained their disease remission. The other CD patient who was placed on MMF to prevent post-surgical recurrence was still in remission. All patients in remission at 8 wk also had normal CRP levels. Three of the 14 patients (2 CD and 1 UC/IBDU) were intolerant to MMF and took the medication for 1 mo or less. In only 1 patient was MMF ineffective after 8 wk of therapy, with the patient undergoing surgery 6 mo after commencing the MMF. The surgical pathology

Table 4 Individual patient data of disease extent, age at treatment, duration of MMF therapy and response

	Sex	Diagnosis	Age at diagnosis	Age at MMF	Indication for MMF	Disease extent	Duration of MMF (mo)	Response after 8 wk	Steroids continued at 8 wk
1	M	CD	27	28	Steroid dependant	Pancolitis	30	Remission	Ceased
2	M	CD	54	55	Steroid dependant	L Sided colitis/fistula	12	Remission	Ceased
3	F	CD	50	67	Severe Psoriasis	Ileocolonic disease	48	Remission	N/A
4	M	CD	41	41	Steroid dependant	Ileocolonic disease	12	Remission	Ceased
5	M	CD	53	63	Recurrent TI resections	Recurrent ileal disease	15	Remission	N/A
6	F	CD	32	58	Steroid intolerant	Colectomy/2x TI resection/ recurrent ileal disease	< 1	Intolerant	Continued
7	F	CD	19	28	Steroid dependant	Subtotal colectomy/recurrent ileal disease/fistula	< 1	Intolerant	Continued
8	M	CD	21	48	Steroid dependant	Ileal disease	6	Ineffective	Surgery
9	F	UC/IBDU	43	50	Steroid dependant	Pancolitis	12	Remission	Ceased
10	M	UC/IBDU	31	33	Steroid dependant	L Sided colitis	9	Remission	Ceased
11	M	UC/IBDU	53	64	Steroid dependant	L Sided colitis	22	Remission	Ceased
12	F	CD	50	50	Recurrent flares	Pancolitis	12	Remission	Ceased
13	M	UC/IBDU	63	63	Steroid dependant	Pancolitis	8	Remission	Ceased
14	F	UC/IBDU	30	58	Steroid dependant	Subtotal colectomy/proctitis	< 1	Intolerant	Continued

demonstrated chronic active inflammation and fibrosis of the previous ileocolonic anastomosis.

Efficacy at 6 mo

Of the 10 patients on MMF who responded or were in remission at 8 wk, all were still on MMF at 6 mo. Only one patient suffered a disease flare in that 6-mo period. This patient flared 10 wk after commencing the MMF and required further steroids and a single dose of infliximab to induce remission, but continued on the MMF with subsequent successful withdrawal of the steroids and no further need for infliximab therapy. None of the other patients required an increase in their dose of MMF over the 6-mo period in order to maintain their remission. The patient who was on the MMF for recurrent inflammation following previous terminal ileal resections for uncontrolled CD inflammation underwent a colonoscopy at 6 mo, which demonstrated no ileal or colonic CD inflammation.

Efficacy at 12 mo

Ten patients (Table 4) had been on MMF for more than 6 mo (mean 18.1 ± 12.1 mo, max 48 mo) with 8 patients taking MMF for 12 mo or more. Of the 10 patients, 1 flared at 8 mo and was withdrawn from MMF due to lack of efficacy. One of the patients died 12 mo after commencing the MMF from an unrelated cause while in remission from his CD. One patient who flared after 30 mo of MMF was withdrawn and commenced on adalimumab with good effect. A total of 12 patients were followed for 12 mo or more and of these 8 were in remission (66.7%). All the 8 patients on MMF maintained their remission without the need for dose escalation.

Adverse effects

There was one serious adverse event (SAE) in this patient cohort. This patient died from decompensated alcoholic liver disease. He had previously denied any significant alcohol consumption on numerous occasions

and had been on a stable dose of MMF for over 10 mo. The patient presented to hospital jaundiced with ascites and blood results consistent with an acute hepatitis. The MMF was ceased and the patient was subsequently diagnosed with acute severe alcohol-induced hepatitis. His condition deteriorated over a 2-wk period and he died from liver failure. This SAE was considered to be 'unlikely related' to the MMF use. Adverse events that resulted in cessation of the medication occurred in 3 (21.4%) patients (2 CD and 1 UC/IBDU). These were GI disturbances (nausea and vomiting) and severe headaches. There were no other adverse events that required modification of the MMF dose.

DISCUSSION

The treatment of refractory IBD has always been one of the most challenging aspects in the clinical practice of luminal gastroenterology. MTX has been the primary alternative therapy for CD patients who are treatment refractory or intolerant to AZA/6MP. Although MTX has demonstrated efficacy in CD, the rate of adverse events at the higher doses often required to achieve clinical response/remissions has limited its use[15]. At low doses, however, MTX is often ineffective[15] and definitely less effective than AZA/6MP[16] with longer-term studies demonstrating a frequent loss of efficacy over time[17]. A systematic review of 5 trials identified only one large randomized trial that recommended high dose parenteral MTX to induce clinical remission[18]. The remaining studies using oral forms have disappointing results[15] and because of its route of administration MTX is not acceptable to many patients. Despite some evidence justifying the use of MTX in UC[19], and fistulising CD[20], data remains limited and confined to retrospective chart reviews. AZA/6MP, therefore, has been the mainstay of immunosuppressive maintenance therapy in IBD. The use of MMF has, therefore, been proposed as an alternative immunosuppressive therapy for patients who either are refractory or intolerant to AZA/6MP.

The aim of our study was to prospectively evaluate the short and long-term efficacy and safety of MMF in patients who were either steroid refractory, or dependent, as well as intolerant or allergic to AZA/6MP therapy. We also wanted to examine the need for dose escalation of MMF over time as this has been suggested as a problem with the use of MMF by some studies[13]. As with many of the other published data on MMF, ours was a small cohort of IBD patients with open-label use of MMF. Our patients, however, were assessed at numerous time points and were followed for over a year. The patients in our cohort were also medication resistant, with two thirds failing anti-TNF-α therapy, suggesting a more difficult-to-treat population of patients compared to some other studies. Despite this the results were encouraging. Overall the response rate observed was 71% of patients achieving or maintaining a complete clinical remission after 8 wk of therapy. Excluding the 3 patients who were in remission and off steroids at the time of commencing the MMF, the response/remission rates were still 63.6% at 8 wk. These findings are in contrast with current literature, which reports short-term response rates of only between 25%-40%[8,13,14].

A proportion of MMF-treatment failures in previous studies have been attributed to discontinuation secondary to significant adverse effects. In our study MMF was generally well tolerated, but discontinuation of the MMF secondary to adverse effects was still 21.4%, similar to the 30% observed in other studies. This does not explain the difference, however, in the overall response rates and the reasons behind the difference remains unclear. Relapses over time have also been previously reported as common[8,13,14]. Early relapse in our cohort, however, was not commonly observed and even after 12 mo of MMF therapy, 57.1% (8/14) of our IBD patients were still in remission. Of particular note is the lack of dose escalation required over time in our patients responding to MMF. None of the 8 patients on MMF in remission at 12 mo had their dose of MMF increased in the previous 6 mo.

In our experience, the efficacy of MMF appears to differ in some aspects to the published data. Our data demonstrate that MMF can be efficacious and well tolerated in treating refractory IBD patients who are intolerant to AZA/6MP. Problems of lack of long-term efficacy and early disease flare as well as the need for dose escalation over time did not eventuate. Our findings support the use of MMF in the management algorithm of resistant IBD, but its role needs further clarification in larger randomized, double-blind studies comparing it to conventional immunosuppressants. Long-term efficacy would appear to be demonstrated in our study and our current experience suggests that MMF can and should be considered in patients who have failed conventional immunosuppressive therapy.

COMMENTS

Background

Treatment for patients with inflammatory bowel disease (IBD) refractory, or intolerant, to conventional immunosuppressive therapy such as azathioprine/6-mercaptopurine and methotrexate is difficult. The advent of biological therapies has alleviated this problem to a certain degree but there are still a proportion of patients who fail to respond to them or develop drug reactions. The need for alternative effective immunosuppressive agents in the management of IBD are thus required.

Research frontiers

This study aimed to further define the role of mycophenolate mofetil (MMF) in the treatment of inflammatory bowel disease. The use of this immunosuppressant has been studied in patients refractory, or intolerant, to conventional treatments and results have varied with some studies showing a lack of efficacy or high rates of adverse events. The authors describe a single center experience in the use of MMF for difficult-to-treat IBD patients.

Innovations and breakthroughs

In contrast to previous reports the study identified MMF to be a safe and efficacious choice in the treatment of difficult IBD and found that the agent to be well tolerated and the response to be sustained. The reported clinical remission rates also seem to be higher than those in previous studies.

Applications

The findings of study supported the use of MMF in the treatment of patients with IBD who are refractory or intolerant to conventional therapies such as azathioprine/6-MP or methotrexate.

Terminology

Inflammatory bowel disease is a group of chronic diseases involving the gastrointestinal tract particularly in the small and large bowel. It is divided into 2 groups: Crohn's disease and ulcerative colitis. Crohn's disease is characterized by transmural rather than superficial mucosal inflammation and often presents as a discontinuous disease involving the small or large intestine, or both. Ulcerative colitis/IBD unclassified is the Montreal classification of patients with IBD but without the features needed to diagnose Crohn's disease.

Peer review

The authors examined the use of mycophenolate mofetil in the treatment of inflammatory bowel disease and found it to be a good alternative immunomodulator in those with IBD who have either failed or become intolerant to conventional therapy. The presence of a good response in those who previously failed biological agents suggests a possible role of MMF in the management of this subgroup of patients as well.

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