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Observations and Research

Mycophenolate Mofetil Appears Effective for the Treatment of Patients With Refractory Crohn's Disease

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Background: Medically refractory Crohn's disease (CD) is associated with a high risk of complications. Mycophenolate mofetil (MMF), a small molecule immunosuppressant, has limited data in patients with CD, and objective endoscopic response to MMF has not been reported.

Aims: We evaluated the safety and clinical, endoscopic, and biochemical effectiveness of off-label MMF for refractory CD as monotherapy or in combination with a biologic in patients with CD.

Methods: We retrospectively assessed adverse events (AEs), clinical response (Harvey–Bradshaw index), endoscopic response (simple endoscopic score in Crohn's disease), and physician global assessment at an academic medical center and county hospital.

Results: 60 patients received MMF as monotherapy ($n = 40$) or in combination with a biologic ($n = 20$) between 2008 and 2021 at a dose ranging from 1000 to 4000 mg daily. Median age was 39 years and median disease duration was 12 years. All patients previously failed ≥ 1 advanced therapy (median = 4). The median MMF therapy duration was 27 weeks. 54% achieved clinical response and 19% achieved clinical remission after a mean of 19.5 weeks (SD 14.5). Endoscopic response occurred in 32%, endoscopic remission in 16%, and endoscopic healing in 4% after a mean of 46.6 weeks (SD 31.0). 48% of patients experienced AEs, most commonly mild infection, nausea/vomiting, and headache. One serious AE occurred, which was assessed as unrelated to MMF.

Conclusions: MMF resulted in clinical, endoscopic, and biochemical benefits in some patients with refractory CD, and was tolerated by most patients. Further randomized controlled trials are needed to define optimal dosing and long-term efficacy and safety.

Lay Summary

In a retrospective study, 60 patients with refractory Crohn's disease were treated with mycophenolate mofetil—a small molecule immunosuppressant. Mycophenolate mofetil was tolerated in the majority of patients and resulted in clinical, endoscopic, and biochemical benefit for some patients.

Key Words: mycophenolate mofetil, Crohn's disease, refractory, combination therapy

Introduction

Despite advances in medical therapy, the minority of patients with Crohn's disease (CD) will achieve endoscopic remission, one of the primary goals of treatment.[1] Even with dose optimization of medical therapy in patients achieving response, but not endoscopic remission with standard dosing, only the minority of patients will successfully reach endoscopic remission.[2,3] Additionally, secondary loss of response and/or intolerance to advanced therapies further limits treatment options.[4] For patients with clinical and/or endoscopic response to a given single therapy, the improvement is clinically significant, but if patients do not achieve endoscopic remission, then ongoing endoscopic disease activity increases the risk of fistulizing and stricturing disease complications, malnutrition, poor quality of life, and colorectal cancer.[5–7] There remains a need for treatment options for patients with severe CD who are either non-responsive to medical therapy or who have had a response but have not achieved endoscopic remission to FDA-approved therapies. Mycophenolate mofetil (MMF) is a small molecule immune suppressant that exhibits a cytostatic effect on T and B lymphocytes, resulting in decreased recruitment of lymphocytes and monocytes and thus decreased TNF-α and IL-1.[8] Historically, MMF has been utilized in allograft transplant recipients as well as for autoimmune disorders, including atopic dermatitis, psoriasis, and lupus.[9–11]

A variety of studies have considered the role of MMF in CD therapy with the majority, but not all studies reporting significant improvement in clinical response and ability to taper corticosteroids.[8,12–27] While studies suggest that MMF may be effective for the treatment of CD, most were completed prior to the FDA approval of biologic and small molecule advanced therapies. After the advent of these highly effective therapies, few studies have revisited the utility of MMF for patients who are refractory or intolerant to advanced therapy.[8] Although endoscopic remission is currently considered the gold standard therapeutic target of CD therapy,[28] the majority of prior MMF studies evaluated clinical response and ability to taper corticosteroids as their primary outcomes. Thus, the endoscopic response to MMF is largely unknown.[28,29]

Therefore, there is a need to examine MMF within the context of patients who are refractory to biologic and

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Key Messages

- What is already known?

Medically refractory Crohn's disease (CD) is associated with a high risk of complications. Mycophenolate mofetil (MMF), a small molecule immunosuppressant, has limited data in patients with CD who failed advanced therapies, and objective endoscopic response has not been reported.

- What is new here?

This retrospective study of 60 patients with refractory CD reports that MMF appears tolerated in the majority and results in clinical, endoscopic, and biochemical benefits for some patients. We report the first objective data on endoscopic response to MMF.

- How can this study help patient care?

MMF may be a therapy option for patients with refractory CD, however further randomized controlled trials are needed to define optimal dosing and long-term efficacy and safety.

small molecule advanced therapy, incorporating endoscopic outcomes. Furthermore, most studies evaluated MMF at a dose between 1000 and 2000 mg daily, whereas, in our clinical practice, the target prescribed doses were higher than previously studied (ie, up to 4000 mg daily). Beyond the use of MMF as a monotherapy, we hypothesize that in patients with response, but not remission to dose-optimized biologic monotherapy, combining MMF with a biologic agent may offer therapeutic benefit to some patients. This retrospective study aimed to evaluate the effectiveness and safety of off-label use of MMF in patients with severe, refractory CD either in combination with a therapy to which the patient responded but did not achieve adequate endoscopic or clinical control of disease or as monotherapy if no other clinical options were available. We assessed the clinical, biochemical, and importantly, endoscopic response to MMF therapy in a real-world practice setting in patients who were refractory or intolerant to FDA-approved advanced therapies.

Materials and Methods

Patient Population and Ethics

Institutional review board approval was received for this retrospective cohort study. Eligible patients were ≥18 years old, had a confirmed diagnosis of CD, and received MMF for the treatment of CD. Patients received care between 2008 and 2021 at a single healthcare system including an academic center and county hospital in Washington State.

Demographic and disease characteristics were collected from medical records including patient sex, age, disease duration, location, and behavior, age at diagnosis, concomitant medications, prior CD therapy, tobacco use, and medical/surgical history. Disease activity assessments were collected prior to and after MMF treatment including simple endoscopic activity score in CD (SESCD),[30] Harvey–Bradshaw index (HBI),[31] C-reactive protein (CRP), hematocrit, and albumin. Per our standard of practice, patients are asked to complete the HBI questionnaire at each clinic encounter and SESCD is assessed at the time of each colonoscopy. The physician global assessment (PGA; 0 = remission, 1 = mild, 2 = moderate, and 3 = severe disease activity) of both clinical and endoscopic disease activity was retrospectively assessed by 2 gastroenterologists (S.L. and S.R.) with consensus scoring.

Safety was assessed during therapy until 8 weeks after discontinuation or the date of the last data capture. An adverse event (AE) was defined as any untoward medical occurrence during the study period and a serious AE (SAE) was defined as an AE that resulted in death, was life-threatening, required inpatient hospitalization, prolonged hospitalization, or resulted in significant disability. AE causality was assessed by 2 gastroenterologists (S.L. and S.R.) as not related, unlikely related, possibly related, probably related, and highly probably related to therapy.

Endpoints

Endpoint definitions were predefined and include active clinical disease (baseline HBI ≥ 5); clinical response (≥3-point decrease in HBI compared to baseline); clinical remission (HBI ≤ 4), steroid-free clinical remission (not on steroids at the time of clinical remission); active endoscopic disease (baseline SESCD ≥ 6, or ≥4 for isolated ileal disease); endoscopic improvement (≥50% decrease in SESCD); endoscopic remission (SESCD ≤ 3); and endoscopic healing (SESCD = 0), steroid-free endoscopic remission (not on steroids at the time of endoscopic remission). Response assessed with PGA was defined as ≥1 decrease in PGA score, remission as a PGA score of 0 or 1. Biochemical outcomes (eg, CRP, hematocrit and albumin) were assessed as normalization of prior lab abnormality.

Statistical Analysis

STATA 17.0 (StataCorp LLC) and R studio were used for data analysis. Demographics and clinical characteristics are presented using numbers and frequencies for categorical

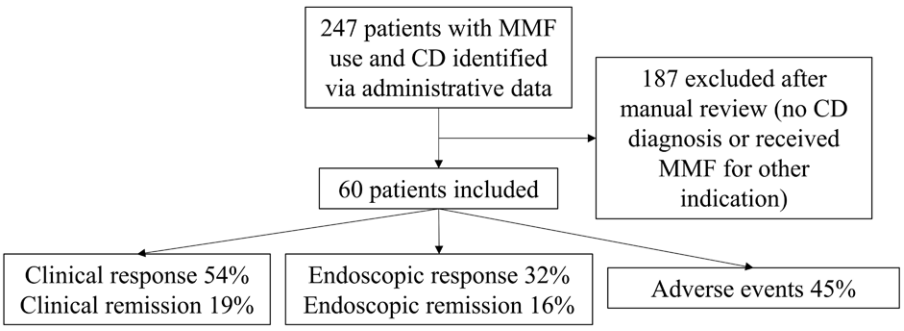

Figure 1. Patient selection and study overview, CD: Crohn's disease, MMF: mycophenolate mofetil.

Table 1. Demographics and disease characteristics of patients on mycophenolate mofitil for refractory Crohn's disease.

Characteristics	All patients on MMF *N* = 60	Patients on MMF monotherapy *n* = 40	Patients on MMF + biologic *n* = 20
Female sex, *n* (%)	21 (35)	12 (30)	9 (45)
Median age; years (range)	39 (19-69)	41 (22-69)	38 (19-63)
BMI; mean (SD)	26 (7.5)	27 (8)	25 (6)
Age at diagnosis; *n* (%)			
Less than 16 years old	20 (33)	11 (28)	9 (45)
17-40 years old	36 (60)	26 (65)	10 (50)
Over 40 years old	4 (7)	3 (8)	1 (10)
Disease location, *n* (%)			
Ileal	4 (7)	4 (10)	0 (0)
Colonic	13 (22)	8 (20)	5 (25)
Ileocolonic	43 (72)	28 (70)	15 (75)
Disease behavior; *n* (%)			
Nonstricturing, nonpenetrating	24 (40)	16 (40)	8 (40)
Stricturing	14 (23)	10 (25)	4 (20)
Penetrating	9 (15)	4 (10)	5 (25)
Stricturing and penetrating	13 (22)	10 (25)	3 (15)
Perianal fistulizing disease	23 (38)	15 (38)	8 (40)
Median disease duration; years (range)	12 (2-54)	11 (3-54)	14 (2-38)
History of gastrointestinal surgery; *n* (%)	27 (45)	18 (45)	9 (45)
Prior number of advanced therapies; *n* (%)			
Naïve	0	0	0
1	1 (2)	1 (3)	0
2	2 (3)	1 (3)	1 (5)
3	11 (18)	7 (18)	4 (20)
4	18 (30)	11 (28)	7 (35)
≥5	28 (47)	20 (50)	8 (40)
Prior immunosuppressive therapies; *n* (%)			
Infliximab	58 (97)	40 (100)	18 (90)
Adalimumab	51 (85)	34 (85)	17 (85)
Certolizumab pegol	23 (38)	14 (35)	9 (45)
Golimumab	3 (5)	2 (5)	1 (5)
Ustekinumab	43 (72)	27 (68)	16 (80)
Vedolizumab	49 (82)	32 (80)	17 (85)
Tofacitinib	18 (30)	13 (33)	5 (25)
Ozanimod	2 (3)	2 (5)	0 (0)
Cyclosporine	5 (13)	3 (8)	2 (10)
Tacrolimus	3 (5)	3 (8)	0 (0)
Thalidomide	1 (3)	0 (0)	1 (5)
History of immunomodulator use; *n* (%)	59 (98)	39 (98)	20 (100)
History of corticosteroid use; *n* (%)	59 (98)	39 (98)	20 (100)
Concomitant corticosteroids at baseline; *n* (%)	23 (38)	17 (43)	6 (30)
Tobacco use; *n* (%)			
Never used tobacco	46 (77)	31 (78)	15 (75)
Former tobacco user	9 (15)	7 (18)	2 (10)
Current tobacco user	5 (8)	2 (5)	3 (15)

variables and either mean/standard deviation or median/range for continuous variables. Median treatment duration was estimated using Kaplan–Meier drug survival. The impact of MMF therapy was evaluated using a paired *t*-test for changes in means, proportions for outcome rates and adverse events, and a chi-square test to assess for differences between proportions. When multiple values were available, the lowest score was utilized. Surgically absent bowel was scored as zero (SESCD). Scores were excluded from analysis if missing, if surgical anatomy invalidated the score (HBI), or if the patient

did not meet predefined active clinical or endoscopic disease score at baseline. For the clinical/endoscopic response analysis, patients were required to have disease activity prior to treatment, which was predefined. The response was calculated in patients with available scores (eg, HBI, SESCD, and PGA) both prior to and after MMF therapy. All eligible patients were included in the safety analysis.

Results

Patient Population

A review of administrative databases identified 247 patients with MMF use and CD diagnosis,[32] of whom 60 met inclusion criteria upon manual review; 40 patients were treated with MMF as monotherapy, and in 20 patients MMF was added to an existing biologic therapy (Figure 1). Of the patients taking concomitant biologic therapy, the biologic was adalimumab (n = 2/20), infliximab (n = 1/20), ustekinumab (n = 9/20), vedolizumab (n = 6/20), and golimumab (n = 2/20). Median disease duration was 12 years, 60% of patients had penetrating and/or stenosing disease, 38% had perianal fistulizing disease, and 45% had prior gastrointestinal surgery. All patients had prior exposure to advanced therapies, and 38% were taking concomitant steroids (Table 1).

Table 2. Reasons for withdrawal of mycophenolate mofetil.

Reason for withdrawal of therapy	N = 60
Non-responder	19
Medication intolerance[a]	13
Inadequate response	13
Other medication availability[b]	4
Patient choice	1
Poor adherence	1

[a]Nausea, vomiting, and/or diarrhea (n = 10), anemia/leukopenia (n = 2), and pruritis (n = 1).
[b]Patients were switched to an alternative medication after it became available (clinical trial, vedolizumab, tofacitinib, and ustekinumab).

Treatment Duration

The median MMF treatment duration was 25.3 weeks. At the end of data collection, 85% (n = 51/60) discontinued MMF for nonresponse (n = 19/60), intolerance (n = 13/60), inadequate response (n = 13/60), other medication availability (n = 4/60), patient choice (n = 1/60), and poor adherence (n = 1/60) [Table 2]. For patients who discontinued MMF treatment, the median time on MMF therapy was 21.0 weeks (range 0.4 weeks-264.1 weeks)."

Approach to Treatment

MMF was utilized in the context of off-label compassionate care in patients with refractory CD with prior failure of FDA-approved therapy. All patients had failed advanced therapies [Table 1]. Overall, patients previously failed a median of 4 advanced therapies. The indication to start MMF was active endoscopic disease (n = 46); active symptoms (n = 10), active disease based on biochemical parameters (n = 2), peristomal pyoderma gangrenosum (n = 1), and active disease based on imaging (n = 1). Monotherapy MMF was used primarily if the patient had nonresponse to multiple advanced therapies. For other patients, MMF was added to an established biologic agent if the patient had achieved objective response, but not objective remission to the current biologic. MMF dosing was initiated at 500-1500 mg BID and the dose was titrated based on tolerance and response to a goal dose of 2000 mg BID. In the case of intolerance (eg, nausea, vomiting, or diarrhea), MMF was decreased to the highest tolerable dose.

Effectiveness

In patients receiving MMF with adequate data, mean HBI scores decreased from 14.0 (SD 6.8) to 11.5 (SD 7.5) (P = .098) after a mean treatment duration of 19.5 weeks

Table 3. Mean Harvey Bradshaw Index, Simple Endoscopic Score in Crohn's disease and biochemical values prior to and after mycophenolate mofetil therapy.

	Prior to MMF, mean (SD)	Post MMF, mean (SD)	P value	Weeks to response, mean (SD)
Clinical response (HBI)				
All patients	14.0 (6.8)	11.5 (7.5)	.098	19.5 (14.5)
MMF monotherapy	14.7 (6.6)	11.8 (7.0)	.089	17.3 (12.5)
MMF plus biologic	12.3 (7.6)	10.4 (9.3)	.642	25.5 (18.9)
Endoscopic response (SESCD)				
All patients	17.4 (8.8)	15.0 (10.3)	.245	46.6 (31.0)
MMF monotherapy	19.2 (9.1)	18.5 (9.8)	.777	43.7 (32.9)
MMF plus biologic	12.9 (6.6)	6.0 (4.5)	.120	54.1 (26.0)
CRP (mg/L, reference range 0-10)				
All patients	40.3 (26.3)	25.6 (30.5)	.013*	16.8 (10.6)
MMF monotherapy	37.3 (24.5)	25.0 (26.9)	.059	16.7 (11.0)
MMF plus biologic	48.7 (31.9)	27.3 (42.0)	.143	16.9 (10.4)
Albumin (g/dL, reference range 3.5-5.2)				
All patients	3.0 (0.3)	3.5 (0.7)	.012*	21.1 (12.4)
MMF monotherapy	3.0 (0.3)	3.6 (0.6)	.003*	23.3 (12.6)
MMF plus biologic	3.2 (0.2)	3.2 (1.0)	Too small to calculate	12.8 (9.2)

Abbreviations: CRP: C-reactive protein; HBI: Harvey–Bradshaw Index; MMF: mycophenolate mofetil; SESCD: simple endoscopic score Crohn's disease

Table 4. Rates of clinical and endoscopic response to mycophenolate mofetil therapy.

	All patients treated with MMF $N = 60$ n (%)	MMF monotherapy $N = 40$ n (%)	MMF + biologic $N = 20$ n (%)
HBI[a] clinical assessment; *n*	26	19	7
Response[b]	14 (54)	11 (58)	3 (43)
Steroid-free response	13 (50)	10 (53)	3 (43)
Remission[c]	5 (19)	3 (16)	2 (29)
Steroid-free remission	5 (19)	3 (16)	2 (29)
PGA[d] clinical assessment; *n*	46	33	13
Response[e]	14 (30)	8 (24)	6 (46)
Remission[f]	9 (20)	5 (15)	4 (31)
SESCD[g] endoscopic assessment; *n*	25	18	7
Response[h]	8 (32)	4 (22)	4 (57)
Steroid-free response	7 (28)	3 (17)	3 (43)
Remission[i]	4 (16)	1 (6)	3 (43)
Steroid-free remission	4 (16)	1 (6)	3 (43)
Endoscopic healing[j]	1 (4)	1 (6)	0 (0)
Steroid-free healing	1 (4)	1 (6)	0 (0)
PGA[d] endoscopic assessment; *n*	33	25	8
Response[k]	10 (30)	6 (24)	4 (50)
Remission[l]	9 (27)	5 (20)	4 (50)

[a]HBI: Harvey–Bradshaw index.
[b]Clinical response: HBI decreased by ≥3.
[c]Clinical remission: HBI ≤ 4.
[d]PGA: physician global assessment.
[e]PGA clinical response: improved by ≥1.
[f]PGA remission: score 0 or 1.
[g]SESCD: simple endoscopic score Crohn's disease.
[h]Endoscopic response: SESCD reduction by ≥50%.
[i]Endoscopic remission: SESCD ≤ 3.
[j]Endoscopic healing: SESCD = 0.
[k]PGA endoscopic response: improved by ≥1.
[l]PGA remission: score 0 or 1.

(SD 14.5) (Table 3). Clinical response was achieved in 54% of patients, and 19% achieved clinical remission. (Table 4). Subjective clinical assessment via PGA showed that 30% achieved clinical response and 20% achieved remission.

In the entire cohort, 32% of patients achieved endoscopic response and 16% reached endoscopic remission. SESCD scores improved from a mean of 17.4 (SD 8.8) to 15.0 (SD 10.3, $P = .245$) after a mean of 46.6 weeks of treatment (SD 31.0). Subjective endoscopic assessment via PGA showed that 30% achieved endoscopic response, and 27% achieved endoscopic remission. Clinical and endoscopic effectiveness stratified by those receiving MMF monotherapy or MMF in combination with a biologic is presented in Tables 3 and 4.

CRP values of the entire cohort improved significantly from a mean of 40.3 (SD 26.3) to 25.6 (SD 30.5, $P = .013$) after a mean of 16.8 weeks of therapy (SD 10.6) (Table 3) with 35% normalizing CRP (Supplemental Table 1). Albumin values of the entire cohort improved significantly from mean 3.0 (SD 0.3) to 3.5 (SD 0.7) ($P = .012$) after mean 21.1 weeks (SD 12.4) (Table 3) with 50% normalizing albumin values (Supplemental Table 1).

Adverse Events

Of patients treated with MMF, 48% reported ≥1 AE. Most AEs were mild and did not require treatment modification. The most common AEs were infections (3 upper respiratory infections, 1 pneumonia, 1 herpes zoster infection, and 1 cutaneous fungal infection) (Table 5). Other AEs included nausea/vomiting, abdominal pain, diarrhea, and headache. 12 patients discontinued therapy due to intolerance (nausea/vomiting ($n = 4$), diarrhea/high volume ostomy output ($n = 3$), abdominal pain ($n = 2$), anemia/leukopenia ($n = 2$), and pruritis ($n = 1$)). One serious adverse event (SAE) occurred in a patient receiving MMF monotherapy, supraventricular tachycardia requiring hospitalization. This was assessed as unlikely related to MMF.

Discussion

Patients with active inflammatory CD are at increased risk of fistulizing and stricturing disease, colorectal cancer, and need for surgery. Despite the recent approval of novel advanced therapies for moderate to severe CD, there remains a need for additional treatment options as the majority of patients will not achieve endoscopic remission, are intolerant of, or lose response to advanced therapies.[1] Additionally, patients who are non-responsive to approved therapies are at high risk for disease complications and are usually on chronic corticosteroids with the inherent side effect profile. For those who are responsive to FDA-approved therapies but unable to achieve remission, there has been growing interest in combining therapies with different mechanisms of action rather

Table 5. Adverse events of patients treated with mycophenolate mofetil for refractory Crohn's disease.

Category	All patients treated with MMF *n* = 60	AE causality
Serious adverse events (SAE)		
Total number of SAEs, *n*	1	
Number of patients reporting SAE, *n* (%)	1 (2)	
SAE description, *n*		
Supraventricular tachycardia	1	Not related
Adverse events (AE)		
Number of AE, *n*	36	
Number of patients reporting AE, *n* (%)	29 (48)	
AE description, *n*		
Infection	6	
Upper respiratory infection	3	Possible
Pneumonia	1	Probable
Herpes zoster	1	Probable
Fungal rash	1	Possible
Nausea and/or vomiting	6	Highly probable
Abdominal pain	1	Probable
Diarrhea	2	Probable
Headache/migraine	5	Probable
Other	16	Unlikely

Other adverse events: worsened Crohn's disease (*n* = 5), edema, ankle fracture, eye pain, neuroendocrine tumor, appendicitis, fever, rash, skin fragility, abnormal liver enzymes, pruritis, and insomnia.

than increasing the dose of a single therapy, with the hope of synergistic effects to achieve higher remission rates.[33–35]

Our study reports that MMF is tolerated in the majority of patients as monotherapy or in combination with a biologic and that treatment results in clinical, endoscopic, and biochemical improvement for some patients. While previously the endoscopic response to MMF was not well defined, we report that about one-third of patients reduced endoscopic inflammation after treatment, and 16% achieved endoscopic remission. While the minority of patients achieved endoscopic remission with MMF in our study, our endoscopic remission rate is comparable to the endoscopic remission rates reported in pivotal clinical trials.[36]

Many of the prior trials describe MMF response in patients with prior steroid and thiopurine failure, but few included patients with prior failure of biologic or small molecule advanced therapies. We report one of the first studies to describe MMF response in patients previously exposed to advanced therapy or in patients who were treated with concomitant biologic therapy. Additionally, most prior studies of MMF report variable rates of clinical improvement ranging from 20% to 81%, and there is significant variation in the definitions of clinical improvement, treatment duration, and study population.[8,12–23,25–27] We report similar clinical response as a retrospective study that included patients with prior biologic failure, which described that 45.6% and 19.1% of subjects achieved remission and clinical response, respectively, over a similar treatment period,[8] however that study did not report endoscopic efficacy.

Notably, our study population had complicated CD with 38% of patients having a history of perianal fistulizing disease and 45% with prior gastrointestinal surgery. Patients had long disease duration (median 12 years) and prior failure of a median of 4 prior advanced therapies, which is a more refractory population than many of the prior studies.[12–15,17–23,25–27] Another factor that distinguishes our study is that we prescribed a higher dose of MMF (goal 4000 mg daily) than most prior studies, which generally reported on doses of 1000-2000 mg daily. Finally, we present the first study showing objective endoscopic improvement with MMF in CD. Refractory disease and failure of available therapies were the primary factors for introducing off-label MMF therapy and these results may not be generalizable to patients with less severe and less refractory disease. We do not advocate MMF as first-line therapy for CD given other therapies have better-defined safety and efficacy profiles, and would position MMF as a therapy option for those patients without other viable FDA-approved therapy options.

With regard to safety, we observed findings consistent with the known safety profile of MMF, even when utilizing higher doses. While some patients discontinued treatment due to intolerance (eg, nausea and vomiting), the majority of patients tolerated therapy well, with the most common AE being minor infections that did not require MMF discontinuation. We also did not observe significant renal toxicity in our study. The single SAE, supraventricular tachycardia (SVT), occurred in a patient on MMF monotherapy. This patient had a history of ascending aortic aneurysm and ultrasound showed that their existing PICC line appeared to be located in the atrium. SVT was controlled on metoprolol and the PICC was adjusted as it was felt to be a potential trigger for SVT. This SAE was assessed as not related to MMF therapy. With regard to the subgroups, MMF appeared to be well tolerated by the majority of patients and the safety profile did not differ in the groups on MMF monotherapy versus the MMF in combination with a biologic.

This study was limited by retrospective study design with variable time to assessment, lack of comparator, small sample size, inherent bias in clinical decision-making, and difficulty in blinding data interpretation. Some patients did not have a complete set of assessments available based on predefined endpoints making the number of patients included for analysis variable (eg, missing HBI, CRP, or SESCD values), however subjective assessment of patient's response to therapy, which was completed for the majority of patients, correlated well with the available objective outcomes.

Overall, MMF was tolerated in the majority of patients and improved the clinical, endoscopic, and biochemical parameters in some patients with refractory CD. Further randomized controlled trials are needed to define the long-term safety and efficacy of MMF for CD. Future trials also would help define optimal MMF dosing. Our study, which utilized higher doses than previously reported, shows that even with higher doses, MMF was tolerated by the majority of patients; however, the optimal dosing is still unknown.

Supplementary Data

Supplementary data is available at *Crohn's & Colitis 360* online.

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Conflicts of Interest

S.L.: consultant AbbVie Pharmaceuticals, Janssen Pharmaceuticals, Inc., Bristol-Myers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc., Janssen Pharmaceuticals, Inc., Eli Lilly and Company, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Applied Molecular Transport Inc., Protagonist, Pfizer Pharmaceuticals, Inc., Celltrion, Inc. Kindra Clark-Snustad, DNP, ARNP: consultant for Janssen, Takeda, Abbvie, and BMS.

Ethical Approval

Institutional review board approval was received for this retrospective cohort study.

Data Availability

Data not publicly available.

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