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Alimentary Tract

Real-world use of mycophenolate mofetil in inflammatory bowel disease: Results from the ENEIDA registry

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ABSTRACT

Background: Studies to evaluate the use of mycophenolate mofetil (MMF) in inflammatory bowel disease (IBD) are limited after the appearance of biological treatments.
Aims: Our primary objective was to evaluate the effectiveness and safety of MMF in IBD.
Methods: IBD patients who had received MMF were retrieved from the ENEIDA registry. Clinical activity as per the Harvey-Bradshaw Index (HBI), partial Mayo score (pMS), physician global assessment (PGA) and C-reactive protein (CRP) were reviewed at baseline, at 3 and 6 months, and at final follow-up. Adverse events and causes of treatment discontinuation were documented.

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Results: A total of 83 patients were included (66 Crohn's disease, 17 ulcerative colitis), 90% of whom had previously received other immunosuppressants. In 61% of patients systemic steroids were used at initiation of MMF, and in 27.3% biological agents were co-administered with MMF. Overall clinical effectiveness was observed in 64.7% of the population. At the end of treatment, 45.6% and 19.1% of subjects showed remission and clinical response, respectively. MMF treatment was maintained for a median of 28.9 months (IQR: 20.4–37.5).

Conclusion: Our study suggests, in the largest cohort to date, that MMF may be an effective alternative to thiopurines and methotrexate in IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disorder of the digestive tract that comprises Crohn's disease (CD) and ulcerative colitis (UC). It is characterized by dysregulated immune responses and altered cytokine production, which ultimately lead to damage of the gastrointestinal tract [1]. The association with the host genetic susceptibility, immunological abnormalities, the role of gut microbiota and its metabolites, and other environmental factors, have been recently investigated [2].

Immunomodulatory drugs have been widely prescribed for the treatment of active IBD. However, efficiency for the maintenance of remission is limited, and AEs lead to treatment discontinuation in 25% and 20% of patients on thiopurines and methotrexate, respectively [3]. In addition, a subset of patients may experience multiple failures of immunosuppressants and/or biologics [4]. Thus, a need for alternative immunomodulatory medications remains.

Mycophenolate mofetil (MMF) is a potent immunomodulator that inhibits T and B cells [5]. Mycophenolic acid is a non-competitive, reversible inhibitor of inositol monophosphate dehydrogenase, a key enzyme required for the *de novo* synthesis of guanosine nucleotides [6], necessary substrates for DNA and RNA synthesis. MMF is thought to suppress proliferation of B and T lymphocytes, as they depend solely on *de novo* nucleotide synthesis [5]. It decreases the recruitment of lymphocytes and monocytes, and consequently reduces the production of TNFα and IL-1 into inflammatory sites in vivo [7,8]. Besides, MMF decreases leucocyte adhesion in vitro [9,10]. It was approved for the prevention of rejection after heterologous renal allografting [5], and has shown considerable efficacy and good tolerability in patients with autoimmune disorders [11,12]. In IBD, several series and two prospective studies support its use in patients refractory to conventional treatment [13,14]. Nevertheless, studies to evaluate its use in IBD are limited, particularly after the availability of biological treatments [4,5,14–19], and MMF is not contemplated in most of major international guidelines.

The primary objective of this study was to evaluate the efficacy of MMF for the treatment of IBD in clinical practice. Secondary aims were to evaluate its safety and retention rate in these patients.

2. Materials and methods

Based on the ENEIDA registry (a large, prospectively maintained database of IBD patients promoted by the Spanish Working Group in IBD—GETECCU—and initiated in 2007) [20], IBD patients aged $\geq$ 18 years who had ever received MMF were identified. Only IBD patients with an established diagnosis of CD or UC in whom oral MMF was prescribed for these conditions (except for perianal disease) were evaluated. IBD had to be diagnosed according to standard criteria [21,22].

Demographic and IBD clinical data (time from diagnosis, IBD phenotype and extent, concomitant treatments, steroid use) were collected. Clinical activity by means of the Harvey-Bradshaw Index (HBI) and partial Mayo score (pMS) and physician global assessment (PGA), as well as C-reactive protein (CRP) levels, were reviewed at baseline (first dose of MMF), at pre-established time points during treatment (3 and 6 months after starting the drug), and at the end of follow-up (at MMF discontinuation or at last visit using MMF) as long as these values were available.

PGA was categorized as remission (absence of symptoms), clinical response (improvement of symptoms) or absence of response (no change or worsening).

AEs, surgeries, and hospitalizations during MMF therapy, as well as causes of treatment discontinuation, were recorded from treatment onset to one month after treatment end.

2.1. Definitions

Clinical response in CD was defined as any improvement in disease symptoms (improved PGA or an HBI reduction $\geq$3 points) from baseline, and as a progressive dose reduction of systemic steroids. In UC, clinical response was defined as any improvement in disease symptoms (improved PGA or a reduction in pMS $\geq$ 3 points) from baseline, and as a progressive dose reduction of systemic steroids.

Clinical remission was defined in CD as a HBI score $\leq$ 4 points together with disappearance of symptoms according to PGA, and no use of steroids. In UC, it was defined as a pMS $\leq$ 1 point, with a rectal bleeding subscore of 0 points with disappearance of symptoms according to PGA, and no use of steroids.

2.2. Statistical analysis

Continuous variables are expressed as mean and standard deviation or median and interquartile range (IQR) as needed, and are compared using Student's *t*-test. Categorical variables are expressed as proportions and compared by means of the Chi-squared test.

The potential association of different factors with drug efficacy was analysed by means of a logarithmic regression model. Besides, a Kaplan-Meier survival analysis was performed to determine the retention rate of MMF treatment. The time until treatment failure among UC and CD patients was determined with a log-rank test. A Cox regression model was used to determine the association between different factors and the risk of therapeutic failure.

A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS V. 15.0 software package.

3. Ethical considerations

This cohort study used data from the ENEIDA (Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes Genéticos y Ambientales (*Spanish National Study on Inflammatory Bowel Disease: Genetic and Environmental Determinants*) database [20]. The

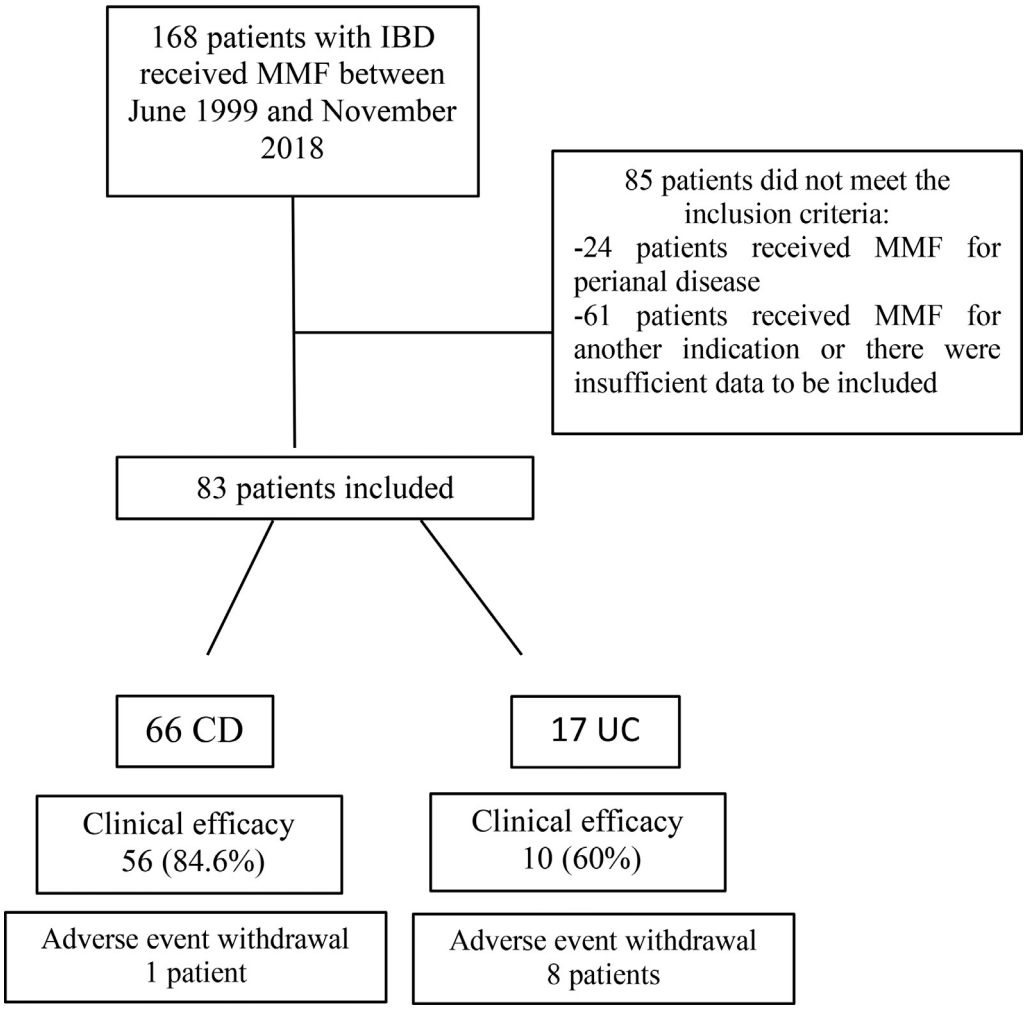

Fig. 1. Flow-chart of the study. CD: Crohn's disease; UC: Ulcerative colitis; MMF: Mycophenolate mofetil; IBD: Intestinal Bowel Disease.

ENEIDA registry was approved by the Research Ethics Committees of all participating centres.

All patients included in ENEIDA signed an informed consent form authorizing the use of their clinical data for research purposes. Registration with the Spanish Data Protection Agency means that use of the information contained in the registry meets all legal requirements.

This project was approved by the Committee of GETECCU in 2019. To improve the accuracy of ENEIDA data, all variables were double-checked and updated by each participating centre.

4. Results

4.1. Baseline characteristics of the cohort

Among the 52,000 IBD patients registered in the ENEIDA registry at the time of data extraction, a total of 168 received MMF between June 1999 and November 2018. Eighty-five patients were excluded because they did not meet the inclusion criteria. Finally, 83 patients were included in the study, 66 of whom were diagnosed with CD and 17 with UC. MMF was indicated before 2010 in 59% of the patients ($n = 49$). The flow-chart of the study is shown in Fig. 1.

The demographic and clinical characteristics of patients are summarized in Table 1. Males and females were evenly distributed. On average, MMF was administered 8.5 years after IBD diagnosis. Of the total population, seventy-five patients (90%) had previously received immunosuppressants (67% thiopurines and/or methotrexate), and in eight patients (10%) MMF was the first immunosuppressive therapy. Twenty-three patients (27.7%) used MMF combined with biologics. Forty-four patients (53%) had previously undergone surgery, and thirty-eight (45%) presented with extraintestinal manifestations. As for clinical activity, HBI and pMS were available in 58 of 66 (87.8%) and 17 of 17 (100%) CD and UC patients. Disease was active in fifty-two (78.7%) CD patients and fifteen (88.2%) UC patients. The mean values of HBI and pMS were 7.6 ± 4 and 4.8 ± 2.5, respectively.

The indications for MMF were maintenance (50%), induction of remission (43.6%), and postoperative recurrence (6.4%). Systemic steroids were co-administered when MMF treatment was initiated in 61% of cases, and in 27.3% of patients they were used concomitantly with biologic agents (52% added MMF to their biological treatment, and 48% required initiation of a biologic despite being on MMF). Treatment characteristics are shown in Table 2.

4.2. Clinical efficacy of mycophenolate mofetil

Overall clinical efficacy comprising both clinical remission and clinical response, as determined by PGA, was observed in 64.7% of the study population at the end of follow-up.

When assessed by type of IBD, 84.6% and 60% of UC and CD patients showed clinical efficacy, respectively. At the end of treatment, 45.6% of the total population were in clinical remission, corresponding to 69.2% and 40% of UC and CD patients, respectively.

Table 1
Characteristics of the study population. Data are expressed as mean ± SD, median (interquartile range), or number (%).

	$N = 83$
Age (years) mean +/- SD	36.4 ± 12
Female gender, n (%)	52 (62)
Type of disease: CD/UC n (%)	66(80)/ 17(20)
Months since diagnosis until MMF use, mean ± SD	102 ± 77
Disease location (%)	
CD (L1/L2/L3/L4/p)	17 / 22 / 48 / 13 / 40
UC (E1/E2/E3)	12 / 29 /59
Previous use of immunosuppressants, n (%)	75 (90)
MMF as first immunosuppressant, n (%)	8 (10)
Previous surgery, n (%)	44 (53)
Extraintestinal manifestations, n (%)	38 (45)
Clinical activity	
HBI (CD)	
mean +/- SD	7,6 ± 4
median (IQR)	8 (6.5–8.8)
pMS (UC)	
mean +/- SD	4.8 ± 2.5
median (IQR)	6 (3.5–6.1)

SD: standard deviation; IQR, interquartile range; CD: Crohn's disease; UC: ulcerative colitis; MMF: mycophenolate mofetil; L1: ileal, L2: colonic, L3: ileocolonic, L4: isolate upper disease, p: perianal disease; E1: ulcerative proctitis, E2: left-side UC, E3: extensive UC; HBI: Harvey-Bradshaw Index score; pMS: partial Mayo score.

Table 2
Treatment characteristics.

Characteristic	$N = 83$
MMF indication, (%)	
Induction of remission	44
Maintenance of remission	50
Post-surgical prophylaxis	6
Mean MMF dose (mg/day), mean ± SD	1269.8 ± 741
Concurrent IBD medications, n (%)	
Immunosuppressants, n (%)	47 (56.6)
Biologics, n (%)	23 (27.7)
IFX/ADA/VEDO/UST, n	18/3/1/1
Corticoids, n (%)	51 (61.4)
Duration of MMF treatment (months)	
Median (interquartile range)	13 (20.4–37.5)

SD: standard deviation; MMF: mycophenolate mofetil; IFX: infliximab; ADA, adalimumab; VEDO: vedolizumab; UST: ustekinumab.

Additionally, clinical response without clinical remission was observed in 19.1% of patients, corresponding to 15.4% and 20% of UC and CD patients, respectively.

In CD patients, a statistically significant reduction in HBI was observed from baseline (7.6 ± 4.3) to 6 months (5.9 ± 4.8, $p = 0.04$) and to end of follow-up (5.7 ± 5, $p = 0.014$) but not at 3 months (7.1 ± 4.9; $p = 0.4$) (Fig. 2A). Similarly, in UC patients we observed a statistically significant reduction in pMS from baseline (4.8 ± 2.5) to 6 months (2.1 ± 2.7, $p = 0.018$) and to end of follow-up (1.8 ± 2.6, $p = 0.003$), but not at 3 months (2.8 ± 2.7; $p = 0.06$) (Fig. 2B).

Clinical efficacy was observed in 52% (12/23) of the patients who received MMF combined with biologics. Biological treatment was added to previous MMF in 16 patients, reaching clinical efficacy in 43% ($n = 7$) of them, while MMF was added to biological therapy in 7 patients, with clinical efficacy in 71% ($n = 5$) of them. The concomitant use of biologics and MMF was significantly associated with clinical response (OR, 1.36, 95% CI [1.08–1.73]), though the regression model performed separately in both situations did not reveal any association with clinical response.

When we explored the changes in CRP values (available in 60 patients) during follow-up, no significant differences were found at any of the pre-established time points versus baseline (baseline median 2.3 mg/L; IQR [7.4–21]).

Hospitalization was required by 27% (22/83) of patients (CD 24.2% CD and UC 35.3%). Ten percent (8/83) of patients (12% CD and 0% UC) underwent surgery during MMF treatment. No deaths occurred during MMF administration. No association was found between clinical response and use of steroids or IBD type.

4.3. Retention rate and safety profile of mycophenolate mofetil

MMF treatment was maintained for a median of 28.9 months (IQR: 20.4–37.5) (Fig. 3), with 69.1% of patients receiving the drug for at least 6 months. MMF was maintained as a combined treatment with biologic agents for a median of 6 months (IQR: 5.5–22.3).

Treatment with MMF was terminated during follow-up in 84% (68/83) of patients (41 due to insufficient response; 14 because of loss of response; 12 due to remission, and 1 because of other causes).

There were no severe AEs. A total of 22.8% (19/83) patients developed AEs related to MMF, with abdominal pain being the most frequent (Table 3). In 47.3% (9/19) of these patients AEs resulted in drug discontinuation.

5. Discussion

In our study, including 83 patients with IBD, MMF has shown long-term benefits in both UC and CD selected patients, with a manageable safety profile when used either in monotherapy or in combination with biologics. A statistically significant reduction in clinical scores was observed from baseline to 6 months and to end of follow-up. To our knowledge, this is the largest clinical real-world study of IBD patients in which the clinical benefit of MMF has been assessed.

The efficacy of MMF has been clearly demonstrated in allograft transplant recipients, and in several autoimmune [7,23–26] and chronic inflammatory disorders [6,27,28]. In IBD, despite its potential application, data on the efficacy of MMF have not been obtained in hard-to-treat patients [18–22,32–36]. Most of the studies have been retrospective, using heterogeneous endpoints and small populations leading to inconsistent outcomes [15–19,32–34]. The use of MMF in IBD has been reported particularly in patients who are steroid-dependent, and refractory or intolerant to more conventional therapies [16–19,29-33]. Neurath et al. found that MMF combined with prednisolone may be an effective and well-tolerated treatment for patients with active CD, with beneficial effects comparable to those of thiopurines [30].

In our study, 90% of patients had previously received immunosuppressants. At the beginning of MMF treatment systemic steroids were co-administered in 61% of cases, and were used concomitantly with biologic agents in 27.3%. To date, data on MMF efficacy among patients previously exposed to anti-TNFα agents were only available in 13 patients from 3 different case series [15–17]. Indeed, one of the most appealing potential applications of MMF may be in patients developing secondary non-response to anti-TNFα monotherapy [4,34]. As could be expected, in our study the concomitant use of biologics was significantly associated with clinical response, as shown by the regression model.

We observed a clinical benefit in nearly 65% of our cohort, with 45.6% of patients achieving steroid-free clinical remission at the end of follow-up. Of note, a statistically significant reduction from baseline in both HBI and pMS was observed at 6 months and at the end of follow-up. Fellerman et al. revealed contradictory findings in a population of thiopurine-naïve IBD patients, with only 4% achieving remission with MMF at 6 months [5]. In a retrospective

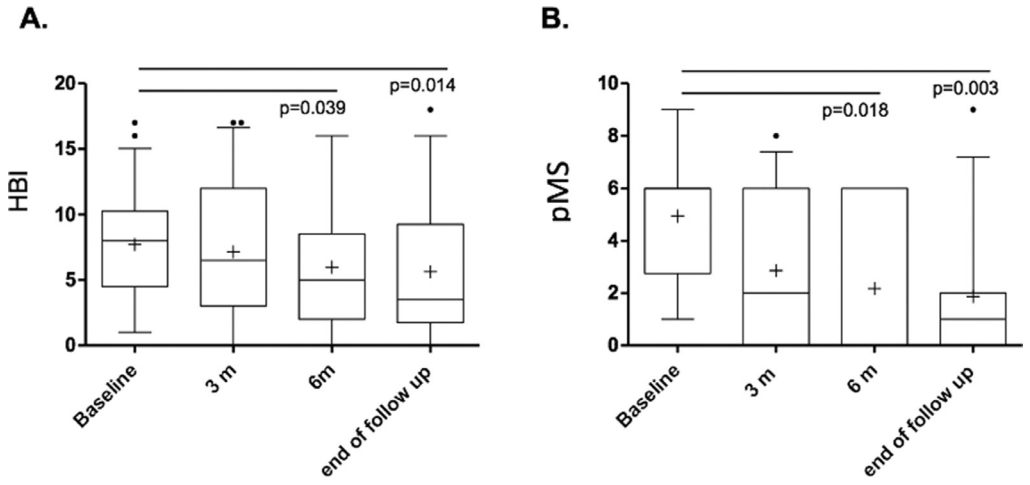

Fig. 2. Clinical activity during follow-up of treatment with mycophenolate mofetil in Crohn's disease (A) and ulcerative colitis (B) patients. Activity was determined at baseline, at 3 and 6 months, and at the end of follow-up. HBI: Harvey-Bradshaw Index; pMS: partial Mayo score; m: months.

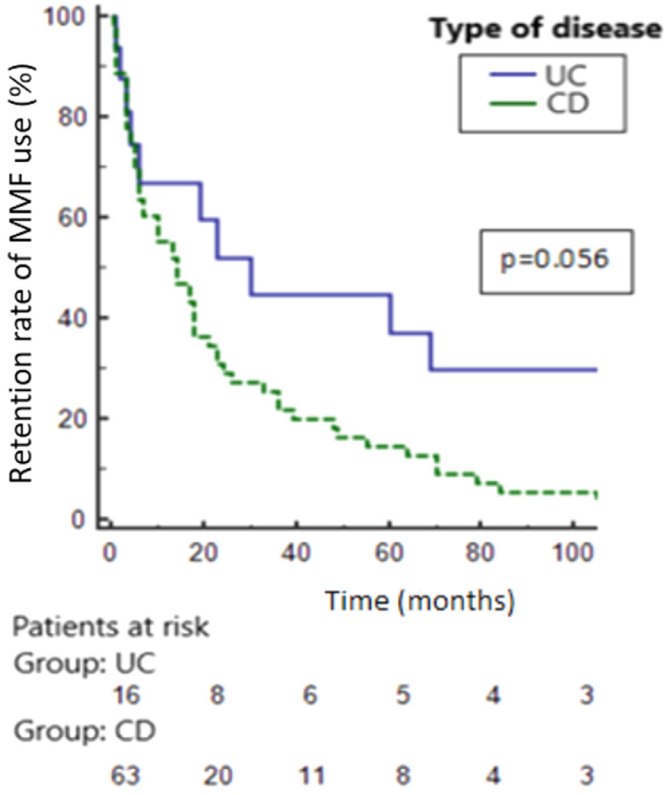

Fig. 3. Mycophenolate mofetil retention rate by disease type. CD: Crohn's disease; UC: Ulcerative colitis; MMF: Mycophenolate mofetil.

UK case series of 70 patients with IBD, 24% achieved steroid-free remission after a mean follow up of 28 months [16], similar to the figures reported by McDermott et al. with a remission rate of 29% at 1 year [35]. A higher remission rate has been described in a more recent retrospective analysis performed by Smith et al. on 36 IBD patients treated with MMF for a median of 21.5 months [15]. At 8 weeks, 81% of patients had either achieved or maintained remission, and after 6 months 58% were in sustained steroid-free remission. At the end of the observation period, 81% of patients remained on MMF. Thirteen patients maintained steroid-free remission, with a median time of 21.4 months in remission.

Table 3
Adverse events, surgeries, and hospitalizations observed during the study. Data are expressed as number (%).

Adverse events	
Total	19
Abdominal pain	10 (52.6)
Nausea	3 (15.7)
Diarrhea	3 (15.7)
Arthralgia	2 (10.5)
Esophageal candidiasis	1 (0.05)

Fifty-two percent of the patients who used MMF combined with biologics in our study showed clinical efficacy. These values were 43% and 71% when biological treatment was added to previous MMF or when MMF was added to the biological therapy, respectively. The regression model performed separately in both schemes did not reveal any association with clinical response, probably due to the small sample size, even though globally there was a signifficant association between the concomitant use of biologics and MMF and the clinical response.

In 2015, Eigner et al. [14] evaluated MMF in combination with an anti-TNFα agent in 17 patients intolerant to azathioprine who were compared to 29 randomly chosen patients treated with MMF in combination with azathioprine for a median follow up of 12 months. Treatment response for both groups was similar. Macaluso et al. [4] reported in 2017 the clinical benefit of MMF in 24 patients with IBD and multiple previous failures of other immunosuppressants and/or biologics. Four weeks after MMF initiation steroid-free remission was achieved in 16.7% of patients, and clinical response in 54.1%. At the end of follow-up, half of the patients remained on MMF. Six achieved and maintained steroid-free remission throughout the study period (25%), and a further 6 patients achieved a clinical response with complete discontinuation of steroids.

In our study, MMF treatment was maintained for a median duration of almost 29 months, with 69.1% of patients receiving the drug for at least 6 months. With respect to its side-effect profile, the available studies reported discontinuation rates due to EAs of 8–36% [11–14,29–34], with one of the commonest adverse events being diarrhea (enterocytes are vulnerable to its antimetabolic effects, which hamper their growth and replication, and alter fluid absorption) [36]. Nevertheless, it has also been reported that MMF has fewer side effects than other immunosuppressants [18]. Smith

et al. [15] found MMF to be well tolerated: 19% of patients had EAs but only 6% discontinued MMF for this reason, with dose reduction being a useful strategy perhaps not employed in other studies. In our study, 22.8% of patients developed AEs related to MMF. There were no serious EAs, only one case of infection and no cases of neutropenia. Diarrhea was present in less than 1% (3/83) of the study population. In the previously cited study by Macaluso et al. 5 of 12 patients (considered as treatment failures) underwent surgery [4]. This reduced number of adverse events could be due to the retrospective collection of data, particularly if they were mild. In our population, surgery was required for 10% of patients during MMF treatment.

The advent of new agents has revolutionized the therapy of moderate-to-severe IBD patients. However, the IMM like MMF still could play a role in the treatment of patients with IBD who have particular characteristics, in specific scenarios and in places where the access to biologic is not optimal. In this context, our study of the role of MMF can offer a wide range of useful clinical data.

The present study is subject to a series of limitations. First, as is often the case in retrospective, multicenter, and observational studies, data collection is heterogeneous; however, in order to reduce this bias, data were double-checked. As it is a real-world study, treatment prescription and patient monitoring were performed at the physician's discretion, with the attendant inter-observer variability. Second, we used HBI because, in a retrospective study, the variables associated with this index are easier to collect from the clinical history, though they may not be very objective. The retrospective review only allowed us to collect scarce data on the endoscopic evolution of these patients, so they are not included in the results presented. Finally, HB and pMS data were not available for all patients. However, and to our knowledge, this is the largest population of IBD patients in which the benefit of MMF in a real-world setting has been analysed, shedding light on a field were data are scarce.

6. Conclusion

In conclusion, we report data on the efficacy and safety of MMF in IBD patients, administered either as monotherapy or in combination with biologic agents. Our results show the effectiveness and safety of the drug in selected CD and UC patients, thus suggesting the benefits of MMF administration for patients with primary non-response to or contraindication of IMMs or biologics. We propose that MMF might be an option for patients refractory or not tolerant to IMMs, and could also be used concomitantly with biologics. Prospective studies are necessary to clarify these recommendations and further evaluate these findings.

Conflict of interest

• AH-C has served as speaker for, or has received research or education funding from AbbVie, Takeda, Kern Pharma, Pfizer, Janssen, Adacyte Therapeutics, and Ferring

• MV has served as peaker, consultant and advisory member for and has received funding for MSD, Abbvie, Pfizer, Ferring, Shire Pharmaceuticals, Takeda and Jannsen.

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• MC has served as a speaker or has received research or education funding or advisory fees from Takeda, Janssen, Faes Farma, Kern, Ferring, Pfizzer and MSD.

• CT reports personal fees from MSD, personal fees from AbbVie, personal fees from Pfizer, personal fees from Janssen, personal fees from Ferring, personal fees from Dr. Falk Pharma, outside the submitted work

• MG has received financial support for travelling and educational activities from MSD, Janssen, Abbvie, Takeda and Ferring.

• MI reports personal fees from MSD, personal fees and advisory board fees from Janssen, and personal fees from Takeda during the conduct of the study.

• IR-Lhas received financial support for travelling and educational activities from or has served as an advisory board member for MSD, Pfizer, Abbvie, Takeda, Janssen, Tillotts Pharma, Roche, Shire Pharmaceuticals, Ferring, Dr. Falk Pharma, Otsuka Pharmaceutical and Adacyte, and research support from Tillotts.

• DB has served as speaker for AbbVie, Takeda, Pfizer, Janssen and Ferring.

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• LR, AL, SM, GS,ES-R, AYC, MC, AM-C, CT, JH, LB, AC and OM have no conflicts to declare.

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Summary

In the largest cohort to date, MMF showed long-term benefits in IBD patients, with a statistically significant reduction in HBI and pMS at 6 months and final follow-up, and a manageable safety profile.

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Appendix A. Additional member of the Spanish GETECCU group

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References

[1] Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. J Med Life 2019;12(2):113–22.
[2] Loddo I, Romano C. Inflammatory Bowel disease: genetics, epigenetics, and pathogenesis. Front Immunol 2015;6:55.
[3] Godat S, Fournier N, Safroneeva E, et al. Frequency and type of drug-related side effects necessitating treatment discontinuation in the Swiss Inflammatory Bowel Disease Cohort. Eur J Gastroenterol Hepatol 2018;30(6):612–20.
[4] Macaluso FS, Maida M, Renna S, et al. Mycophenolate mofetil is a valid option in patients with inflammatory bowel disease resistant to TNFα- inhibitors and conventional immunosuppressants. Dig Liv Dis 2017;49(2):157–62.

[5] Fellermann K, Steffen M, Stein J, et al. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. Aliment Pharmacol Ther 2000;14:171–6.
[6] Ng SC, Chan FK, Sung JJ. Review article: the role of non-biological drugs in refractory inflammatory bowel disease. Aliment Pharmacol Ther 2011;33(4):417–27.
[7] Doukaki S, Platamone A, Alaimo R, et al. Mycophenolate mofetil and enteric-coated mycophenolate sodium in the treatment of pemphigus vulgaris and pemphigus foliaceus. J Dermatol Treat 2014;26:67–72.
[8] Maripuri S, Kasiske BL. The role of mycophenolate mofetil in kidney transplantation revisited. Transplant Rev 2014;28:26–31.
[9] Wang KJ, Zhang HT, Li YP, et al. Safety of mycophenolate mofetil versus azathioprine in renal transplantation: a systematic review. Transplant Proc 2004;36:2068–70.
[10] Van Leuven SI, Kastelein JJ, Allison AC, et al. Mycophenolate mofetil (MMF): firing at the atherosclerotic plaque from different angles? Cardiovasc Res 2006;69:341–7.
[11] Van Gelder T, Hesselink DA. Mycophenolate revisited. Transpl Int 2015;28:508–15.
[12] Nousari HC, Sragovich A, Kimyai-Asadi A, et al. Mycophenolate mofetil in autoimmune and inflammatory skin disorders. J Am Acad Dermatol 1999;40:265–8.
[13] Orth T, Peters M, Schlaak J, et al. Mycophenolate mofetil versus azathioprine in patients with chronic active ulcerative colitis: a 12-month pilot study. Am J Gastroenterol 2000;95:1201–7.
[14] Eigner W, Vafai-Tabrizi F, Bashir K, et al. Azathioprine versus mycophenolate mofetil in combination with anti-TNF alpha agents in the management of Crohn's disease. J Crohns Colitis 2015;9(suppl):S326.
[15] Smith MR, Cooper SC. Mycophenolate mofetil therapy in the management of inflammatory bowel disease–a retrospective case series and review. J Crohns Colitis 2014;8(8):890–7.
[16] Palaniappan S, Ford AC, Greer D, et al. Mycophenolate mofetil therapy for refractory inflammatory bowel disease. Inflamm Bowel Dis 2007;13:1488–92.
[17] Tan T, Lawrance IC. Use of mycophenolate mofetil in inflammatory bowel disease. World J Gastroenterol 2009;15(13):1594–9.
[18] Hassard PV, Vasiliauskas EA, Kam LY, et al. Efficacy of mycophenolate mofetil in patients failing 6-mercaptopurine or azathioprine therapy for Crohn's disease. Inflamm Bowel Dis 2000;6:16–20.
[19] Skelly MM, Logan RF, Jenkins D, et al. Toxicity of mycophenolate mofetil in patients with inflammatory bowel disease. Inflamm Bowel Dis 2002;8:93–7.
[20] Zabana Y, Panés J, Nos P, et al. The ENEIDA registry (Nationwide study on genetic and environmental determinants of inflammatory bowel disease) by GETECCU: design, monitoring and functions. Gastroenterol Hepatol 2020;43(9):551–8.
[21] Gomollón F, Dignass A, Annese V, et al. ECCO. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohns Colitis 2017;11:3–25.
[22] Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis 2017;11:649–70.
[23] Ensley RD, Bristow MR, Olsen SL, et al. The use of mycophenolate mofetil (rs-61443) in human heart transplant recipients. Transplantation 1993;56:75–81.
[24] Behrend MA. Review of clinical experience with the novel immunosuppressive drug mycophenolate mofetil in renal transplantation. Clin Nephrol 1996;45:336–41.
[25] Kobashigawa J, Miller L, Renlund D, et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients1. Transplantation 1998;66:507–15.
[26] Dooley MA, Cosio FG, Nachman PH, et al. Mycophenolate mofetil therapy in lupus nephritis clinical observations. J Am Soc Nephrol 1999;10:833–9.
[27] Herrera J, Ferrebuz A, MacGregor EG, et al. Mycophenolate mofetil treatment improves hypertension in patients with psoriasis and rheumatoid arthritis. J Am Soc Nephrol 2006;17:S218–25.
[28] Daudén E, Pedraz J, Álvarez-Ruiz S, et al. Therapeutic drug monitoring of mycophenolic acid in patients with psoriasis. Eur J Dermatol 2010;20:321–2.
[29] Fickert P, Hinterleitner TA, Wenzl HH, et al. Mycophenolate mofetil in patients with Crohn's disease. Am J Gastroenterol 1998;93:2529–32.
[30] Neurath MF, Wanitschke R, Peters M, et al. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. Gut 1999;44:625–8.
[31] Miehsler W, Reinisch W, Moser G, et al. Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? Am J Gastroenterol 2001;96:782–7.
[32] Hafraoui S, Dewit O, Marteau P, et al. Mycophenolate mofetil in refractory Crohn's disease after failure of treatments by azathioprine or methotrexate. Gastroenterol Clin Biol 2002;26:17–22.
[33] Wenzl HH, Hinterleitner TA, Aichbichler BW, et al. Mycophenolate mofetil for Crohn's disease: short-term efficacy and long-term outcome. Aliment Pharmacol Ther 2004;19:427–34.
[34] Orlando A, Armuzzi A, Papi C, et al. Italian Society of Gastroenterology; Italian Group for the study of Inflammatory Bowel Disease. The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: the use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease. Dig Liv Dis 2011;43:1–20.
[35] McDermott E, Keegan D, Hall B, et al. Mycophenolate mofetil following intolerance or failure of thiopurine therapy in inflammatory bowel diseases. Aliment Pharmacol Ther 2011;34:1030–46.
[36] Lee FD. Importance of apoptosis in the histopathology of drug related lesions in the large intestine. J Clin Pathol 1993;46:118–22.