Off-label use of mycophenolate mofetil in the treatment of rare and complex rheumatic connective tissue diseases

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ABSTRACT

Objective. *We aimed to investigate the clinical off-label use of mycophenolate mofetil (MMF), including its safety and efficacy in patients with rare and complex rheumatic connective tissue diseases (rCTDs).*

Methods. *A survey was distributed across experts from ERN-ReCONNET reference centres to assess the experience with MMF off-label use. Patient-level data of patients with rCTDs under treatment with MMF was also collected for analysis of safety and efficacy.*

Results. *Twelve experts from eleven centres distributed throughout Europe (7 countries) answered the survey. The experience was concordant in that, despite its off-label use, experts reported opting frequently for this therapeutic alternative with robust confidence on its efficacy and safety. The analysis of 108 patients with rCTDs under MMF revealed a good safety profile, as well as good clinical outcomes, especially for systemic lupus erythematosus and idiopathic inflammatory myopathies. The presence of interstitial lung disease was, as expected, associated with a worse clinical outcome despite use of MMF.*

Conclusion. *MMF is widely used in reference centres for rCTDs. Its safety profile and efficacy seem to be recognised by experts and demonstrated with patient-level analysis. While selected rCTDs will likely remain an off-label indication for MMF, robust data seem to support this therapy as an appropriate alternative for safely and effectively treating many manifestations of rCTDs.*

Introduction

Mycophenolate mofetil (MMF), the pro-drug of mycophenolic acid, is an immunosuppressive agent that inhibits lymphocyte proliferation. It is used since the 1990s in the context of transplant rejection prevention(1), its only labelled use so far. It is, however, often used off-label as a glucocorticoid-sparing drug in various rare and complex rheumatic connective tissue diseases (rCTDs).

MMF use in systemic lupus erythematosus (SLE) is already quite common, albeit it is used as an off-label treatment in concordance with the European Medicines Agency (EMA) labelling. Only in Germany MMF is approved for severe lupus nephritis. It is, thus, vital for the treatment of lupus nephritis and non-renal SLE, except for neuropsychiatric disease (2, 3). Its use in SLE has been vastly studied with two major trials worth mentioning. In the induction phase of the ALMS study (4), MMF showed equivalency to intravenous cyclophosphamide for lupus nephritis. The ALMS maintenance (5) and MAINTAIN (6) trials reached different conclusions regarding the benefit of MMF when compared to azathioprine, with MMF' superiority only found in the former. There are some distinct features of both trials, with a considerable majority of recruited patients in MAINTAIN being Caucasian and different induction regimens in both trials (7). It should also be mentioned that trial design in SLE is complex, with several challenges in terms of patient recruitment, baseline treatment, and outcome definition. Nevertheless, it can be stated that despite its off-label use, there is good evidence to support the efficacy and safety of MMF for the treatment of renal and non-renal SLE, either individually or as combination therapy (8, 9).

MMF has also been proposed as a glucocorticoid-sparing agent for patients with Sjögren's syndrome (SS) and severe organ involvement (10), with a

lack of evidence to firmly recommend between different immunosuppressive drugs. Some reports suggest efficacy in SS-associated ganglioneuropathy (11) or cryoglobulinaemic vasculitis (12), among other rare manifestations (13).

Interestingly, besides inhibiting lymphocyte proliferation, MMF decreases fibroblast proliferation *in vitro* (14). This could explain its encouraging results in interstitial lung disease (ILD) and systemic sclerosis (SSc) (15). In bleomycin-treated mice, a model for SSc, MMF showed anti-fibrotic effects, raising the question for potential use in SSc as it seems to decrease conversion of resident fibroblasts into potentially pathogenic myofibroblasts (16). In line with these preclinical data, the role of MMF in the management of SSc-ILD has been vastly studied in the last few years. MMF has proved to be better tolerated and as effective as cyclophosphamide in improving lung function, ILD imaging features, dyspnoea and skin involvement (17).

Idiopathic inflammatory myopathies (IIM) also seem to respond to MMF, used for resistant myositis, severe cutaneous involvement and ILD (18-20). Within the spectrum of IIM, antisynthetase syndrome (ASS) is yet another entity in which the associated ILD is reported to respond to MMF and rituximab (21). There are also reports of successful MMF use in other rCTDs, such as IgG4-related disease (IgG4-RD) (22), relapsing polychondritis (RP) (23) and mixed connective tissue disease (MCTD) (24).

It is, therefore, evident that despite its sole EMA approved indication for transplant recipients, MMF is a widely used therapy for severe and/or rare manifestations of rCTDs. Whereas in some areas, such as lupus nephritis, existing guidance is clear and unanimous, the use of MMF in other off-label clinical situations is less established and more heterogeneous. Further, in many instances, the evidence supporting treatment with MMF is limited to case reports, case series or small case-control or cross-sectional studies (11-13). More data is unequivocally warranted for such indications, aiming at guiding therapeutic decisions in the management of patients with rCTDs. This will also reassure both patients and physicians, when jointly deciding to start this off-label treatment.

Thus, we aimed to investigate the current off-label use of MMF in several European reference centers, focusing on patients with less frequent rCTDs or manifestations. Moreover, we investigated its safety and efficacy in a sample of such patients.

Material and methods

We conducted a multicentre review of the experience of reference centres integrating the European Reference Network (ERN) ReCONNET, with the use of MMF in the management of patients with rCTDs. We specifically focused on the less common off-label use of MMF in patients with diseases such as SLE, IIM, SSc, SS, IgG4-RD, and RP.

Design and implementation of the expert survey

With the aim of exploring the off-label use of MMF in rCTDs, experts from ERN ReCONNET centres were invited to share their insights within the framework of a survey. A questionnaire was developed for this purpose and sent via e-mail to all ERN ReCONNET centres, which were invited to participate (Supplementary Fig. S1). The survey was voluntary and not anonymous. Experts did not have access to each-other's responses. Regarding efficacy of MMF, experts were asked to report outcomes of the patients, regarding the activity of the specific manifestation for which MMF was started. "Partial response" was defined as an improvement but not a complete remission of symptoms and/or imaging/laboratory findings and "Complete response" as complete normalisation of both symptoms and imaging/laboratory values. "Stabilisation" was defined as an absence of improvement or deterioration of clinical, imaging or laboratory features and "Worsening" was considered when disease progression requiring addition/switch to another immunosuppressant drug was present.

Patient-level data

As a secondary objective, in order to further examine MMF off-label use in rCTDs, reference centres were also invited to provide patient-level data. Inclusion criteria comprised adult patients with a rCTD who were using or had started MMF in the context of their rheumatic disease in the last 5 years. Since the major and most well-researched off-label indication for MMF use is lupus nephritis, and the main objective of this study was to evaluate MMF use in rare indications, lupus nephritis was excluded from this second part of the study.

Clinical data were collected retrospectively through the review of clinical files and regular patient follow-up visits. The database for analysis was completed with randomised codes to identify the patients in a confidential way and performed according to the Helsinki Declaration of 1975/83. The study was approved by the Ethical Board of Lisbon Academic Medical Centre.

Outcomes were expressed as having either stabilised, improved or worsened disease as defined above. This was defined by the evolution of the disease and specific involvement for which MMF was started. Both laboratory findings and clinical findings/symptoms were accounted for in this analysis. At least 2 months of immunosuppression with MMF were deemed necessary in order to define a given outcome.

Muscle involvement was assessed by muscle enzymes and muscle strength progression, as assessed by manual muscle testing (MMT) (25). Neurologic disease was evaluated through symptoms and imaging or function tests, such as electromyography in peripheral nervous system involvement. Skin disease was evaluated through disease activity score (DAS)-skin, clinician's perception on physical examination, as well as inflammatory parameters in lab work, where relevant. ILD progression was assessed by lung function tests, imaging and patient symptoms. There are no universal guidelines for the assessment of rCTDs-associated ILD progression, but it has been suggested that worsening should be perceived when, in a 1-to-2-year time period, at least one of the following is present: ≥10% decline in forced vital capacity (FVC) from baseline; a 5–9% decline in FVC

with a ≥15% decline in carbon monoxide diffusing capacity; or an increase in the radiographic extent of ILD on high resolution CT (26).

Results

Expert survey

Twelve experts from 11 European centres answered the questionnaire. Findings of this survey indicate that MMF is widely used in centres that have significant experience with rCTDs. Around 14722 patients with rCTDs were followed in the past 5 years in the 11 reference centres who replied to the survey (7 countries). Reference centres followed a mean of 1227 patients with rCTDs per centre in the last 5 years, with a minimum of 300 and maximum of 3500. From these patients, in this period of 5 years, a mean of 165±102 (range 31-300), rCTD patients per centre were treated with MMF (13.4%). During the previous year, a mean of 81±46 patients per centre had been treated with MMF, with one centre (specialised in SLE) reporting a maximum of 170 patients treated with this drug. In addition, 11/12 experts reported a slight (n=9) or substantial (n=2) increase in MMF use in their centres in the previous two years, whereas the frequency was unchanged in one centre.

Experts reported to have used MMF for a number of rCTDs, most commonly for SLE (n=12/12) and SSc (n=11/12; Fig. 1). Six experts recognised SSc as the most common diagnosis in which they use MMF, almost all of whom (5/6) mentioned SLE as the second. Five experts found SLE to be the main diagnosis for MMF use and 1 mentioned IIM as the diagnosis in which they use MMF the most. Together, IIM and ASS were common indications for MMF use, reported by more than 80% and 70% of experts, respectively. Between all the mentioned rCTDs, SS was the diagnosis that was reported the least as the leading indication for MMF (n=1). Still, 58% of experts reported using off-label MMF for this condition. Over 30% of experts used MMF for treating RP, whereas 17% reported using MMF to treat IgG4-RD. Conditions such as overlap syndromes, sarcoidosis, polyneuritis, undifferentiated connective tissue disease (UCTD), MCTD and thrombotic thrombocytopenic purpura secondary to SLE were other, rarer, indications for MMF use.

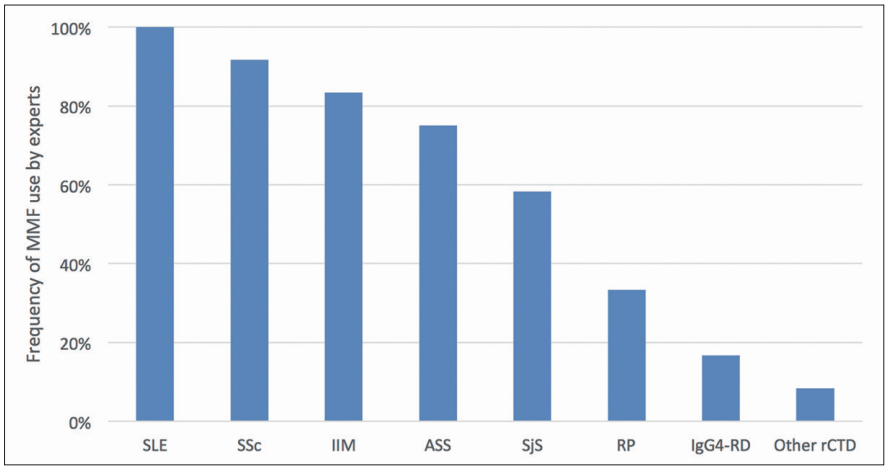

Fig. 1. Indication for MMF off-label use according to rCTD. Data represents percentage of experts (n=12) reporting having used MMF to treat specific rCTDs manifestations within the last 5 years. Other rCTDs as listed in the text.

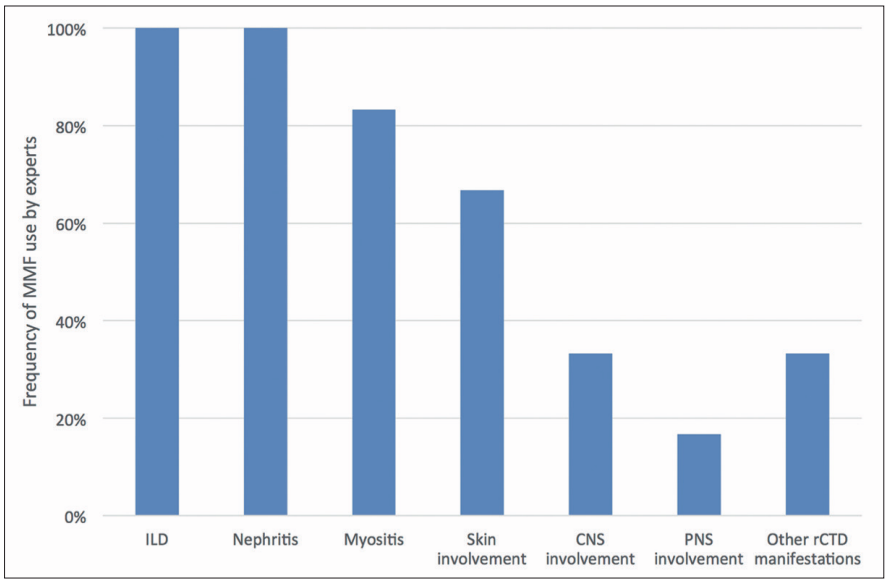

Fig. 2. Indication for MMF off-label use according to rCTD manifestations. Percentage of experts (n=12) reporting having used MMF to treat specific rCTDs manifestations within the last 5 years. Other rCTDs manifestations as listed in the text.

The most common rCTD manifestation for which experts have used MMF in the treatment of patients with rCTDs were ILD (n=12/12 experts), nephritis (n=12/12), myositis (n=10/12), skin disease (n=8/12), central nervous system (CNS) (n=4/12) and peripheral nervous system (PNS) affection (n=2/12) (Fig. 2). Other rCTDs manifestations included: chondritis in RP (n=2), thrombocytopenia in SLE (n=1), vasculitis (n=2) and myocarditis in SLE (n=1). MMF was also aimed at treating some cases of primary vasculitis, but these entities were not included in this study's scope.

When considering MMF use per disease and manifestation, lupus nephritis was, as expected, the most common indication (58.3%) for MMF use in patients with SLE. Other SLE manifestations treated with MMF included myositis, skin disease, ILD and CNS involvement, as well as vasculitis and haematologic disease associated with SLE.

Overall, MMF was considered an effective therapy by experts in the management of rCTDs. Three quarters of the experts reported a partial (67%) or

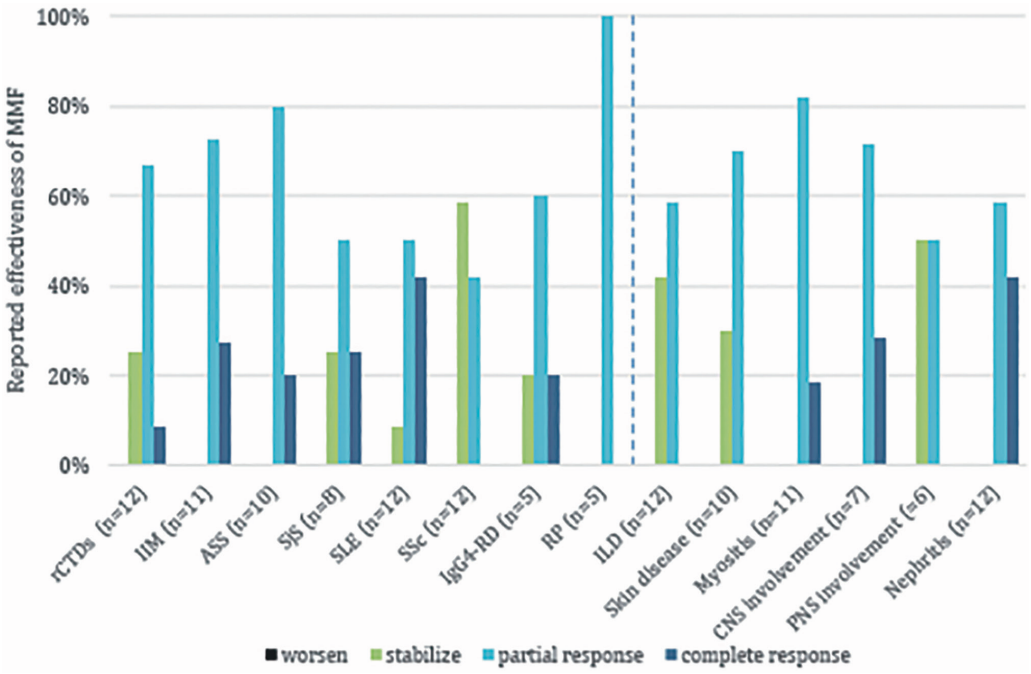

Fig. 3. Effectiveness of MMF use according to rCTD and specific manifestations. Percentage of experts (n=12) reporting the differential effectiveness of MMF on the majority of patients with specific rCTDs and rCTDs manifestations when asked "In your expert opinion, how does the majority of patients treated with MMF respond?"

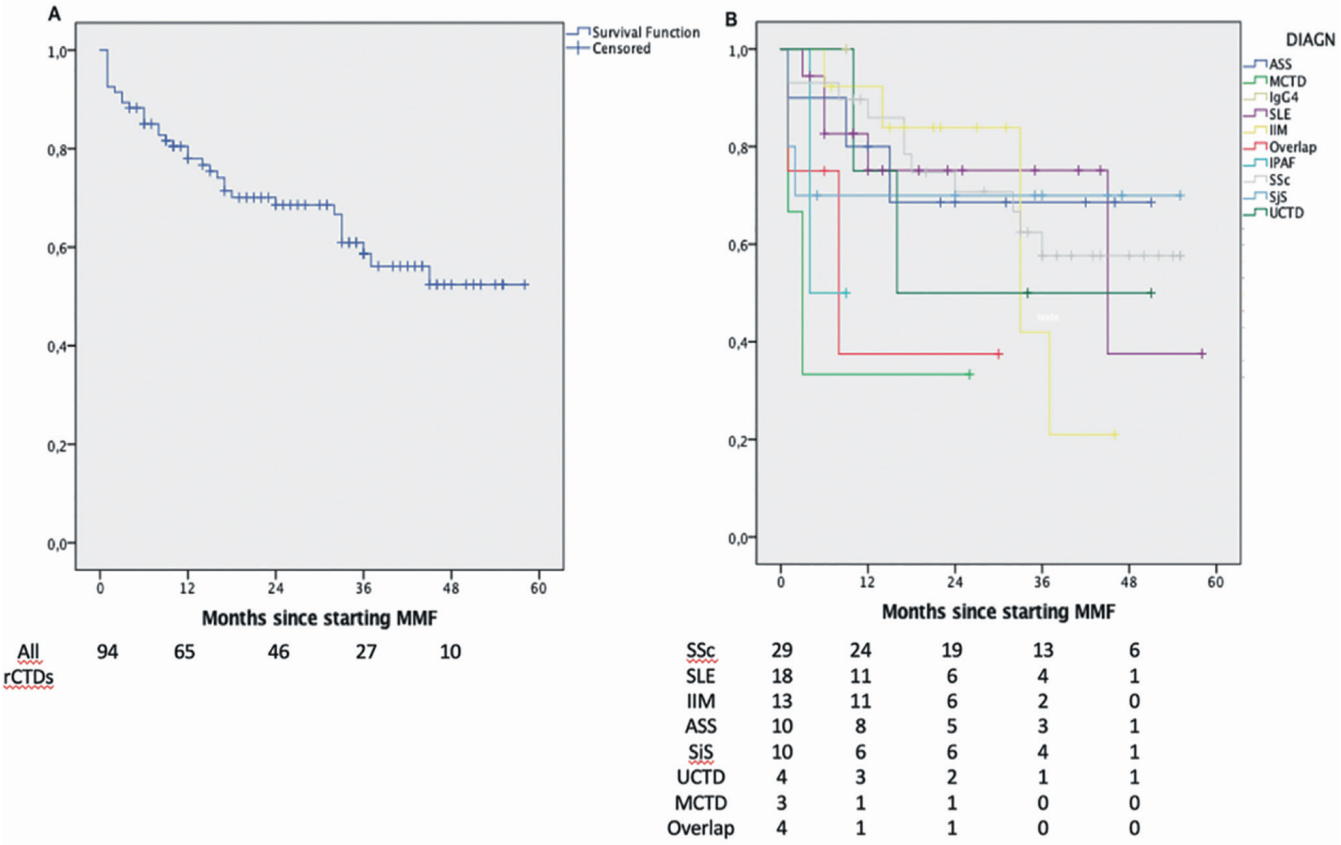

Fig. 4. Discontinuation of MMF in our cohort (**A**); discontinuation of MMF according to diagnosis (**B**). Data shown displayed with a Kaplan Meier graph and at-risk table.

complete (8%) response for rCTDs as a whole (Fig. 3). None of the experts reported that the majority of patients had worsened when MMF was used to treat any of the rCTDs or specific manifestations. These results indicate an important therapeutic effect. A partial response was most commonly observed in patients with RP (100%), ASS (80%), and IIM (72.7%), whereas a complete response was more frequent in patients with SLE (41.7%). In turn, in the expert's opinion, MMF stabilised the disease in the majority of patients with SSc (58.3%). Concerning specific

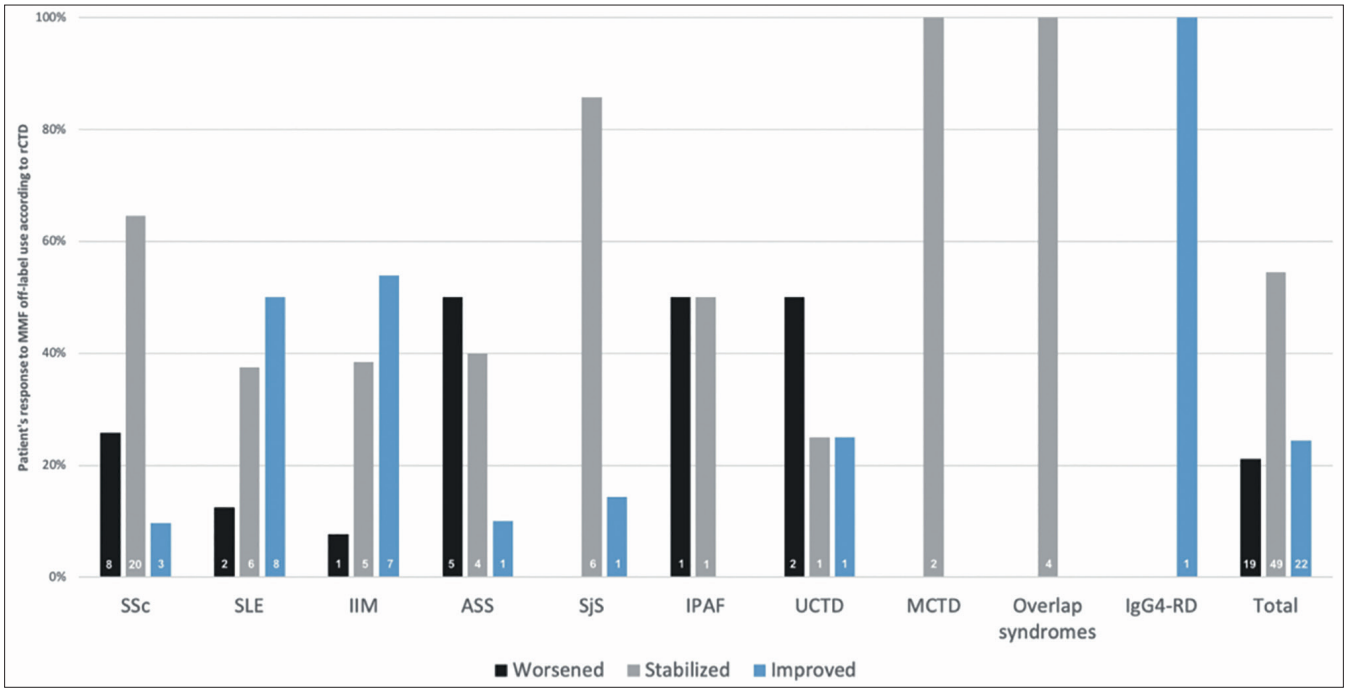

Fig. 5. Efficacy of MMF off-label use according to rCTD in our cohort.

manifestations, most patients experienced a partial response. Nephritis, namely lupus nephritis, and CNS involvement were the most commonly observed indications where a complete response was observed.

Regarding safety, MMF was, overall, considered a safe treatment. When asked about the safety profile of MMF, experts classified it with a mean safety of 7.9±0.9/10 points in a scale from 1 to 10 (where 10 is the safest possible). The main reasons reported for MMF suspension were intolerability (n=7), mainly gastrointestinal, haematologic or infectious; lack of efficacy (n=5) and costs/difficulties of supply (n=2). Of note, some experts underlined that the difficulty in supply and lack of financing is worsened by the fact of its off-label use.

Patient-level data

A total of 108 patients (79.6% female) from 2 different centres (from 2 different countries), with different rCTDs, were treated with MMF within the last five years, with a mean age of 58±17 years (Supplementary Table S1). The most frequent diagnosis was SSc (32%) followed by SLE (17%) and IIM (16%). The most common indications across rCTDs were ILD (n=60), followed by myositis (n=11) and cutaneous manifestations (n=7). Of note, MMF was used for a variety of disease manifestations, from multiple organ systems, as well as for patients with adverse events (AE) to other DMARDs.

MMF discontinuation rate one year after the start of MMF was 31% (Fig. 4A). In addition, after 5 years, more than 50% of the patients were still being treated with MMF. For those patients discontinuing MMF, the mean time to drug discontinuation was 183±205 days. When analysing the results according to the individual rCTD, treatment persistence was higher in patients with ASS, with over 70% of patients still on treatment after 5 years (Fig. 4B). This contrasts with conditions with similar indications, such as SSc and IIM, where persistence was closer to 50–60%. Persistence was lower in patients with MCTD or overlap syndromes, although the numbers were small in each condition. The most frequent reasons for discontinuation (Supplementary Table S2) were adverse events/intolerability (n=20, 53%) and lack of efficacy (n=6, 16%). The most common adverse event was GI intolerability (n=12, 60%).

Concerning efficacy, treatment with MMF resulted more frequently in stabilisation (54%) or improvement (24%) of the disease during the period of follow-up. In only 21% of cases was disease worsening reported despite treatment with MMF (Fig. 4, Table I).

Of note, MMF use resulted in improvement of all cases of myositis (regardless of underlying rCTD) (Table I). On the contrary, in patients for whom MMF was started to treat ILD, only 6% (n=3) improved, and 33% (n=16) had disease progression. These outcomes were less favourable when compared to patients without confirmed ILD (n=29), in whom 59% (n=17) improved, 34% (n=10) stabilised, and only 7% (n=2) experienced a worse outcome. Thus, the presence of ILD appeared to be associated with a worse clinical outcome despite MMF use.

Rarer indications such as neurolupus, lupus cystitis, lupus peritonitis, and IgG4-RD-associated idiopathic retroperitoneal fibrosis, all improved on MMF (Table I). Neurological involvement was another less common indication for MMF, in patients with UCTD, SjS and SLE, and resulted in improvement or stabilisation of the disease.

Discussion

Our study shows that MMF is reported to be widely used by connective tissue disease experts in European reference

centres, and supports its use in most rCTDs, even in rare disease manifestations. MMF, according to the data provided by this study, seems to be an effective, safe, and well-tolerated immunosuppressive drug, with a good maintenance profile over time.

The 5 most common off-label indications for MMF use in our cohort match the 5 most common ones reported by experts in the survey, in almost the exact same order. The only exception is SLE, which was the second most frequent diagnosis in the cohort but the first indicated by most of the experts. This is likely due to the fact that lupus nephritis was excluded from the patient-level analysis, considering its widespread and established, albeit off-label, use for this indication.

In terms of efficacy, most experts reported that patients respond to MMF with a partial improvement in the majority of the off-label indications. A complete response is more commonly observed in SLE and renal involvement, whereas in ILD and SSc disease stabilisation appears to be more commonly achieved. This is in agreement with the data from our cohort, with better outcomes reported for patients with diagnoses such as SLE, IIM and SS.

In fact, outcomes seem to be less favourable in SSc and ASS, an observation that is likely explained by the more frequent lung involvement in these conditions, as well as with the poor outcome typically associated with diffuse cutaneous SSc (27). In fact, we found that ILD was associated with a worsening outcome despite MMF treatment in our cohort.

Current literature also recognises a higher mortality rate in patients with rCTD-associated ILD, compared to those without lung involvement (28). There are, however, few available treatment options for these patients. A recent study comparing MMF and placebo in SSc related ILD showed a significant improvement on dyspnoea, lung function tests and skin sclerosis (15). The positive results were more evident in the first 12 months, with a less evident benefit in the long-term follow-up. This is in agreement with the general stabilisation in patients with ILD/SSc treated with MMF that most experts feel is obtained and confirmed by our patient-level analysis.

ASS seemed to have worse outcomes with MMF, but it also had one of the lowest rates of discontinuation. These conflicting results might be due to the fact that worsening ILD is not always an indication to wean off MMF but actually to add other immunosuppressive drugs such as rituximab, while maintaining treatment with MMF.

Nevertheless, our results can be considered, as a whole, encouraging, providing evidence to guide treatment decisions, and support off-label MMF use in the context of rCTDs and rare disease manifestations. Most importantly, they reassure patients regarding the safety and effectiveness of MMF.

From the patients' perspective, the off-label use of MMF can be a potential treatment option, especially when its safety, efficacy and tolerability is dully demonstrated in clinical practice. rCTDs patients frequently have quite few-to-no treatment alternatives, and a shared decision to opt for an off-label drug may help restore patients' quality of life and contribute to better health

Table I. MMF efficacy according to rCTD and specific manifestation in our cohort.

rCTD	Disease manifestation	Worsened (%)	Stabilised (%)	Improved (%)
SSc	ILD	7 (35)	11 (55)	2 (10)
	Myositis	0 (0)	0 (0)	1 (100)
	Skin disease	0 (0)	3 (100)	0 (0)
	Renal disease	1 (100)	0 (0)	0 (0)
	Constitutional symptoms/arthritis	0 (0)	1 (100)	0 (0)
	Haematologic involvement	0 (0)	1 (100)	0 (0)
	Intolerability/AE of other DMARDs	0 (0)	4 (100)	0 (0)
SLE	ILD	1 (100)	0 (0)	0 (0)
	Myositis	0 (0)	0 (0)	1 (100)
	Alveolar haemorrhage	0 (0)	1 (100)	0 (0)
	Constitutional symptoms/arthritis	0 (0)	2 (100)	0 (0)
	Haematologic involvement	0 (0)	1 (33.3)	2 (66.7)
	Pulmonary hypertension	0 (0)	0 (0)	1 (100)
	Cystitis	0 (0)	0 (0)	1 (100)
	Peritonitis	0 (0)	0 (0)	1 (100)
	Vasculitis	0 (0)	0 (0)	1 (100)
	Intolerability/AE of other DMARDs	0 (0)	1 (50)	1 (50)
	PNS involvement	0 (0)	1 (100)	0 (0)
	CNS involvement	0 (0)	0 (0)	1 (100)
IIM	ILD	0 (0)	5 (83.3)	1 (16.7)
	Myositis	0 (0)	0 (0)	3 (100)
	Skin disease	1 (25)	0 (0)	3 (75)
ASS	ILD	5 (55.6)	4 (44.4)	0 (0)
	Myositis	0 (0)	0 (0)	1 (100)
SS	ILD	0 (0)	3 (100)	0 (0)
	Myositis	0 (0)	0 (0)	1 (100)
	Constitutional symptoms/arthritis	0 (0)	1 (100)	0 (0)
	Ophthalmologic involvement	0 (0)	1 (100)	0 (0)
	PNS involvement	0 (0)	1 (100)	0 (0)
IPAF	ILD	1 (50)	1 (50)	0 (0)
UCTD	ILD	2 (66.7)	1 (33.3)	0 (0)
	PNS involvement	0 (0)	0 (0)	1 (100)
MCTD	ILD	0 (0)	1 (100)	0 (0)
	Intolerability/AE of other DMARDs	0 (0)	1 (100)	0 (0)
Overlap syndromes	ILD	0 (0)	4 (100)	0 (0)
IgG4-RD	Idiopathic retroperitoneal fibrosis	0 (0)	0 (0)	1 (100)
Total		18	49	23

outcomes. Clinicians who do not feel at ease with off-label use, should refer patients to expert centres and ask for support from their peers. This is crucial, as sometimes this may be the only treatment option for their patients. Nevertheless, further research, collection of clinical data, and dissemination of results is required. Cross-border care should not be forgotten, and efforts must be made to integrate and expand local care at the European level, especially keeping in mind the difficulties in supply and possible lack of financing for MMF.

The present study has some limitations. Its retrospective design and the limited number of patients in our cohort confines the scope of conclusions we can derive from these results. The number of experts that responded to the survey is also limited, and expert opinions may be biased, although it is important to report how experts manage clinical and treatment decisions in daily clinical practice, particularly in areas where there are few available therapeutic options. Another limitation was the fact that the definition of "response" is subjective and may vary for each disease. Patient-level data from more centres would have allowed for a more robust evaluation of outcomes, although these were consistent with currently available evidence. The fact that the patients in our cohort had different durations of follow-up is also a limitation in our study, especially when considering MMF's benefit in SSc' skin disease and ILD is more significant in the first 12 months of treatment.

In summary, this study reassures both patients and rCTDs experts alike, regarding the off-label use of MMF, confirming its position as a valuable alternative for patients requiring immunosuppressive treatment for a variety of manifestations of rCTDs. This may allow for a reduction or even withdrawal of glucocorticoids, diminishing treatment burden. It should be noted, though, that in some contexts the use of MMF may be delayed or even restricted by the off-label nature of the treatment, especially in countries that require private insurance funding. Efforts should be made in order to overcome this barrier. In addition, further studies would be useful to support a more robust rationale for the inclusion of rCTDs in MMF's labelled uses, facilitating its prescription and financial support.

In conclusion, our study shows that MMF is widely used by experts in the management of rCTDs, despite its off-label indication. It appears to be safe, effective well-tolerated and with an excellent maintenance profile over time and is therefore a valuable option to treat patients with rCTDs, including rare disease manifestations.

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