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REVIEW

Efficacy and safety of mycophenolate mofetil in the treatment of rheumatic disease-related interstitial lung disease: a narrative review

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Abstract

Mycophenolate mofetil (MMF) is an antimetabolite with a potent inhibitory effect on proliferation of T and B lymphocytes used since the early 1990s for the prevention of acute allograft rejection after organ transplant. MMF is also widely used for the treatment of a variety of rheumatic diseases (RDs) and their pulmonary involvement. Interstitial lung disease (ILD) is a heterogeneous group of progressive fibrotic diseases of the lung, which is often secondary to RD and represents a major cause of morbidity and mortality. MMF is considered the main alternative to cyclophosphamide as a first-line agent to treat RD-related ILD or as possible maintenance therapy after cyclophosphamide, with a lower rate of side-effects. However, as for other immunosuppressive agents, the use of MMF in RD-ILD is supported by poor scientific evidence. In this narrative review, we describe the available data and recent advances on the effectiveness and safety of MMF for the treatment of ILD related to RD, including rheumatoid arthritis, systemic sclerosis, primary Sjögren syndrome, systemic lupus erythematosus, idiopathic inflammatory myopathies, undifferentiated connective tissue disease, interstitial pneumonia with autoimmune features and antineutrophil cytoplasmic antibody-associated vasculitis.

Keywords: connective tissue diseases, efficacy, interstitial lung disease, lung fibrosis, mycophenolate mofetil, rheumatic diseases, safety.

Citation

Cassone G, Sebastiani M, Vacchi C, Erre GL, Salvarani C, Manfredi A. Efficacy and safety of mycophenolate mofetil in the treatment of rheumatic disease-related interstitial lung disease: a narrative review. Drugs in Context 2021; 10: 2020-8-8. DOI: 10.7573/dic.2020-8-8

Introduction

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase, which inhibits de novo guanosine nucleotide synthesis and exerts a series of immunosuppressive effects.[1] MMF has been used since the early 1990s for the prevention of acute allograft rejection and is also widely used for the treatment of a variety of rheumatic diseases (RDs) (dose usually ranging from 1 to 3 g).[2,3]

Interstitial lung disease (ILD) is a heterogeneous group of progressive fibrotic diseases of the lung, often secondary to RD, and represents a major cause of morbidity and mortality.[4–7] RD-ILDs represent the second most common diagnosis in tertiary ILD referral centres.[8] In particular, ILD can complicate connective tissue diseases (CTDs) and rheumatoid arthritis (RA), yet it also complicates antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and sarcoidosis, with variable prevalence and different grade of severity of pulmonary involvement and mortality rate according to the specific RD.[5,9–17] Moreover, increasing interest and a deeper knowledge have been emerged regarding a subgroup of patients with ILD and clinical and/or serological findings suggestive but not diagnostic for a definite RD, defined as interstitial pneumonia with autoimmune features (IPAF).[18–20]

RD-ILD can be characterized by all the histological/radiological patterns described for idiopathic interstitial pneumonias.[4,21] Some authors speculated about more favourable responses to immunosuppressive therapy for non-specific interstitial pneumonia (NSIP) or organizing pneumonia patterns. However, no strong evidence-based data support this hypothesis.[22,23]

The pathogenesis of ILD in CTD, AAV, and IPAF shares some similarities and is substantially characterized by long-term

and aggressive systemic inflammation and immune activation with consecutive damage to lung tissues and the development of a profibrotic microenvironment.[15,24–28] The main actors of the fibrotic process are inflammatory cytokines, activated macrophages, fibroblasts, T and B cells, adaptive immunity and antibodies, and reactive oxygen species.[15,24–28] Usual interstitial pneumonia (UIP) in RD-ILD also shows analogies with idiopathic pulmonary fibrosis (IPF), in particular regarding their natural history and clinical behaviour with a progressive fibrosing phenotype.[29–31] Moreover, the same genetic predisposition has been described for the IPF and UIP patterns in RA-associated and AAV-associated ILDs.[31–35] Finally, similarly to IPF, patients with RD-ILD may also experience an acute exacerbation (AE).[36]

The management of ILD in patients with RD is challenging and could be decisive to improve their quality of life and decrease mortality and the high utilization of healthcare resources. However, due to the paucity of randomized controlled trials (RCTs) and the substantial heterogeneity in disease behaviour, the therapeutic choice for RD-ILD is currently based on an empirical approach dependent on the personal experience and expertise of the medical team. The best available evidence has been generated in systemic sclerosis-associated ILD (SSc-ILD).[37,38]

Several therapeutic agents have been suggested and current treatment is essentially based on immunosuppression. The scientific background supporting the use of an immunosuppressive drug in RD-ILD comprises a direct anti-inflammatory effect on the primary aetiopathogenetic process of ILD and an indirect effect by decreasing the RD activity, which could influence the ILD progression. Recently, the use of antifibrotic agents has also been proposed.[30,37,38]

The pharmacological immunosuppressive properties of MMF, as described (see pharmacodynamic effects section) support the scientific rationale for the use of MMF as a treatment for severe RD-ILD. Indeed, MMF is usually considered the main alternative to cyclophosphamide (CYC) as a first-line agent to treat RD-ILD or as possible maintenance therapy after CYC, with a lower rate of side-effects.[3,39–42]

In this review, we describe the available data and recent advances on the effectiveness and safety of MMF for the treatment of ILD related to RD, including RA, SSc, primary Sjögren syndrome (pSS), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIMs), undifferentiated CTD (UCTD), IPAF, and AAV (Table 1).

Methodology and study selection

A systematic literature review was conducted by two authors (GC and CV) using PubMed, Web of Science, Scopus, Embase, Latin American and Caribbean Health Sciences Literature, and Cochrane Central databases. The research strategy was ((mycophenolate mofetil* OR mycophenolate sodium*) AND (interstitial lung disease* OR interstitial pneumonia* OR lung fibrosis*) AND (rheumatoid arthritis* OR connective tissue diseases* OR systemic sclerosis* OR primary Sjögren syndrome* OR systemic lupus erythematosus* OR idiopathic inflammatory myopathies* OR undifferentiated CTD* OR interstitial pneumonia with autoimmune features* OR ANCA-associated vasculitis* OR small vessel vasculitis* OR sarcoidosis*)) in the text, title, and abstract fields. We considered RCTs, systematic reviews, observational studies, case series, and case reports. We did not consider abstract or grey literature. We also used the snowballing technique to search the bibliographies for relevant references from the reference list or moving forward to the citing articles. No language restriction was considered, no years of publication restriction were applied, and only published articles were considered. A narrative review was conducted due to the low quality of available studies, consisting mainly of case reports or case series and retrospective studies.

Pharmacological properties of MMF

Clinical pharmacokinetics

MMF is an ester of MPA and was synthesized to increase the bioavailability of MPA. Following administration, MMF is rapidly and completely absorbed and is entirely metabolized by liver carboxylesterases 1 and 2 to MPA by a pre-systemic de-esterification. MPA is almost completely metabolized by the enzyme glucuronyl transferase to the pharmacologically inactive and stable phenolic glucuronide MPAG, which is excreted in urine and represents almost all of the administered dose. The glucuronide metabolite is then converted to MPA through enterohepatic recirculation. MMF escaping metabolism in the intestine enters the liver via the portal vein and is transformed to pharmacologically active MPA in the liver cells. In addition to MPAG, other major metabolites of MPA are MPA acyl-glucuronide, 7-O-MPA glucoside, and small amounts 6-O-des-methyl-MPA.

Almost all of the whole administered dose is excreted in the urine as MPAG. The average apparent half-life of MMF is 17.9 (±6.5) hours after oral administration and 16.6 (±5.8) hours after intravenous administration. Plasma clearance of MMF is 193 mL/min after an oral dose and 177 (±31) mL/min after an intravenous dose. Effectively, oral MMF is 100% bioavailable as MPA in healthy individuals. These properties of MMF lead to a small intra-individual and inter-individual variability for plasma MPA and to predictable pharmacokinetics changes in pathophysiological situations.[43,44]

Pharmacodynamics

The immunosuppressive effects of MMF are mainly derived from its cytostatic effect on T and B lymphocytes and, hence, on the inhibition of antibody production. Three other mechanisms may also contribute to the anti-inflammatory

Table 1. Available evidence for the use of mycophenolate mofetil in RD-ILD.

Author, year (ref.)	Article type	Number of patients
Rheumatoid arthritis		
Fischer et al., 2013 ([40])	Retrospective	18
Oldham et al., 2016 ([66])	Retrospective	8
Saketkoo et al., 2008 ([41])	Case series	3
Systemic sclerosis		
Tashkin et al., 2016 ([42])	RCT: SLS II	63
Volkmann et al., 2017 ([70])	RCT: SLS I-II	69
Naidu et al., 2020 ([71])	RCT	20
SLS III (NCT03221257) ([94])	RCT: SLS III	NA
Stratton et al., 2001 ([73])	Prospective	13
Liossis et al., 2006 ([85])	Prospective	6
Vanthuyne et al., 2007 ([86])	Prospective	16
Derk et al., 2009 ([82])	Prospective	15
Simeón-Aznar et al., 2011 ([83])	Prospective	14
Mendoza et al., 2012 ([81])	Prospective	25
Panopoulos et al., 2013 ([92])	Case–control	26
Tzouvelekis et al., 2012 ([77])	Retrospective + systematic review	10 (total 69)
Nihtyanova et al., 2007 ([78])	Retrospective	109
Zamora et al., 2008 ([88])	Retrospective	17
Gerbino et al., 2008 ([87])	Retrospective	13
Koutroumpas et al., 2010 ([74])	Retrospective	10
Le et al., 2011 ([75])	Retrospective	98
Owen et al., 2016 ([89])	Retrospective	18
Baqir et al., 2017 ([91])	Retrospective	46
Adler et al., 2018 ([79])	Retrospective	NA
Saketkoo et al., 2009 ([68])	Case series	4
Yilmaz et al., 2014 ([80])	Case series	12
Herrick et al., 2010 ([84])	NA	NA
Primary Sjögren syndrome		
None		
Idiopathic inflammatory myopathies		
Morganroth et al., 2010 ([106])	Retrospective	16
Mira-Avendano et al., 2013 ([103])	Retrospective	9
Hanaoka et al., 2019 ([104])	Retrospective	19
Huapaya et al., 2019 ([105])	Retrospective	44
Cozzani et al., 2013 ([110])	Case report	1
Girard et al., 2013 ([128])	Case report	1
Sundaragiri et al., 2014 ([116])	Case report	1

(Continued)

Table 1. ***(Continued)***

Author, year (ref.)	Article type	Number of patients
Tsuchiya et al., 2014 ([109])	Case report	1
Kulkarni et al., 2015 ([117])	Case report	1
Gil et al., 2016 ([108])	Case report	1
Hayashi et al., 2017 ([126])	Case report	1
Hisanaga et al., 2017 ([127])	Case report	1
Koyama et al., 2017 ([107])	Case report	1
Ruegg et al., 2019 ([115])	Case report	1
Systemic lupus erythematosus		
Al Rashidi et al., 2011 ([132])	Case report	1
UCTD and IPAF		
McCoy et al., 2018 ([135])	Retrospective	28
ANCA-associated vasculitis		
None		
Sarcoidosis		
Brill et al., 2013 ([147])	Retrospective	10
Hamzeh et al., 2014 ([146])	Retrospective	37
Papiris et al., 2019 ([145])	Retrospective	8
Other articles: cumulative data on more diseases or drugs		
Zhang et al., 2015 ([67])	RCT	23 RD-ILD
Swigris et al., 2006 ([39])	Retrospective	28 RD-ILD
Saketkoo et al., 2009 ([68])	Retrospective	10 RD-ILD
Fischer et al., 2013 ([40])	Retrospective	125 RD-ILD

ANCA, antineutrophil cytoplasmic antibody; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; NA, not available; RCT, randomized controlled trials; RD, rheumatoid disease; SLS, Scleroderma Lung Study; UCTD, undifferentiated connective tissue disease.

activity of MMF.[1–3,45] First, MMF can induce apoptosis of activated T lymphocytes and suppress the T lymphocytic response to allogeneic cells and other antigens. MPA also suppresses dendritic cell maturation decreasing their capacity of antigen presentation to T lymphocytes. Second, MMF inhibits the glycosylation and expression of adhesion molecules as well as the recruitment of lymphocytes and monocytes into sites of inflammation. Third, by depleting tetrahydrobiopterin, MMF decreases the production of NO by inducible NO synthase and the consequent tissue damage mediated by peroxynitrite. Moreover, by decreasing the recruitment of monocyte-macrophage lineage cells, MMF decreases the production of TNFα and IL-1, both of which are cytokines implicated in the recruitment and proliferation of fibroblasts.

Adverse effects and contraindications

MMF is usually safer and better tolerated than CYC. Unlike azathioprine (AZA), the deficiency in thiopurine methyltransferase is not a potential concern when prescribing MMF. On the contrary, MMF should theoretically be avoided in patients with the rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl transferase (e.g. Lesch–Nyhan or Kelley–Seegmiller syndromes).

Adverse effects and monitoring

Gastrointestinal (GI) symptoms and bone marrow suppression are the most frequent adverse effects of MMF. Other common side-effects include hepatitis and increased risk of

infections. A higher risk of cancer and progressive multifocal leukoencephalopathy have also been described.[46,47]

Common and uncommon side-effects of MMF are listed in Table 2. GI side-effects are usually dose related and tend to reduce over time. In patients with GI intolerance to MMF (mainly diarrhoea), the enteric-coated mycophenolate sodium can be an alternative formulation. However, it has not been formally tested in any controlled studies, and some authors demonstrated similar rates of GI side-effects for both drugs.[48,49] In some patients, compliance improves by increasing the number of divided daily doses (maintaining the same total daily dose). Other patients may require dose adjustments. In patients with active peptic ulcer or other GI disease, such as inflammatory bowel diseases, MMF should be used with caution.

Cytopenia is the major potential concern and requires regular monitoring, which should also include renal and liver function and signs of lymphoma or myeloproliferative disorders.[50] The risk for malignancies, mainly lymphoproliferative disorders, is related to the intensity and duration of therapy. Moreover, even if a direct association between lung fibrosis and cancer is still missing, emerging evidence, mainly in IPF, suggest that progressive lung fibrosis represents a risk factor for lung cancer development. In IPF, lung cancer often occurs in the peripheral areas and lower lobes where fibrotic changes are predominant.[51] Furthermore, radiologic features of RD-ILD and lung cancer can overlap substantially. Thus, the interpretation of chest high-resolution computer tomography (HRCT) can be difficult and should be done with caution, notably regarding atypical nodes or masses and/or lymph nodes.[52]

There are no large studies examining the incidence of infections in patients with rheumatic illness treated with MMF. The existing studies[53,54] are too small to allow generalizations. On the other hand, data from larger studies regarding solid organ transplants showed conflicting results.[55–57]

MMF has antimicrobial properties and seems to exert a protective effect against *Pneumocystis jirovecii*.[58,59] Therefore, the use of prophylaxis for *Pneumocystis* pneumonia is controversial. The association between MMF and possible viral infections, such as herpes zoster and cytomegalovirus infection, is also disputable.[60–63]

Nevertheless, patients with RD are not directly comparable to patients with solid organ transplants. In fact, in patients with RD, the increased risk of infections can derive from the exposure to other immunosuppressive agents and to higher cumulative doses of corticosteroids (CSs).[64] Furthermore, the aetiopathogenetic alteration of the immune system in RD may lead itself to an increased susceptibility to infections.

In addition, pulmonary infections can be more frequent and more severe in a context of ILD.[64] Infections have been suggested to play a role both in the pathogenesis of ILD and as potential triggers of AE, mainly in IPF. Thus, diagnosis and treatment of acute lower respiratory tract infections as early as possible is required to prevent a life-threatening condition like AE. In this context, the use of an immunosuppressive drug such as MMF, especially in combination with high-dose steroids, may increase the risk of severe pulmonary complications and mortality in patients with RD-ILD.[65]

For all these reasons, vaccinations, excluding live attenuated vaccines, are highly recommended in patients with rheumatic conditions who take MMF.

Contraindications

MMF has been associated with an increased risk of congenital abnormalities and should be avoided during pregnancy. Reliable contraception should be employed by women of childbearing age. MMF is excreted in breast milk and is contraindicated during breastfeeding. A pregnancy test should be performed immediately prior to initiation and 8–10 days later in females of childbearing age, followed by repeat tests during therapy.

Rheumatoid arthritis

ILD is the most common manifestation of lung involvement in RA. Unlike CTD-ILD, the most common histopathologic type is UIP. In addition to the histological/radiological pattern, RA-ILD shares many other analogies with IPF. It shows a similar clinical behaviour, often with a progressive fibrosing phenotype, and a comparable prognosis and survival.[29–31]

Evidence-based use of MMF in RA-ILD is still missing; moreover, it is ineffective for the articular manifestations of the disease. No controlled studies are available to recommend the use of MMF in RA-ILD.[40,41,66–68] Saketkoo et al.[68] described a clinical improvement in physiological lung assessment and radiological stabilization in a small case series of three patients with RA-ILD. In 2016, a retrospective study from the UK observed a better survival of patients with RA-ILD treated with MMF than with AZA.[69] The relative risk of death for any cause was increased in patients treated with prednisone, whereas it was unaltered for AZA and decreased for MMF. The authors suggested a better outcome following treatment with MMF rather than with CSs or AZA in patients with RA-ILD. In a series of 125 patients with CTD-ILD, including 18 with RA, MMF was associated with modest improvements in forced vital capacity (FVC) and in diffusing capacity of the lungs for carbon monoxide (DLCO) and a reduction in the prednisone dose.[40] Finally, in 2016, Oldham et al.[66] compared the use of AZA and MMF in patients with fibrotic CTD-ILD, including 15 patients with RA-ILD. Both groups demonstrated pulmonary function stability over time, with the AZA group demonstrating a marginal improvement but much more side-effects.

Connective tissue diseases

MMF is one of the most common immunosuppressive agents currently used for the treatment of CTD-ILD. However, there have been no prospective studies about the safety or

Table 2. Side-effects of mycophenolate mofetil. Incidences include concomitant use of corticosteroids and other immunosuppressants.

	>10%	1% to 10%	Rare
Cardiovascular	Hypertension, hypotension, tachycardia, lower extremity oedema	Exacerbation of hypertension, peripheral oedema, phlebitis, thrombosis	Endocarditis, venous thrombosis
Central nervous system	Pain, headache, insomnia, dizziness, depression, chills, confusion, drowsiness, hypertonia, malaise, myasthenia, paraesthesia	Anxiety, fatigue	Meningitis, progressive multifocal leukoencephalopathy
Dermatologic	Skin rash, ecchymoses, cellulitis	Acne vulgaris, pruritus	Alopecia, hypersensitivity reaction, Kaposi sarcoma
Endocrine and metabolic	Hyperglycaemia, hypercholesterolaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, increased lactate dehydrogenase, hyperkalaemia, acidosis, weight loss, hyperuricaemia, hyperlipidaemia, hypophosphataemia	Diabetes mellitus	
Gastrointestinal	Abdominal pain, nausea, diarrhoea, constipation, vomiting, decreased appetite, dyspepsia, oesophagitis, gastric ulcer, gastritis, gastrointestinal haemorrhage, hernia of abdominal cavity, intestinal obstruction, stomatitis, upper abdominal pain, flatulence	Abdominal distension, gastroesophageal reflux disease, gingival hyperplasia, oral candidiasis	Mucocutaneous candidiasis, anorexia, colitis, duodenal ulcer, oesophageal ulcer, gastrointestinal perforation, haematemesis, haemorrhagic colitis, haemorrhagic gastritis, melena, pancreatitis, peritonitis
Genitourinary	Urinary tract infection, haematuria	Urinary retention	
Haematologic and oncologic	Leukopenia, anaemia, leukocytosis, thrombocytopenia, benign skin neoplasm, disorder of haemostatic components of blood, neoplasm, pancytopenia, skin carcinoma	Lymphocele, severe neutropenia, malignant neoplasm, malignant lymphoma, lymphoproliferative disorder	Agranulocytosis, bone marrow failure, hypogammaglobulinaemia lymphadenopathy, lymphopenia, pure red cell aplasia
Hepatic	Increased liver enzymes, hepatitis, increased serum alkaline phosphatase	Abnormal hepatic function tests	
Infection	Bacterial infection, viral infection, cytomegalovirus disease, fungal infection	Influenza, wound infection, herpes simplex infection, herpes zoster infection, sepsis	Protozoal infection, atypical mycobacterial infection, BK virus, polyomavirus infection, reactivation of Hepatitis C virus (HCV), reactivation of Hepatitis B virus (HBV), tuberculosis
Neuromuscular and skeletal	Asthenia, tremor, back pain, arthralgia	Muscle cramps, myalgia, peripheral pain	Osteomyelitis
Renal	Increased serum creatinine, increased blood urea nitrogen	Renal insufficiency, renal tubular necrosis	
Respiratory	Dyspnoea, cough, pleural effusion	Dyspnoea on exertion, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract infection	Pharyngitis, respiratory tract infection, bronchiectasis interstitial pulmonary disease, pulmonary oedema, pulmonary fibrosis, wheezing, xerostomia
Miscellaneous	Fever		

This table is adapted from the Medication Guide of MMF.[44]

efficacy of this approach. The best available evidence has been generated only in a small number of RCTs for SSc-ILD.[37,42,70,71]

MMF demonstrated stability of lung function and a low rate of adverse events in a small cohort of patients with mixed CTD-ILD.[39,40,67,68] In another longitudinal retrospective study of 125 patients with CTD-ILD, MMF seemed to either stabilize or improve FVC and DLCO over a median of 2.5 years of follow-up, with a low rate of discontinuation.[40] In CTDs and vasculitides, MMF is largely used for the treatment of systemic manifestations other than lung involvement as well as for maintenance after induction therapy with other immunosuppressants such as CYC. Unfortunately, it is not effective in treating joint arthritis.

Systemic sclerosis

ILD is a frequent complication of SSc, often progressive and with a poor prognosis. The most common histopathologic subtype is NSIP.[72] However, the optimal treatment and the therapy's timing for SSc-ILD is still area of uncertainty. Since 2001, many retrospective reviews and small prospective case series[68,73–88] have assessed the role of MMF in SSc-ILD, providing encouraging results in terms of improvement or stability in lung function and symptoms as well as a good safety profile.

In 2015, Omair et al.[76] performed a systematic review to evaluate the GI adverse events of MMF in patients with SSc. The secondary end-point was the evaluation of the effectiveness of the drug on lung disease in terms of pulmonary function tests (PFTs). Among 13 studies included, 7 observational studies reported improvement or stabilization in FVC.[68,73–76,81–88] According to Omair et al.,[76] the Australian Scleroderma Cohort Study and Japanese Respiratory Society observed stability or improvement in FVC in patients with SSc.[89,90] In 2017, another retrospective study of 46 patients with SSc-ILD treated for at least 1 year showed that the use of MMF slowed the rate of decline of lung function, even at doses lower than 3 g/day.[91] On the contrary, Panopoulos et al.[92] cautioned about replacing CYC with MMF in SSc-associated ILD. A deterioration of lung HRCT findings at 2 years was noticed in the MMF group but not after CYC, even if the CYC group had more extended ILD at baseline. Recently, a network meta-analysis compared the efficacy and safety of different treatments in SSc-ILD. Compared to the placebo, MMF did not significantly reduce FVC decline nor DLCO.[93]

To date, only two RCTs have evaluated the safety and efficacy of MMF in patients with SSc-ILD.[42,70] The Scleroderma Lung Study (SLS) II included 142 patients with moderate-to-severe SSc-ILD. It compared MMF 3 g daily for 2 years with oral CYC for 1 year finding no differences in efficacy but better tolerance to MMF.[42] The average FVC presented a modest decline between 21 and 24 months of follow-up in both arms, and a complete loss of efficacy was not observed in the CYC arm, as occurred in SLS I. Notably, DLCO decreased in both groups, although this finding was significantly greater in the CYC *versus* the MMF group. The study also demonstrated a greater safety and tolerability of MMF compared with CYC, although no differences in the incidence of infection, bleeding, or death were recorded.[42] Volkmann et al. compared the outcomes for the MMF arm of SLS II with the placebo arm of SLS I.[70] Considering the limits inherent in the design of the study, MMF showed a long-lasting efficacy on PFT parameters and dyspnoea and showed a high safety profile.

Recently, a double-blind, randomized, placebo-controlled, pilot trial conducted at a tertiary care hospital in north India (NCT02896205) aimed to assess the efficacy and safety of MMF in patients with SSc-ILD and mildly impaired lung function (FVC ≥70% predicted); 41 patients were included in the study, and treatment with MMF did not result in a significant improvement of lung function over 6 months.[71] Finally, SLS III (NCT03221257) is now ongoing to compare the efficacy of MMF alone or in combination with pirfenidone in patients with active and symptomatic SSc-ILD. The estimated study completion date is in March 2022 and no preliminary data are available yet.[94]

Primary Sjögren syndrome

ILD is the most frequent pulmonary manifestation of pSS. Although not frequent, lymphoid interstitial pneumonia is the radiological/histological pattern most closely associated with pSS. Recent studies indicated UIP as the most frequent pattern in pSS patients.[95] Lung hematologic malignancies have also been described.[96] Management strategies for Sjogren-associated lung diseases (pSS-ILD) remain empiric because no controlled studies have been performed.

The few available data about MMF in pSS are extrapolated from retrospective studies describing mixed cohorts of patients with CTD-ILD. These small case series suggest that MMF may be effective and safe on lung function. Moreover, it could have a glucocorticoid-sparing effect.[39,40,67,68]

Idiopathic inflammatory myopathies

ILD represents the most common non-muscoloskeletal manifestation of IIMs.[97] The majority of patients with IIM who develop ILD have a clinical and histopathological pattern of NSIP or organizing pneumonia; thus, immunosuppressants are usually the first therapeutic choice.[97,98] No evidence-based guidelines exist regarding IIM-ILD therapy regimens.[99] Most patients follow a chronic, slowly progressive course that does not require specific treatment. However, early evidence suggests that some subtypes of antibodies correlate with the development of ILD and with worse severity,[98,100–102] as mentioned below. Immunosuppressants are usually the first therapeutic choice in those patients.

A retrospective review of treatment outcomes in IIM-ILD reported the same efficacy in stabilizing lung function and in glucocorticoid dose tapering for oral CYC, AZA, and MMF.[103] In 2019, Hanaoka et al. evaluated the efficacy and tolerability of MMF alone (12 patients) or associated to calcineurin inhibitors (7 patients) in resistant inflammatory myopathy. No significant improvement in %FVC and HRCT images and no differences in death or ILD progression were found in patients with ILD in either group.[104] In the largest cohort of IIM-ILD treated with MMF,[105] 44 patients showed improvement in FVC and in reaching lower prednisone dose, but no improvement of the DLCO was detected. Apart from these studies, only sporadic small case series and case reports are available on this topic.[39,40,67,68,106–110]

Antisynthetase syndrome

ILD is a hallmark of antisynthetase syndrome (ASSD), with a prevalence ranging from 67% to 100% of cases.[111] This IIM is characterized by the presence of antiaminoacyl-tRNA synthetase antibodies.[112,113] Anti-Jo1 positivity has been shown to have a favourable prognostic value; on the contrary, anti-PL7 and anti-PL12 autoantibodies are often associated with a more aggressive ILD and a poor survival.[100,101,114] In the study by Mira-Avendano et al.,[103] approximately 50% of the patients were positive for anti-Jo1. As mentioned earlier, the use of CYC, AZA, or MMF was similarly associated with the stability of PFTs, a reduction in dyspnoea, and the steroid dose. Other anecdotal case reports showed similar results in patients with ASSD positive for anti-Jo1 antibodies.[115–117]

No studies have directly evaluated the efficacy and safety of MMF in non-anti-Jo1 ASSD patients. Non-anti-Jo1 antisynthetase antibodies (anti-KS, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12) are less frequent in ASSD. Therefore, evidence for these specific subgroups is very poor. However, many patients with these autoantibodies are included in studies on CTD-ILD or IIM-ILD. It has been suggested that patients with anti-KS and anti-OJ antibodies would be most likely to have a good response to CSs.[118,119]

Antimelanoma differentiation-associated gene 5 (MDA5) dermatomyositis

Anti-MDA5-positive dermatomyositis is characterized by an elevated risk of ILD with a rapidly progressive and potentially fatal course.[120–124] The 6-month survival rate in some studies is 40% despite therapies.[125] In 2017, Hayashi et al.[126] described the case of a patient with anti-MDA5-ILD successfully treated by the addition of MMF to an immunosuppressive therapy including CSs, oral cyclosporine, and intravenous CYC. The same year, Hisanaga et al.[127] presented a case of worsening ILD despite treatment with high-dose prednisolone combined with cyclosporine and intravenous CYC in a patient positive for anti-MDA5. The addition of direct hemoperfusion with polymyxin-B, MMF, intravenous immunoglobulin, and rituximab (RTX) led to remission of the disease. On the other hand, Girard et al.[128] reported a case of anti-MDA5-ILD treated with intravenous immunoglobulins, CYC, MMF, AZA, and RTX in combination with oral CSs, without any improvement in respiratory function. Gil et al.[108] described a case series of patients with clinically amyopathic dermatomyositis-ILD, including a patient with anti-MDA-5 antibodies who received MMF and intravenous immunoglobulins. The patient died of pneumonia 30 months after initial presentation.

Systemic lupus erythematosus

ILD can rarely complicate SLE,[129,130] and evidence for the treatment of SLE-ILD is of low quality, as no clinical trial or guidelines are available. A consensus conference on the management of SLE in 2015 proposed the use of MMF as induction therapy in association with corticosteroids in patients with lung involvement. MMF was also indicated as maintenance strategy or for the treatment of mild-to-moderate disease.[131] Only one case report described the use of MMF for SLE-related diffuse alveolar haemorrhage, with some efficacy as a maintenance therapy (no further diffuse alveolar haemorrhage episodes).[132] Only one of ten patients with CTD-ILD had a diagnosis of SLE in the case series by Saketkoo et al.,[68] while Fisher et al.[40] included four patients with SLE-ILD in their retrospective study.

Undifferentiated CTD

ILD can be a clinical manifestation of UCTD, even if the available classification criteria do not consider lung manifestations in UCTD.[133] The management of ILD-UCTD is usually based on immunosuppression, including MMF. However, no evidence-based therapeutic regimens are available to date.

Interstitial pneumonia with autoimmune features

IPAF is a clinical condition characterized primarily by ILD associated to other features (clinical, serological, and/or morphological) suggestive of a CTD that does not meet established classification criteria for a given autoimmune disease.[18] For IPAF, both the use of immunosuppressants[134–137] and antifibrotic agents[138–140] have been proposed. Unfortunately, to date, no controlled clinical trials are available to guide evidence-based therapeutic regimens. McCoy et al.[135] recently described a retrospective case–control series of 28 patients with IPAF exposed to MMF. Changes in FVC% and DLCO% between the MMF-treated and -untreated groups were not significantly different. In patients treated with MMF, FVC and DLCO slightly improved after exposure to the drug but without statistical significance.

ANCA-associated vasculitis

Pulmonary involvement is frequently observed in AAV patients, and ILD is an emerging possible phenotype. The

prevalence of ILD is higher in microscopic polyangiitis than in granulomatosis with polyangiitis, and anti-MPO antibodies are the main ANCA subtype associated to ILD. Lung fibrosis in oeosinophilic granulomatosis with polyangiitis or associated to anti-PR3 is rare.[141] Cases of patients positive for ANCA, mainly MPO-ANCA, without vasculitis and concomitant ILD have also been reported in the literature. Only retrospective case series and a few case reports have been published and no controlled clinical trials are available to guide the treatment of AAV-ILD or ANCA-positive ILD.

Despite contrasting data, standard treatment of systemic vasculitis is also considered for ILD and includes systemic glucocorticoids with or without immunosuppressants.[141,142] MMF is mainly used both as remission and maintenance therapy[143] and its efficacy was demonstrated in all the clinical aspects of AAV. Immunosuppressive agents, including MMF, are also considered for the treatment of NSIP pattern, despite the presence of systemic vasculitis.[141]

Sarcoidosis

Sarcoidosis is a granulomatous systemic disease of unknown aetiology. Pulmonary involvement is present in about 90% of cases. Usually, pulmonary sarcoidosis is self-limited and does not require treatment. However, some patients may develop chronic progressive pulmonary involvement with fibrotic alterations, requiring long-term therapy with CS and/or other immunosuppressants as CS-sparing agents.[144]

The effect of MMF on chronic pulmonary sarcoidosis has been poorly investigated. A retrospective study evaluated the effectiveness and safety of MMF in eight patients with both pulmonary and extrapulmonary sarcoidosis. A statistically significant improvement in FVC was reported, and symptoms and chest radiological findings improved in all patients.[145] On the contrary, another retrospective study of 37 patients with sarcoidosis found no statistically significant changes in PFT or DLCO measurements both before and after MMF therapy.[146] Finally, Brill et al.[147] retrospectively investigated the efficacy of MMF and systemic CSs in ten patients with biopsy-proven chronic pulmonary sarcoidosis. Pulmonary function, symptoms, and radiological signs improved in four patients, while six patients remained stable after 6 months.

Discussion

Although the pathogenesis of RD-related pulmonary disease is poorly understood, there is an assumption that it arises as a sequela of immune-mediated injury to the lung. As a result, immunosuppressive agents still represent the mainstay of treatment for RD-ILD.

MMF is an antimetabolite with a potent inhibitory effect on proliferation of T and B lymphocytes. MMF is well known and widely used since the early 1990s as immunosuppressant to treat oncologic disorders and to prevent acute allograft rejection after organ transplant.

As for other immunosuppressive agents in relation to RD-ILD, the use of MMF is supported by poor scientific evidence. Its efficacy has only been demonstrated by three RCTs in patients with SSc, with questionable results.[42,70,71] Furthermore, MMF is often used in association with CSs with high heterogeneity in drug dosages and timing, making it difficult to extrapolate efficacy data on the single drug. Of note, all patients evaluated in retrospective studies describing the use of MMF in mixed RD-ILD were treated with concomitant CSs.[39,40,67,68]

Numerous other therapies have been proposed for RD-ILD, including novel agents such as antifibrotics, and biologic and non-biologic disease-modifying antirheumatic drugs. Clinical trials are ongoing.[37,38] However, the manageable use of the 'old drug' MMF, its low rate of side-effects, the clinicians' decades of experience in its use in real life, and the lack of other evidence make MMF a preferred therapeutic option for the treatment of severe forms of RD-ILD. The decision to start therapy in patients with RD-ILD should be evaluated in the single patient, balancing comorbidities, the possible adverse effects of treatment, and disease prognosis in each patient.

Moreover, the immunosuppressants historically used for the treatment of ILD, such as MMF as well as CYC and AZA, are usually of low efficacy for the articular manifestations of most RD. CYC is widely used in the treatment of RD-ILD, and it is usually the first choice in patients with rapidly progressive ILD. A recent systematic review found that a small benefit may be derived from the use of CYC in CTD-ILD when compared with placebo but not when compared with MMF.[148] In particular, no significant impact on health-related quality of life, all-cause mortality, dyspnoea, or cough severity was found in the CYC group compared with the MMF group. Only four RCTs were included in the analysis, mostly on SSc, and the evidence was found to be of low quality as dropout rates were high in the intervention groups. Moreover, the risk of side-effects was increased with CYC *versus* MMF, in particular leukopenia and thrombocytopenia.

Among the disease-modifying antirheumatic drugs, the use of RTX has been suggested for RD-ILD, mainly in case reports and retrospective uncontrolled studies, showing encouraging short-term and long-term results with an acceptable safety profile.[37,38] Recently, Atienza-Mateo et al.[149] published a retrospective single centre study focusing on RTX in the treatment of RD-ILD. They found a sustained improvement in PFTs and a statistically significant increase in DLCO in patients treated with RTX, regardless of the radiological pattern or the underlying RD. However, only one RCT including eight patients with SSc-ILD[150,151] and a nested case–control study[152] have been published. No results from the RECOVER and RECITAL trials are yet available.[153,154]

The use of abatacept, tocilizumab, and Jak inhibitors for RD-ILD has also been proposed in anecdotal reports.[37,38,155–157]

Another point to consider is the wide spectrum of clinical phenotypes and the heterogeneity in disease behaviour of RD as well as of the pulmonary involvement in RD that does not allow us to make generalized dissertations on this topic. Different diseases may benefit from different therapeutic approaches or different timing of treatment. The clinical behaviour of pulmonary and extrapulmonary manifestation, the presence of comorbidities, and the potential adverse effects of treatments globally influence the therapeutic approach to the patient. Therefore, treatment should be based on the balance between possible benefits and burden of disease in each single patient. As a result, a multidisciplinary evaluation including at least a rheumatologist and pulmonologist, and possibly a radiologist, with expertise in ILD, is always recommended. A deeper knowledge on how to treat such patients requires clear insights into the pathogenesis of RD-ILD and the availability of RCTs – both needs are still unmet.

Conclusion

Further prospective, randomized, controlled clinical studies are required to better define the long-term efficacy and safety of MMF in patients with ILD associated to RD. They should be adequately powered to compare outcomes specifically within different subgroups and different diseases and stratified for histological subtype, disease duration, and extent of pulmonary involvement. Researchers may consider comparing MMF (as other immunosuppressants) *versus* other drugs such as antifibrotic agents, or comparing both *versus* placebo, in particular for those patients with evidence of rapidly progressive fibrotic disease.

Contributions: All authors contributed equally to the preparation of this review. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2020/12/dic.2020-8-8-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/efficacy-and-safety-of-mycophenolate-mofetil-in-the-treatment-of-rheumatic-disease-related-interstitial-lung-disease:-a-narrative-review

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Provenance: Invited; externally peer reviewed.

Submitted: 31 August 2020; **Accepted:** 26 November 2020; **Publication date:** 15 January 2021.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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