Mycophenolate mofetil is an effective and safe option for the management of systemic sclerosis-associated interstitial lung disease: results from the Australian Scleroderma Cohort Study

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ABSTRACT

Objective. *To report the efficacy and tolerability of mycophenolate mofetil (MMF) and azathioprine (AZA) in the management of systemic sclerosis-associated interstitial lung disease (SSc-ILD).*

Methods. *Patients in the Australian Scleroderma Cohort Study treated with at least 3 months of MMF or AZA for SSc-ILD confirmed on high resolution computed tomography (HRCT) chest were identified and their pulmonary function tests (PFTs) retrieved. Individuals with available results for T-1 (12 months prior to treatment commencement), T0 (date of treatment commencement) and at least one subsequent time point were included in the drug efficacy analysis. The Wilcoxon signed-rank test was used to compare absolute FVC at T-1, T0, 12 months (T1), 24 months (T2) and 36 months (T3). Analysis of drug tolerability included all identified patients treated with MMF or AZA.*

Results. *18/22 patients treated with MMF and 29/49 treated with AZA had adequate PFTs for inclusion in the drug efficacy analysis. Median absolute FVC at T-1 for MMF treatment was 2.50L, declining to 2.12L at T0 (p=0.02). Following MMF therapy, FVC results were stable at T1 (2.13L, p=0.86), T2 (2.17L, p=0.65) and T3 (2.25L, p=0.78). In the AZA group, a statistically significant decline did not occur prior to treatment, however FVC results remained stable at T1, T2 and T3.*

Adverse events leading to early discontinuation (<12 months treatment) were less common in the MMF group (4/22 vs. 13/49). Gastrointestinal complications were the main cause of discontinuation in both groups.

Conclusion. *In patients with SSc-ILD with declining pulmonary function, MMF therapy was associated with stability for up to 36 months. Early adverse events leading to discontinuation occurred less frequently in patients treated with MMF than in AZA treated patients.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by endothelial dysfunction and immune dysregulation that ultimately results in microvascular complications and excessive collagen deposition involving multiple organs including the skin.

Interstitial lung disease (ILD) occurs commonly in SSc and can affect patients with both diffuse and limited disease. ILD typically occurs early following a diagnosis of SSc and can be predicted by the presence of anti-topoisomerase antibodies (1-3). Whilst the vast majority of SSc-ILD patients have pulmonary function test abnormalities, many have mild, stable disease that does not require treatment (4). At least 40% do have a moderately severe, progressive course which can result in death due to respiratory failure, secondary pulmonary hypertension and infection (1). Predictors of disease progression include extensive baseline fibrosis on high resolution computed tomography (HRCT) chest, baseline forced vital capacity (FVC) <70% and an annual decline in FVC >10% (4-6).

Despite advances in the treatment of other SSc-related complications including renal crisis and pulmonary arterial hypertension, effective therapies for ILD and diffuse skin disease remain elusive. For the past two decades, cyclophosphamide (CYC) has been utilised as first-line treatment for SSc-ILD. The results of two prospective, randomised, placebo-controlled studies of CYC in SSc-ILD were disappointing with only modest benefit of questionable clinical

significance (7, 8). In the Scleroderma Lung Study I, a sustained benefit over placebo could not be demonstrated at two years, despite a modest improvement of 2.53% in the mean absolute difference in FVC following 12 months of oral CYC therapy. Substantial toxicity was also reported in the oral CYC group (9). Similarly, the Fibrosing Alveolitis in Scleroderma Trial (FAST) which compared monthly intravenous infusions of CYC for six months followed by six months of oral azathioprine (AZA) with placebo found a mean increase in FVC of only 4.19% that failed to reach statistical significance (8).

Mycophenolate mofetil (MMF) is an inosine monophosphate dehydrogenase inhibitor, which reduces T- and B-cell proliferation through a reduction in purine synthesis (10). In systemic lupus erythematosus, MMF has been demonstrated to be an effective alternative to CYC for the management of nephritis without the associated toxicities of amenorrhea, haemorrhagic cystitis and malignancy (12). Since 2006, case reports and small case series of up to 17 patients with SSc-ILD have consistently described favourable outcomes in patients treated with MMF (10-17). More recently, Fischer *et al*. demonstrated sustained improvement in FVC and reduced glucocorticoid requirements in a diverse cohort of 125 patients with connective tissue disease-associated ILD including 44 individuals with SSc (18). The uncontrolled and largely retrospective nature of these studies however, along with the inclusion of patients with heterogeneous disease severity limits the conclusions that can be drawn.

In this study, we sought to assess the efficacy and tolerability of MMF and AZA in SSc-ILD. In particular, the viability of MMF as an alternative therapy to AZA, which is commonly utilised for maintenance therapy following initial treatment with CYC, was examined. Prospectively collected data from a national SSc research cohort were analysed for this purpose.

Methods

Patients

The Australian Scleroderma Cohort Study (ASCS) is a longitudinal cohort study that prospectively records cardiopulmonary complications and outcomes of therapy in SSc. Patients over 18 years of age with a diagnosis of SSc according to the American College of Rheumatology criteria (19) are recruited from community and hospital rheumatology practices throughout Australia. Following informed consent, demographic, clinical, laboratory (including pathology, pulmonary function tests (PFTs), HRCT of the chest and echocardiography) and treatment variables are collected annually, according to a standardised protocol. The ACSC was approved by the relevant human research ethics committees at each of the participating centres.

Demographic, clinical, laboratory and treatment variables

The ASCS database was searched to identify all patients treated with at least three months of MMF or AZA for SSc-ILD since its inception in 2007. The age, sex, race, smoking history, disease duration (time since first non-Raynaud's symptom) and SSc subtype according to the Le Roy and Medsger criteria (20) of these individuals was also retrieved. Other treatments for SSc-ILD (including mean dose and duration) and the reason for MMF or AZA cessation where applicable (including inefficacy and adverse events) were obtained by chart review for all identified patients.

SSc-ILD was defined as the presence of interstitial abnormalities on HRCT of the chest or by lung biopsy. PFTs (absolute and percent predicted FVC and diffusion capacity for carbon monoxide [DLCO] values) recorded at six monthly intervals were retrieved from the relevant centres. According to the start date of MMF or AZA, time points were allocated as follows:

- T-1 – 12 months prior to treatment commencement;
- T0 – date of treatment commencement;
- T1 – 12 months post treatment commencement;
- T2 – 24 months post treatment commencement;
- T3 – 36 months post treatment commencement.

Individuals treated with MMF or AZA and possessing PFTs corresponding to T-1, T0 and at least one subsequent time point were included in the analysis of drug efficacy. In the event that a patient had been treated with both MMF and AZA for SSc-ILD, the individual was grouped according to the most recent treatment received. Data were censored at 1/11/12 for analysis.

Statistical analyses

Patient characteristics are reported as mean ± standard deviation (SD) or median (interquartile range) for continuous variables and proportions (percentages) for categorical variables. The Wilcoxon signed-rank test was used to compare median FVC and DLCO at T-1, T0, T1, T2 and T3. Differences were considered significant at the $p \leq 0.05$ level.

To facilitate additional analyses of the trend in absolute FVC between time points among individual patients taking MMF or AZA, stability was defined as <10% change, whilst ≥10% increase or decrease defined improvement or decline respectively.

All statistical analyses were performed using STATA 12.0 (Statcorp, College Station, TX, USA).

Results

Patient demographics

Twenty-two patients treated with at least three months of MMF for SSc-ILD were identified, of whom 18 had sufficient PFTs recorded for inclusion in the efficacy study. For AZA treatment, 49 patients were initially identified with 29 subsequently included. The demographic data of the 18 patients treated with MMF and 29 treated with AZA for SSc-ILD are summarised in Table I. The mean age at commencement was 55.3±9.3 years for MMF and 54.1±12.2 years for AZA (p=0.72). Patients in both groups were predominantly female (77.8% for MMF vs. 79.3% for AZA, p=0.90) and Caucasian (77.8% for MMF vs. 82.8% for AZA, p=0.67). Fourteen (77.8%) of the patients treated with MMF were lifelong non-smokers, compared with 14 patients (48.3%) in the AZA group (p=0.04). There were few current smokers in the study popu-

Table I. Baseline characteristics for patients taking MMF compared to AZA.

	MMF (n=18)	AZA (n=29)	*p*-value
Mean age at commencement (Years)	55.3 ± 9.3	54.1 ± 12.2	0.72
Female	14 (77.8%)	23 (79.3%)	0.90
Caucasian	14 (77.8%)	40 (82.8%)	0.67
Diffuse disease	11 (61.1%)	15 (51.7%)	0.53
Disease duration (Years)	6.3 ± 3.7	7.1 ± 7.8	0.69
SSc-ILD duration (Years)	3.8 ± 4.9	2.8 ± 3.0	0.41
Lifelong non-Smokers	14 (77.8%)	14 (48.3%)	**0.04**
Previous CYC	14 (77.8%)	22 (75.9%)	0.88
Median FVC at baseline (L)	2.12 (1.92, 2.47)	2.51 (2.29, 2.92)	0.06
Median DLCO at baseline (L)	9.55 (7.71, 12.55)	10.70 (9.24, 14.0)	0.18

MMF: mycophenolate mofetil; AZA: azathioprine; SSc-ILD: scleroderma-associated interstitial lung disease; CYC: cyclophosphamide; FVC: forced vital capacity; DLCO: diffusion capacity.

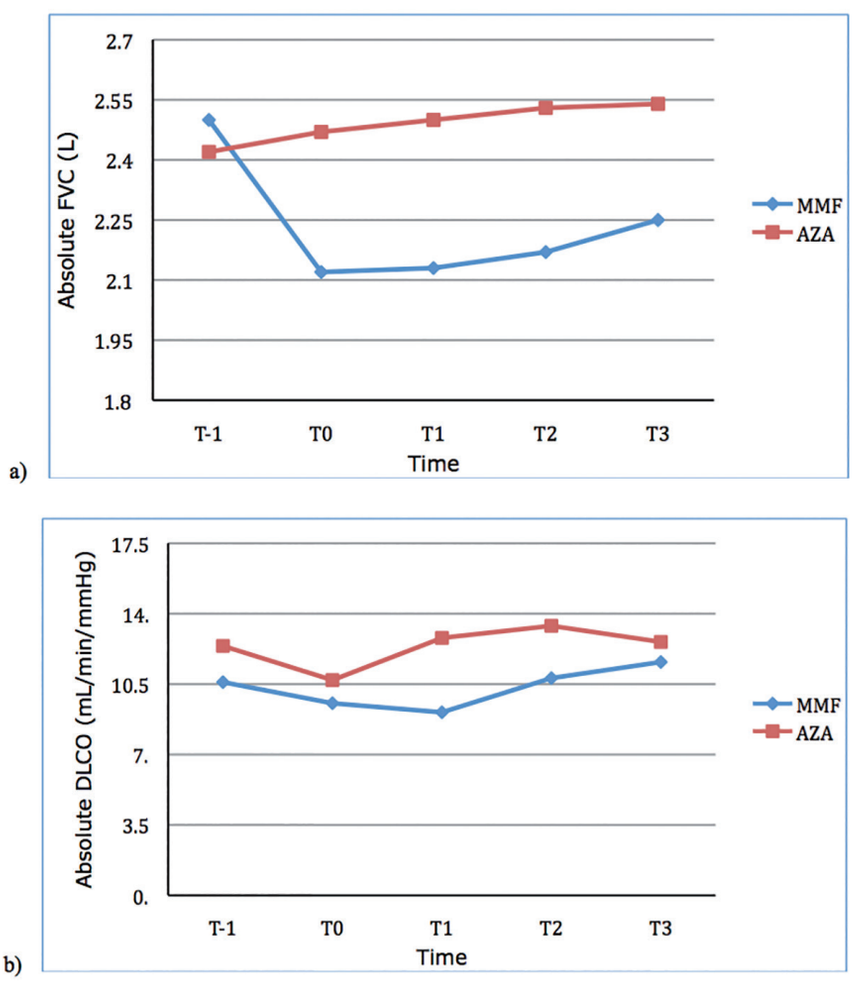

Fig. 1. **a**) Median absolute FVC and **b**) DLCO from T-1 to T3 of MMF and AZA treatment. MMF: mycophenolate mofetil; AZA: azathioprine; FVC: forced vital capacity; DLCO: diffusion capacity for carbon monoxide; T-1: 12 months prior to treatment commencement; T0: date of treatment commencement; T1: 12 months post treatment commencement; T2: 24 months post treatment commencement; T3: 36 months post treatment commencement.

lation (1/18 [5.6%] for MMF and 2/29 [6.9%] for AZA, *p*=0.85).

No significant difference between the groups with respect to SSc disease duration was identified (6.3±3.7 years for MMF and 7.1±7.8 for AZA, *p*=0.69). SSc-ILD duration was 3.8±4.9 years for MMF and 2.8±3.0 for AZA (*p*=0.41). Disease subtype was classified as diffuse in 61.1% of patients taking MMF and 51.7% taking AZA (*p*=0.53). The median FVC result was higher in the AZA group (2.51L) at baseline compared with the MMF group (2.12L) with a trend towards statistical significance [*p*=0.06]). One patient (5.6%) in the MMF group had concomitant pulmonary arterial hypertension diagnosed on right heart catheterisation, compared with six (20.7%) in the AZA group. A statistically significant difference in median DLCO results at baseline was not found however (10.60L for MMF and 12.4L for AZA [*p*=0.18]).

The mean dose for MMF was 1.58g/day (median 2g/day) and 90.74mg/day for AZA (median 100mg/day). Mean treatment duration with MMF was 3.5±1.5 years and 4.5±3.0 years for AZA (*p*=0.20). SSc-ILD was the indication for MMF or AZA therapy in all cases, however one patient in the AZA group was also being concurrently treated for Crohn's disease.

Previous treatment

Only four patients (22.2%) received MMF as *de novo* treatment for SSc-ILD. Fourteen of 18 patients (77.8%) in the MMF group had received prior CYC, ten of these intravenously with a mean cumulative dose of 6.53g. The remaining four received oral treatment with a mean cumulative dose of 46.25g. Four patients (22.2%) included in the MMF group had been treated with AZA previously.

By comparison, 22/29 (75.9%) in the AZA group had been previously treated with CYC; nineteen with intravenous (mean cumulative dose 5.4g) and five with oral therapy (mean cumulative dose 25.95g). Two patients in the AZA group had received treatment with both intravenous and oral CYC.

Concurrent treatment

Seventeen patients (94.4%) in the MMF group and 24 patients (82.76%) in the AZA group had been concurrently treated with prednisolone (mean dose 8.22mg/day and 7.63mg/day respectively).

Pulmonary function

Median absolute FVC 12 months prior to MMF treatment (T-1) was 2.50L

(2.05, 2.83), declining to 2.12L (1.92, 2.47) at baseline (T0) (p=0.02) (Fig. 1a). At T1, FVC was stable at 2.13L (1.79, 2.56 [p=0.86]). Similar results were seen at T2 and T3 with FVC at 2.17L (1.78, 2.54 [p=0.65]) and 2.25L (1.84, 3.19 [p=0.78]) respectively, albeit in a smaller number of patients.

Median DLCO also trended toward decline prior to MMF treatment from 10.60L (8.43, 14.45) at T-1 to 9.55L (7.71, 12.55) at T0 (p=0.07) (Fig. 1b). Relative stability was seen at T1 with DLCO at 9.10L (7.52, 13.50, [p=0.84]), and again at T2 (10.8L [8.5, 14.5], p=0.31) and T3 (11.6 [9.1, 14.2], p=0.34).

In the AZA group, median absolute FVC did not demonstrate a statistically significant decline prior to treatment from T-1 (2.50L [2.0, 2.73]) to T0 (2.51L [2.29, 2.92], p=0.24). Results at T1 (2.54L [1.91, 3.02], p=0.09), T2 (2.55L [1.91, 3.0], p=0.76) and T3 (2.47 [1.98, 3.01], p=0.44) were stable. Median absolute DLCO did decline however prior to AZA treatment from 12.60 (9.90, 15.0) at T-1 to 10.70 (9.24, 14.0) at T0 (p=0.07). Again, relative stability was seen at T1 (12.80 [7.80, 13.6], p=0.34), T2 (13.4 [10.8, 15.5], p=0.55) and T3 (12.6 [8.9, 17.0], p=0.15).

With respect to the trend in absolute FVC among individual patients treated with MMF, stability or improvement was seen in 13/16 (81.2%) patients at T1 (Table II). Similarly, MMF was associated with stability or improvement in absolute FVC in 9/10 (90.0%) patients at T2 and 6/8 (75.0%) patients at T3.

Similar efficacy was observed with AZA. Stability or improvement was seen in 11/13 (84.6%) patients at T1, 9/13 (69.2%) patients at T2 and 9/10 (90%) patients at T3 (Table II).

Drug tolerability

The number of adverse events leading to discontinuation after 12 months treatment for SSc-ILD with MMF or AZA was similar (3/18 [16.6%] vs. 4/29 [13.8%]). When the analysis was extended to include all patients who had received a minimum of 3 months treatment with MMF or AZA, 4/22 (18.2%) in the MMF group compared with 13/49 (26.5%) in the AZA group had experienced an early adverse event resulting in discontinuation.

Reasons for cessation of MMF included gastrointestinal complications (5) and infection (2) as outlined in Table III. In the AZA group, gastrointestinal complications were the most common adverse event (7), followed by abnormal liver function tests (2) and cytopenias (2).

Patient deaths

Two patients (11.1%) were deceased in the MMF group at the time of analysis, compared with three (10.3%) in the AZA group. Acute respiratory failure was the cause of both MMF patient deaths; however, one of these individuals was a smoker who had also previously failed treatment with CYC and AZA for SSc-ILD. Lung cancer was responsible for two deaths after AZA treatment, with the remaining death in this group attributed to respiratory failure.

Table II. Trend in individual absolute FVC following 12, 24 and 36 months treatment with MMF compared to AZA.

	Improvement	Stability	Decline
MMF:			
T1	3/16 (18.5%)	10/16 (62.5%)	3/16 (18.7%)
T2	2/10 (20.0%)	7/10 (70.0%)	1/10 (10.0%)
T3	1/8 (12.5%)	5/8 (62.5%)	2/8 (25.0%)
AZA:			
T1	3/13 (23.1%)	8/13 (61.5%)	2/13 (15.4%)
T2	3/13 (23.1%)	6/13 (46.1%)	4/13 (30.8%)
T3	3/10 (30.0%)	6/10 (60.0%)	1/10 (10.0%)

MMF: mycophenolate mofetil; AZA: azathioprine; T-1: 12 months prior to treatment commencement; T0: date of treatment commencement; T1: 12 months post treatment commencement; T2: 24 months post treatment commencement; T3: 36 months post treatment commencement.

Table III. Adverse events leading to discontinuation for patients taking MMF compared to AZA.

Adverse event	MMF		AZA	
	Minimum 3 months treatment (n=4/22)	Minimum 12 months treatment (n=3/18)	Minimum 3 months treatment (n=13/49)	Minimum 12 months treatment (n=4/29)
Gastrointestinal	3 (13.6%)	2 (11.1%)	5 (10.2%)	2 (6.89%)
Abnormal LFTs			2 (4.1%)	
Cytopenias			2 (4.1%)	
Infection	1 (4.5%)	1 (5.5%)	1 (2.0%)	
Skin Rash			1 (2.0%)	1 (3.4%)
Skin Cancer			1 (2.0%)	1 (3.4%)
Alopecia		1 (2.0%)		
TOTAL %	18.2%	16.6%	26.5%	13.8%

MMF: mycophenolate mofetil; AZA: azathioprine; LFTs: liver function tests.

Discussion

We have examined the effect of MMF on the pulmonary function of 18 patients with SSc-ILD and compared their outcomes with those of 29 patients from the same cohort who were treated with AZA. The majority of patients in both groups were treated with MMF or AZA as maintenance therapy following initial treatment with CYC, reflecting standard clinical practice. In patients with declining pulmonary function treated with MMF, stabilisation was seen with no significant deterioration in median FVC or DLCO at 12 and 24 months. In a smaller subgroup of eight patients, stability was maintained after 36 months of MMF treatment. Further analysis of individual patient outcomes similarly demonstrated that 13/16 (81.2%), 9/10 (90%) and 6/8 (75%) patients in the MMF group achieved pulmonary function that was improved or stable at 12, 24 and 36 months respectively.

Although there was no placebo control group in this study, the stability achieved by the patients treated with MMF is noteworthy. Recent long-term outcome data from the Scleroderma Lung Study found only 14% of patients alive and free of significant physical impairment or organ failure at 11 years (21). The authors concluded that a 12-month course of oral CYC failed to achieve sustained improvement in pulmonary function. Similarly, a mean annual rate of decline in FVC of 4% and DLCO of 8% was observed in the placebo arm of the same study (22). Extensive disease and a decline in FVC of 10% or DLCO of 15% have additionally been identified as poor prognostic factors (5, 6, 23, 24). Therefore, we firmly believe the achievement of stability in this group of SSc-ILD patients with declining pulmonary function represents a good outcome.

A decline in FVC was not observed in the AZA group in the 12 months prior to treatment commencement. Whilst the absence of declining pulmonary function prior to treatment with AZA may reflect the benefits of prednisolone and CYC therapy during this period, it seems likely that the patients treated with AZA had less progressive disease than those who received MMF. Indeed, the median absolute FVC was lower at baseline in the MMF group (2.12L vs. 2.50L for AZA), with a p-value that approached significance (p=0.06) despite small participant numbers. Previous studies indicate that the rate of pulmonary function decline in SSc-ILD is typically greatest in the first four years following diagnosis (1). Given the long mean disease (6.3±3.7 years for MMF vs. 7.1±7.8 years for AZA, p=0.69) and ILD (3.8±4.9 years for MMF and 2.8±3.0 for AZA) duration in both groups and non-statistically significant differences in these parameters, this factor also fails to explain the absence of declining pulmonary function in the 12 months prior to AZA commencement. Consequently, in contrast to treatment with MMF where stability was demonstrated in progressive disease, conclusions regarding the efficacy of AZA in SSc-ILD patients with declining pulmonary function cannot be drawn from our study.

This is the first study in which the efficacy and tolerability of MMF and AZA has been reported in patients from the same cohort being treated for SSc-ILD. Not only do our results substantiate MMF as a viable treatment for SSc-ILD, but we similarly found it was better tolerated in the first 12 months following commencement than AZA. Only 4/22 (18.2%) patients treated with MMF discontinued therapy due to an early adverse event compared with 13/49 (26.5%) in the AZA group. Patients who received less than 3 months treatment with MMF or AZA were not included in the study however, as a significant change in pulmonary function was not expected. Future analysis of this group may yield further information regarding the tolerability of MMF and AZA in the first 3 months following commencement.

Adverse events associated with AZA treatment included abnormal liver function and cytopenias, with one patient also developing a non-melanoma skin cancer. Two patients in the AZA group later died from lung cancer, although the contribution of immunosuppression to the development of this malignancy remains unclear. Gastrointestinal adverse events were the most common cause of discontinuation both before and after 12 months of treatment. It should be noted though that SSc patients commonly experience gastrointestinal symptoms due to the disease affecting their gut. In a study of 14 SSc-ILD patients treated with an alternative mycophenolate preparation (mycophenolate sodium), stability of lung function was achieved without any patients discontinuing therapy due to gastrointestinal adverse events (25). The lack of sustained benefit and unacceptably high toxicity associated with greater than 12 months of treatment with CYC highlight the need for a well-tolerated maintenance therapy in SSc-ILD. Results from our study concur with numerous retrospective and several prospective case series, but also provide further evidence to support the use of MMF by demonstrating stability of pulmonary function in SSc-ILD for up to 36 months and a lesser rate of early adverse events than maintenance AZA. (10-17) Given that recent preliminary data from the Scleroderma Lung Study II published in abstract form has suggested MMF may have comparable efficacy to oral CYC as *de novo* therapy for SSc-ILD, there is now even greater incentive to utilise this agent (26). Moreover, MMF has been previously demonstrated to improve histology on skin biopsy and Rodnan skin scores in diffuse scleroderma, thus offering additional benefits to those patients with concomitant progressive skin and lung fibrosis (27).

There are a number of limitations to our study. Firstly, as the majority of patients in both groups had received initial treatment with intravenous CYC, it is impossible to be certain that the stability observed is attributable to MMF and AZA. That said, sustained stabilisation of pulmonary function beyond 12 months has not been demonstrated following CYC therapy alone (21). Furthermore, a decline in pulmonary function was noted in the MMF group during treatment with CYC, with improvement or stabilisation observed following the commencement of MMF.

A lower mean dose of MMF (1.58 g/day) in this study than that utilised in standard clinical practice may have influenced the results. Typically, we commence MMF at a dose of 500mg/day and gradually up-titrate to 2g/day. Notably, other studies have used MMF doses of up to 3 g/day without significant additional toxicity (18, 26). It is therefore possible that higher doses of MMF may be associated with greater efficacy than that demonstrated in our study.

The use of MMF as *de novo* therapy for SSc-ILD could not be assessed in this study as only four patients had not previously received CYC treatment. It is our practice to use MMF alone in patients with less progressive SSc-ILD, particularly in the elderly in whom the risk of infection with CYC is substantial and in young females in whom preservation of ovarian function is desirable.

The impact of MMF upon concurrent oral prednisolone requirements is simi-

larly unclear. Whilst MMF treatment has been associated with a reduction in median prednisolone dose in previous studies (18) and many individual patients in our cohort were able to significantly reduce their prednisolone dose following treatment, a formal analysis of MMF's steroid sparing capability was not possible in this instance due to incomplete data regarding prednisolone dose.

Our study involved a comparison of patients from the same cohort treated with MMF and AZA for SSc-ILD. Unfortunately, the number of patients in both groups in whom complete data was available was small, and individuals were not randomised to treatment, nor age- and sex-matched. Nonetheless, there were no statistically significant differences in the age, sex, race, disease duration or SSc subtype between the two groups. There was however a higher number of lifelong non-smokers and fewer patients with concomitant pulmonary arterial hypertension among the patients treated with MMF. DLCO is recognised to be lower in cigarette smokers and pulmonary arterial hypertension (28, 29), but as the median DLCO at baseline was not significantly lower in the AZA group (12.4L for AZA cf. 10.60L for MMF [p=0.18]), the impact of these variables are likely to be minimal. On the other hand, the median absolute FVC was lower at baseline (2.12L *vs*. 2.50L for AZA [p=0.06]) and had declined in the 12 months prior to treatment in the MMF group (2.50L at T-1 to 2.12L at T0 [p=0.02]). Despite this, stability of pulmonary function was still maintained with MMF treatment for up to 36 months.

Finally, whilst patients were recruited from a multicentre SSc cohort study where data were collected prospectively and systematically, information regarding other treatments for SSc-ILD and the reason for MMF or AZA cessation where applicable (including inefficacy and adverse events) were retrieved by the treating physician at each centre conducting a retrospective chart review. This may have resulted in variable reporting and consequently introduced reporting bias. Similarly, the choice of agent utilised to treat SSc-ILD was determined by the treating rheumatologist at each centre and may have been unduly influenced by factors such as the accessibility and cost of MMF. Until recently, MMF was not subsidised for this indication on the pharmaceutical benefits scheme (PBS) in Australia and was either privately funded or accessed on a compassionate basis. Recent listing on the PBS is anticipated to improve access to this therapy in the future.

In conclusion, MMF appears to be a safe and well-tolerated therapy for SSc-ILD which is capable of achieving stability in patients with declining pulmonary function. When compared with AZA, MMF is associated with lower rates of early adverse events and discontinuation. Given the disappointing long-term efficacy results from studies of CYC and its known toxicity, the role of MMF for both de novo and maintenance therapy in SSc-ILD warrants further study in larger, prospective, controlled trials.

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