ORIGINAL ARTICLES

Effectiveness and safety of mycophenolate mofetil in connective tissue disorder associated interstitial lung disease: A real-life experience from India

Sham Santhanam [1], Vijil Rahulan[2], Apar Jindal[2]

[1]Department of Rheumatology,Gleneagles global Health City, Chennai, India
[2]Department of Pulmonology, Gleneagles global Health City, Chennai, India

Abstract

Aim: To study the effectiveness and safety of mycophenolate mofetil (MMF) in patients with connective tissue disease (CTD) associated interstitial lung disease (ILD).

Methods: The retrospective observational study was carried out from Jan 2015 to Feb 2019. Symptomatic CTD-LD patients with (HRCT chest) documented ILD and abnormal pulmonary function test (forced vital capacity, FVC< 70%), who were treated with MMF were included. The treatment response was assessed clinically by pulmonary function test and radiology. Clinical assessment and PFT were done at baseline, 6, 12 and 24 months. HRCT chest was done at baseline and 24 months.

Results and analysis: Out of 33 patients, 13 had MCTD, 12 had RA, and remaining 8 belonged to the systemic sclerosis (SSc)-predominant groups (3: diffuse cutaneous SSc, 2: SSc/myositis overlap, and 1 each with Sjogren's syndrome, SLE/ Sjogren's overlap and interstitial pneumonia with autoimmune features). Increased female predominance was noted (90.9%). The mean FVC at baseline noted in MCTD, RA and SSc-predominant groups were 62±6.17, 64±4.17 and 59±6 respectively. Improvement was reported in 4 patients, each in MCTD and RA groups. Eight patients in the MCTD group and 7 each in RA and SSc- predominant groups had a stable lung disease. One patient each in all the groups reported worsening of the disease. There was a positive trend in FEV1 and FVC with treatment. No significant difference in FEV1 and FVC values with treatment was noted across the three groups. Numerical differences in the mean values of FEV1 and FVC between two groups (NSIP and UIP) were noted, but was not statistically significant. All the subjects completed 24 months of follow-up. They were on 2 g/day of MMF for the first 12 months, followed by a maintenance of 1.5- 2 g/day for the next 12 months. None of the subjects discontinued treatment due to intolerance or adverse effects.

Conclusion

MMF was safe, effective and well tolerated. Treatment with MMF over 24 months stabilized the ILD in majority, improved in certain cases and rarely worsened.

Key words: Mycophenolate mofetil, MMF, connective tissue disorder, interstitial lung disease, CTD, ILD, efficacy, safety

Introduction

Interstitial lung disease (ILD) is one of the most common extra-articular manifestations of various connective tissue disorders (CTD) including systemic sclerosis (SSc), mixed connective tissue disorder (MCTD), and rheumatoid arthritis (RA).[1] The presence of ILD is associated with increased mortality and poor prognosis. Some of the poor prognostic factors are male gender, smoking, older age and usual interstitial pneumonia (UIP) pattern.[2] Patients with SSc-ILD had increased mortality in comparison to RA-ILD.[2] We have limited evidence on the drugs used, except for ILD in SSc and the results of the same has been extrapolated to other CTD.

Mycophenolate mofetil (MMF) has antiproliferative and anti-fibrotic action, in addition to anti-inflammatory

properties. The retrospective case series by Swigris *et al.* and Fischer *et al.* corroborated that MMF is a safe and effective alternative to cyclophosphamide.[3,4] Both the study cohorts had a diffuse spectrum of CTD- ILD patients, with majority of cases being SSc- ILD. Evidence from the Scleroderma Lung Study 2, has concluded on the efficacy, tolerability and safety profile of MMF.[5]

However, there is no adequate Indian data on treatment of CTD-ILD. [6-9] Though ILD is a relatively common extra-articular manifestation, most of the studies have been conducted on SSc-ILD. A single-centre retrospective observational study by Shenoy *et al.* found that the effectiveness of both cyclophosphamide and MMF for managing SSc-ILD is comparable.[6] Naidu *et al.* could not find any major improvement in mildly impaired lung function following the use of MMF in SSc-ILD.[7] Similarly, another randomised controlled trial (RCT) found no major difference upon comparison of pirfenidone with placebo in SSc-ILD.[8]

The present study was aimed to evaluate the effectiveness, safety and tolerability of MMF in an Indian cohort diagnosed with CTD-ILD. The type of synthetic DMARDs used in patients with MCTD and RA was also evaluated, as it is always challenging to manage patients with both active arthritis and ILD.

Materials and methodology

The retrospective observational study was carried out at a tertiary care centre between January 2015 and February 2019. All the outpatient electronic medical records with a diagnosis of CTD-ILD were screened . Symptomatic patients with documented ILD through high resolution computed tomography (HRCT) chest and abnormal pulmonary function test (PFT) were included. All patients underwent detailed clinical assessment, serological investigations (baseline blood tests, ESR, CRP, RF, ACPA, ANA, ANA profile, complements), urine routine, PFT HRCT chest and echocardiogram. A multi-disciplinary team comprising of rheumatologist, pulmonologist and radiologist was involved in the management of these patients.

As per the department protocol, clinical assessment and PFT were done at baseline, 6, 12 and 24 months. HRCT chest was done at baseline, 12 and 24 months. Other blood investigations (hemogram, ESR, CRP, serum creatinine, SGPT/SGOT, RBS) were done once in 2 months for routine monitoring of disease activity and side effects. The dose of MMF was 2 grams/day, continued for the initial 12 months, followed by maintenance of 1.5 - 2 grams/day over the next 12 months. All patients (except for diffuse cutaneous SSc) were started on steroids, with 0.5 mg/kg/day initially and tapered over 3-6 months. Ethical committee permission was obtained.

The response of ILD to treatment was assessed clinically by PFT and radiologically (subjective: eye balling). The study also evaluated the various drugs used for arthritis, side effects, compliance and vaccination status of these patients. Improvement was assessed clinically by New York Heart Association (NYHA) grading of breathlessness and for HRCT chest by pulmonologist and radiologist opinion (eyeballing method). Increase/decrease in FVC by 10% was noted for evaluating the improvement/ deterioration in PFT (from the baseline FVC value). Improvement in all the three domains and the same for worsening have been considered for evaluation. Patients who improved clinically and/or by PFT with no radiological progression were considered as stable.

Statistical analysis

For discrete data, proportion was computed and the mean (standard deviation) and median (interquartile range) were computed for the continuous data. For comparison of two population means, paired ‘t’ test was used. One way analysis of variance (ANOVA) was used to find out the statistical difference between the mean of three independent groups.

Results and analysis

Out of 54 patients diagnosed with CTD-ILD, 33 patients were on MMF (32 patients as 1st line and 1 patient as 2nd line due to poor response to azathioprine). For analysis, the patients were divided into three groups based on the number of patients in each disease group.

Among the 33 patients, 13 had MCTD, 12 had RA and remaining 8 were categorized into the third SSc-predominant group (3: diffuse cutaneous systemic sclerosis, 2: systemic sclerosis/myositis overlap, 1 each with Sjogren’s syndrome, SLE/Sjogren’s overlap and interstitial pneumonia with autoimmune features [IPAF]). The patient with IPAF was a 33-year-old female with NSIP pattern of ILD and anti Scl-70 antibody positivity. The third group had patients predominant with SSc spectrum of diseases.

Table 1: Comparing the baseline characteristics and pattern of ILD of the three disease groups

Diseases (n = 33)	Females : Males	Mean Age (S.D)	Median disease duration (months)	P value	
				NSIP	UIP
MCTD (n = 13)	All 13 - Females	44.63 (10.97)	60	10	3
RA (n = 12)	9 : 3	61.69 (9.79)	72	7	5
Others (n = 8)	All 8 - Females	51.37 (11.17)	42	7	1

MCTD: mixed connective tissue disorder; RA: rheumatoid arthritis; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia

Table 2: The mean FEV1 and FVC values at baseline, 6, 12 and 24 months and the treatment response of ILD of the three disease groups

Variables	Mean FEV1 FEV1% (S.D)				Mean FVC FVC % (S.D)				ILD after treatment		
	Baseline	6 months	12 months	24 months	Baseline	6 months	12 months	24 months	Improved	Stable	Worsened
MCTD **(n = 13)**	65 (5.89)	65 (6.57)	67 (7.17)	68 (7.32)	62 (6.17)	63 (8.24)	64 (8.62)	65 (6.51)	4	8	1
RA (n = 12)	62 (6.85)	65 (6.47)	65 (7.41)	65 (8.41	64 (4.19)	65 (4.69)	65 (4.27)	65 (4.89)	4	7	1
Others (n = 8)	60 (7.17)	62 (9.22)	63 (6.9)	64 (9.64	59 (6)	60 (6.48)	61 (6.1)	62 (5.64%)	0	7	1

MCTD: mixed connective tissue disorder; RA: rheumatoid arthritis; ILD: Interstitial lung disease; FEV1: forced expiratory volume; FVC: forced vital capacity

The baseline characteristics of the three groups of patients and the ILD pattern has been briefed in Table 1. All the patients had completed 24 months follow-up. Majority of the patients were females. NSIP pattern was predominant in the MCTD and SSc predominant group, unlike in RA with nearly equal NSIP and UIP pattern. The mean FEV1 and FVC values over various periods of follow-up and the treatment outcome have been briefed in table 2. In all the three groups, there was a positive trend in FVC, either as stabilization or improvement of lung function.

The study categorized patients into the following 3 groups, according to the baseline FVC:

- FVC (60 - 69%) - [MCTD 9 (7 NSIP; 2 UIP); RA 9 (5 NSIP; 4 UIP); OTHERS 4(4 UIP)]
- FVC (50 - 59%) - [MCTD 3(3 NSIP); RA 3 (1 NSIP; 2 UIP); OTHERS 3 (2 NSIP; 1 UIP)]
- FVC (40 - 49%) - [MCTD 1(1 UIP); RA 0; OTHERS 1 (1 UIP)]

Among the groups, all patients with improvement had NSIP pattern and among those with disease worsening, 2 had UIP and 1 had NSIP pattern. Patients with improvement in PFT showed both clinical and radiological improvement. Though there were numerical differences in the mean values of FEV1 and FVC between the two groups (NSIP and UIP), it was not statistically significant (paired ‘t ‘test, P >0.05). There was no significant difference in FEV1 and FVC values with regard to treatment across the three groups (MCTD vs. RA vs. SSc predominant, one-way ANOVA test). There was a positive trend in FEV1 and FVC

Fig. 1a and 1b: Trend of FVC for patients at baseline, 6, 12 and 24 months

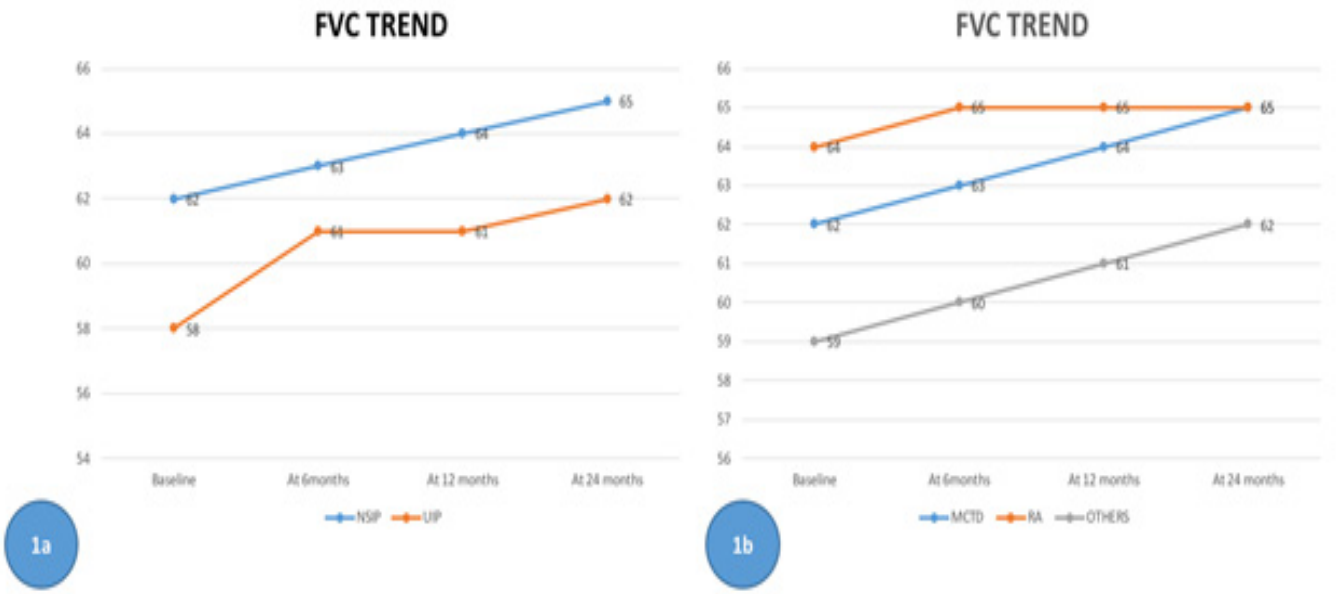

Fig. 1a: Trend of FVC for patients with NSIP and UIP pattern of ILD at baseline, 6, 12 and 24 months. Figure 1b: Trend of FVC for the three disease (MCTD, RA, Others) groups at baseline, 6, 12 and 24 months.

with treatment and majority of the patients either stabilized or improved with treatment. The trend of FVC with treatment over a period of 2 years with respect to ILD pattern and the disease groups is depicted in figure 1a and 1b.

The study has also evaluated the drugs used for arthritis in MCTD (n = 13) and RA (n = 12). Fourteen patients were on sulfasalazine, 7 on hydroxychloroquine, 6 on combination of sulfasalazine and hydroxychloroquine, 4 on methotrexate and 2 on leflunomide.

All patients, except one had demonstrated tolerance to 2g/day of MMF. One patient with gastrointestinal intolerance was changed to enteric-coated preparation of MMF and tolerated the full dose of 1440 mg/day. Among the 33 patients, 25 were vaccinated with influenza and pneumococcal vaccines. One patient with rheumatoid arthritis and ILD (NSIP pattern) was admitted for pneumococcal pneumonia. Along with MMF, she was administered with 10 mg of prednisolone and methotrexate (10mg/week). She was not vaccinated initially and got vaccinated at the time of discharge. Other patients did not have any other side effects.

Discussion

The present study included 33 patients with CTD-ILD and the majority had MCTD (13/33) and RA (12/33). The third group (8/33) had various CTDs with majority having SSc spectrum of diseases.

A meta-analysis by Tzouvelekis *et al*. has reported that the MMF assisted in stabilizing lung function in SSc-ILD patients with better safety profile.[10] In 2013, Fischer *et al.* studied the effect of MMF in CTD-ILD. The same group had published their initial experience in 2006 with 28 patients. The researchers concluded that the MMF is safe, better tolerated and efficacious in stabilizing the lung function.[5] The 2013 study included 125 patients with CTD-ILD with majority diagnosed with SSc (35.2%), followed by inflammatory myositis (25.6%), IPAF (15.2%), and rheumatoid arthritis (14.4%). The mean age of the subjects was 60.6 (±11.6) with majority being males (58%). The mean FVC was 66.7±16.0 and the median duration of MMF use was 2.5 years with a minimal follow-up duration of 6 months. The daily dose of MMF was 3g/day in 65% of patients and 10% had discontinued MMF due to adverse effects.[4]

In the current study, majority were females (90.9%). The MCTD group (44.63 years) and the third (SSc predominant) group (51.37 years) had a lesser mean age in comparison to the RA-LD (61.69 years) group. The age

difference is probably related to the disease onset in each group. The mean FVC at baseline of the three groups were 62 ±6.17% (MCTD), 64±4.17% (RA) and 59±6% (others – SSc predominant). Most of the patients had moderate restriction, similar to the cohort of Fischer *et al.* In the study, all patients had completed 24 months of follow-up. They were on 2 g/day of MMF for the first 12 months, followed by a maintenance of 1.5-2 g/day for the next 12 months. None of the patients had discontinued treatment due to intolerance or adverse effects. The study findings indicate that a dose of 2g/day should be sufficient in Indian setting. The better tolerance and lesser side effects in the present cohort could be attributed to the comparatively lesser dosage.

Majority of our cohort had active inflammatory arthritis with co-existing ILD. Though MMF is effective in managing ILD, its potential in managing inflammatory arthritis is speculative. Hence, a second DMARD is needed to improve the joint symptoms. The study by Lee *et al.*, focusing on drug-induced interstitial lung disease, evaluated the role of methotrexate, leflunomide, TNF blockers and sulfasalazine, in causing pulmonary toxicity.[11] The results from the multivariate analysis of the early RA study (ERAS) and the early RA network (ERAN) inception cohorts clearly showed that methotrexate exposure was associated with reduced risk of ILD, though this has always been a subject of debate.[12] In the present study researchers used sulfasalazine and hydroxychloroquine as the initial treatment for arthritis, followed by methotrexate (MTX) and leflunomide (LEF) upon persistence of disease activity. This protocol was followed to bring down the risk of infections in patients on combined therapy with MMF and MTX/LEF. A meta-analysis by Conway *et al.* noted that methotrexate was associated with increased risk of all respiratory adverse events including respiratory infections, though not associated with increased risk of death.[13]

Singh *et al.* published data from the prospective ILD registry of India with 1084 patients enrolled across 27 centres. CTD-ILD was present in 151 (13.9%) patients. The mean age was 50.8 years with majority being females (73.8%). Rheumatoid arthritis was the predominant disease noted (38.4%) followed by SSc (22.5%). The prevalence of NSIP and UIP patterns were 54.3% and 31.8% respectively with a mean FVC of 56.6%.[14]

The Indian data on the treatment of CTD-ILD is fewer when compared to the frequency of ILD in CTD. The single-centre retrospective study by Shenoy *et al.* comparing cyclophosphamide vs. MMF in systemic sclerosis over a period of 6 months demonstrated a statistically significant improvement in FVC (10.84 ± 13.81 % in CYC group vs 6.07 ± 11.92 % in MMF group) from baseline in both the groups.[6] In the present study, the SSc predominant group had a lower baseline FVC in comparison to other groups. At the end of 2 years, majority of the patients on MMF demonstrated stabilization with no significant improvement in FVC from baseline. A randomized control trial by Naidu et al. compared MMF vs. placebo in patients with SSc-ILD.7 The mean FVC was 75.6 and the study duration was 6 months, and this could be argued as a reason for the lack of response to MMF. Majority in the present cohort had mild to moderate restriction and this could be attributed to the lack of significant change in FVC from baseline, though stabilization was noted in majority. Acharya *et al.* did an RCT comparing pirfenidone vs. placebo (mean FVC 65 VS 62.7) in patients with SSc- ILD over a period of 6 months.[8] The study failed to show a significant beneficial effect, probably due to the short study duration and small sample size.[8] Singh *et al*. studied the acute exacerbation of ILD in a diverse cohort of 105 CTD-ILD patients with a mean follow up duration of 24 ± 18.1 months. Fifteen patients had acute exacerbation with majority having SSc-ILD. Patients with acute exacerbation had lower baseline FVC and PaO2 levels.[9] In the present cohort, throughout the 24 months follow-up only one had an infective exacerbation of ILD. The reason could be due to the relatively lesser severity of ILD.

To the best of our knowledge, the present study is one among the very few Indian studies that has evaluated the treatment for CTD-ILD. The present study had a significant duration (24 months) of follow-up period. The present study reflects the real-life situation of managing patients with active arthritis and active ILD. Based on the findings it could be attributed that choosing the right drug to treat both the components, without any major adverse effect, is a challenge.

There are sufficient studies evaluating the efficacy of MMF in SSC-ILD. But the current study had a different cohort with predominant MCTD and RA patients. But the cohort did not have enough patients with inflammatory myositis and ILD, as many of them were on cyclophosphamide or rituximab in view of the disease severity. The study also did not include advanced ILD with severe restriction, as many of them were already listed under lung transplant program

of the centre. The cohort included ILD patients with mild to moderate restriction, which may be argued as a selection bias and the reason for the good response to MMF. The same reason may hold true for the lack of significant improvement in FVC from baseline.

The current study has a few limitations. It is a retrospective observational study with a smaller sample size. The sample size is small to draw any statistical conclusions. The study had missing data and hence could not analyse parameters like 6-minute walk test and the diffusing capacity for carbon monoxide (DLCO). It did not use a quantitative radiological scoring method to assess the radiological improvement in HRCT chest. In future, prospective studies with a larger sample size and longer duration (five and ten years) of follow-up are needed.

In conclusion, mycophenolate mofetil was found to be safe, effective and well tolerated in patients with CTD- ILD. Treatment with MMF over 24 months stabilized the ILD in majority with rare incidence of worsening.

Competing interests
The authors declare that they have no competing interests.

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*Correspondence: Dr Sham Santhanam, Consultant Rheumatologist, Department of Rheumatology,Gleneagles global Health City, Chennai. itsdrsham@gmail.com

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