**Clinical Investigations**

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**Effect and Safety of Mycophenolate Mofetil in Chronic Pulmonary Sarcoidosis: A Retrospective Study**

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**Key Words**  
Sarcoidosis · Steroid-sparing agent · Mycophenolate · Interstitial lung disease · Pulmonary function

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**Abstract**

**Background:** Treatment of chronic pulmonary sarcoidosis (CPS) is challenging and often requires long-term therapy with systemic corticosteroids and supplementary use of steroid-sparing agents. **Objective:** To examine the efficiency and safety of mycophenolate mofetil (MMF) as a steroid-sparing agent in patients with CPS. **Methods:** We conducted a retrospective study of patients with biopsy-proven pulmonary sarcoidosis, who were treated with MMF and systemic corticosteroids for >6 months between 2004 and 2010. Corticosteroid dose, pulmonary function parameters and radiological and clinical follow-up before and after treatment with MMF were assessed. **Results:** Ten patients received MMF for >6 months. MMF was introduced due to side effects (5/10 patients) and due to an inadequate response to prior therapy (5/10 patients). Median duration of treatment with MMF was 31 months (range 8–66). Therapeutic MMF plasma trough levels of 1–3 mg/l were reached with daily doses of 1,722 ± 440 mg MMF. Daily corticosteroid dose could be significantly reduced from 14.3 ± 13.3 to 6.5 ± 2.3 mg prednisolone during treatment. During follow-up, pulmonary function, symptoms and radiological signs improved in 4 patients, while 6 patients remained stable. Median change in FVC was +8.5 % (range –2 to 16). No severe adverse events that were related to combined immunosuppressive therapy occurred. **Conclusion:** This study indicates that the addition of MMF to corticosteroids is a viable and safe treatment option in CPS. MMF allows a significant reduction of maintenance corticosteroids to levels <10 mg/day while preserving a stable or improved clinical condition.

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**Introduction**

Sarcoidosis is a granulomatous disease of unknown etiology that can affect multiple organ systems. Pulmonary involvement is common and present in about 90% of cases [1]. Only a few patients with pulmonary sarcoidosis require treatment, but some patients may develop chronic progressive pulmonary involvement resulting in fibrotic alterations. As respiratory failure is still the most common cause of death in patients with active sarcoidosis [2], long-term therapy is often required. Corticosteroids (CS) are the mainstay of treatment, but are fre-
frequently accompanied by non-negligible side effects. Immunosuppressive agents have sometimes to be added either to reduce the dosage of CS or, in the case of insufficient treatment response, to intensify therapy. Several immunosuppressive drugs, i.e. methotrexate, azathio- 
prine, pentoxifylline or infliximab, used either alone or in combination with CS, have been suggested for the treatment of sarcoidosis [3–9], but some patients do not respond to or do not tolerate these drugs.

Mycophenolate mofetil (MMF), a reversible inhibitor of inosine monophosphate dehydrogenase, is another promising immunomodulatory agent with anti-inflamma-
tory and anti-proliferative activities [10]. It has proved to be efficient for inflammatory conditions such as bul-
lous pemphigoid [11], autoimmune hemolytic anemia [12] or systemic lupus erythematoses [13], and is well es-
established in transplant medicine. Recently, several case 
reports and case series showed the beneficial effects of 
MMF in the treatment of extrapulmonary sarcoidosis of 
different organs [14–20]. However, the effect of MMF on 
chronic pulmonary sarcoidosis (CPS) is not known. 
Therefore, we investigated the efficiency and safety of 
MMF as a steroid-sparing agent and its effects on lung 
function parameters in a retrospective series of 10 pa-
tients with CPS.

Material and Methods

Patients

Safety and efficacy of MMF for the treatment of CPS were as-
seessed in a retrospective single-center study. After approval by the 
institutional review board and the Cantonal Ethics Commission 
Bern (reference number KEK 25–03–11), patients with biopsy-
proven CPS who received MMF in combination with CS for >6 
months between October 2004 and December 2010 were identi-
ﬁed retrospectively. Patients were eligible if pulmonary function 
testing (PFT) data were available at the start and end of treatment 
with MMF. Patients without predominantly pulmonary disease, 
or without serial routine PFTs, laboratory or radiological data 
available, were excluded. Patients were evaluated on an outpatient 
basis at our clinic at least every 3 months.

Treatment

Immunosuppressive agents other than CS were stopped before the 
initiation of MMF. After excluding contraindications, treatment 
with MMF was performed in a standardized way. MMF (CellCept®, Roche Laboratories, Basel, Switzerland) was started 
at a dose of 0.5 g orally, b.d. MMF serum trough levels were mea-
sured after 5–10 days and the dosage was adjusted if plasma 
trough levels of 1–3 mg/l MMF were not achieved. MMF levels 
were then quantified at least every 1–2 months. A complete blood 
count and liver and kidney function parameters were controlled 
monthly, either in our outpatient clinic or by the patient’s general 
practitioner. The concomitant CS therapy was kept as low as pos-
sible. The decision to stop MMF was based on the individual dis-
ease course of the patient, and was attempted if the patient did not 
improve any further and remained stable for at least 6 months.

Adverse Events

Adverse events were recorded during regular medical visits. 
Mild adverse events were defined as events that allowed for the 
continuation of MMF and only required outpatient treatment. In 
the case of infections, MMF was stopped temporarily. Severe 
events were defined as any event requiring hospitalization or de-
finite cessation of MMF.

Pulmonary Function Testing and Evaluation of Dyspnea

Pulmonary function was assessed routinely every 3–6 months 
according to the American Thoracic Society guidelines [21]. Arter-
ial oxygen partial pressure (PaO₂) was assessed in a standardized 
way at rest and room air. Dyspnea was classified according to the 
American Thoracic Society criteria scales 0–IV [22]. Data that 
were recorded closest to the time that MMF was started were de-
signated as treatment onset and were compared to the values 6 
months before and at the end of treatment with MMF. Changes in 
PFT parameters were defined as clinically signiﬁcant according to 
the deﬁnitions of Pellegrino et al. [21]. For forced vital capacity 
(FVC), forced expiratory volume in the 1st second (FEV₁) and to-
tal lung capacity (TLC), a change from baseline of ±10% and a 
change of ±15% for diffusion capacity (DLCO) were considered 
as a relevant improvement or deterioration. The change in lung 
function parameters is reported in % predicted of the age- 
and gender-adjusted values. The following changes in PaO₂ were predi-
cative for improvement or deterioration: ±15 mm Hg in PaO₂ in 
patients with baseline PaO₂ >80 mm Hg, ±10 mm Hg in patients 
with baseline PaO₂ between 55 and 80 mm Hg, and ±5 mm Hg in 
patients with baseline PaO₂ <55 mm Hg.

Classification of Clinical Course

A scoring algorithm accounting for the different PFT param-
eters and dyspnea [6] were used to evaluate the clinical course. 
Clinical improvement was defined as no change, improvement in 
dyspnea and signiﬁcant improvement in ≥2 parameters (FEV₁, 
FVC, TLC, DLCO or PaO₂) or a signiﬁcant improvement in 1 pa-
rameter and improvement in the patient’s dyspnea. Clinical deteri-
roration was deﬁned as a signiﬁcant decrease in ≥2 parameters 
or a signiﬁcant decrease in 1 parameter and worsening of the pa-
tient’s dyspnea. All other outcomes were considered as stable dis-
ease.

Radiological Changes

Chest X-rays were identiﬁed at the onset and end of treatment 
with MMF and were judged by 2 independent people as: im-
proved, unchanged or worsened, by comparing chest X-rays be-
tween the time points. Chest X-ray stages were classiﬁed accord-
ing to Scadding [23].

Statistical Analysis

Results are expressed as frequencies, numbers, mean ± SD or 
median followed by range in parentheses unless indicated other-
wise. Due to the small sample size, nonparametric tests were ap-
plied. The Wilcoxon test was employed for the comparison of 
lung function parameters and CS dose. The signiﬁcance level of 
all analyses was set to 5% and p values are reported. Data were
analyzed and processed using statistical software [Statistical Package for Social Sciences (SPSS), Version 15.0, Chicago, Ill., USA or Stata Release 11, Stata Corp, College Station, Tex., USA] on a Windows XP operating system (Microsoft, Redmond, Wash., USA).

Results

Patients

Out of 70 screened patients, 13 were treated with MMF. Three had to be excluded from the study [due to a treatment time <6 months (n = 1) or treatment not being indicated due to pulmonary involvement (n = 2)]. The baseline characteristics of enrolled patients are shown in table 1.

Treatment

All patients were on prior immunosuppressive therapy with CS. They were pretreated with CS for a median time of 14 months (range 1–240). Prior to MMF prescription, patients witnessed a mean of 2.0 ± 1.4 relapses whenever CS doses were tapered. This required repetitive intermittent augmentation of CS doses and was the indication for the introduction of additional immunosuppressive steroid-sparing drugs. Nine out of 10 patients were pretreated with 1 or more immunosuppressive drugs for a median treatment time of 11 months (range 2–22). One out of ten patients received MMF as first-line steroid-sparing agent.

MMF was introduced in 5/10 patients due to adverse events caused by the preceding steroid-sparing therapy, and in the other 5 (including the patient with MMF as a first-line steroid-sparing agent who received CS monotherapy) because of an unsatisfactory response to the prior therapeutic regimen. The reasons for starting MMF are listed patient by patient in table 2.

A mean MMF dose of 1,722 ± 440 mg/24 h was prescribed. The median duration of MMF treatment was 31 months (range 8–66) and varied according to clinical response. The daily prednisolone dose was reduced from 14.3 ± 13.3 to 7.9 ± 2.8 mg (p = 0.066) at 6 months (10/10 patients) and to 6.5 ± 2.3 mg (p = 0.043) at 12 months (9/10 patients). After 24 months, 7/10 patients were still treated with MMF. Mean prednisolone dose in these patients could be reduced from 15.5 ± 31.8 mg upon initiation of MMF to 5.7 ± 2.4 mg. Data are shown in figure 1.

Adverse Events

MMF was generally well tolerated. Mild adverse events were documented in 7/10 patients, including 6 episodes of self-limiting upper-airway infections. Two patients had mild community-acquired pneumonia and required

Table 1. Baseline characteristics

| Patients, n | 10 |
| Gender | Male 9, Caucasian 9, African 1 |
| Age at diagnosis of sarcoidosis, years | 42.1 ± 11.4 |
| Age at starting MMF, years | 51.0 ± 9.9 |
| Smoker | 1 |
| Organ involvement | Biopsy-proven pulmonary involvement 10, Pulmonary alone 2, Pulmonary and extrapulmonary 8, Skin 2, Liver 4, Calciuria 5, Musculoskeletal 1, Uveitis 2, Heart 0 |
| Prior treatment (within 2 years before starting MMF) | None 0, Corticosteroids 10, Azathioprine 7, Hydroxychloroquine 1, Pentoxifylline 1, Cyclosporine 1, Infliximab 1 |
| Number of relapses before starting MMF | 2 ± 1.4 |

Data are presented as numbers or mean ± SD.

Fig. 1. Daily prednisolone dose over time. MMF was started at month 0. Significance level compared to month 0 = start of MMF.
antibiotics. They were treated as outpatients and MMF was discontinued for 3 weeks. Four of 10 patients had moderately elevated liver enzymes (i.e. $>3 \times$ upper limit of normal). Four of 10 patients suffered from diarrhea, nausea or vomiting shortly after the initiation of MMF treatment. These gastrointestinal side effects were self-limiting in 3/4 patients and did not require any additional procedures. In 1 patient, diarrhea persisted and MMF was replaced by mycophenolate sodium (Myfortic®; Novartis Pharma Stein AG, Stein, Switzerland). This led to the resolution of gastrointestinal symptoms. Three of 10 patients developed mild leukopenia ($<2.5 \text{ g/l}$) leading to a temporary dose reduction of MMF. Serum trough levels were kept in the lower therapeutic range and the leukopenia resolved in 2/3 patients. Leukocyte count ranged from 3.4 to 11.8 g/l before introduction of MMF and from 2.5 to 9.8 g/l after the introduction of MMF. The lowest leukocyte count measured during MMF treatment was 2.5 g/l. No severe adverse events occurred i.e. infections requiring hospitalization, neoplasia, lymphoproliferative disease, severe leukopenia ($<1.5 \text{ g/l}$) or death related to the treatment with MMF.

**Lung Function and Clinical Course**

Compared to baseline, FVC and FEV$_1$ improved significantly during treatment with MMF and CS. An increase of FVC of $>10\%$ (fig. 2, continuous line) was observed in 4/10 patients, another 4 showed an improvement of $0–10\%$ FVC (dashed line), and the other 2 had a small decline in FVC of $–2\%$ (dotted line) compared to baseline. Median change in FVC was $+8.5\%$ (range $–2$ to 16). Median change in FVC was $+11\%$ (range 8–16) in the subgroup of patients who started MMF treatment because of an insufficient prior response, and $+2\%$ (range $–2$ to 14) in the ‘side effects’ subgroup. TLC and DLCO stabilized. Detailed data are shown in table 3 and in figure 2.

According to the applied clinical algorithm, 4/10 patients were classified as ‘improved’ and 6/10 as ‘sustained stable’ compared to baseline. During follow-up, the treatment regimen was changed to infliximab in 1/10 patients due to uncontrolled extrapulmonary sarcoidosis (uveitis) after 8 months. One of 10 patients died after 36 months due to an acute cardiovascular event unrelated to sarcoidosis or MMF treatment. Of the remaining patients, MMF could be stopped in 7/8 patients. After MMF cessation, treatment was continued with low-dose CS in 2 patients. Two were lost to follow-up (table 2) and 1 is still being treated with MMF and low-dose CS. Three relapsed and had to restart immunosuppressive therapy. Two of the ‘relapse-patients’ were treated with the combination of MMF and CS again (and are

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**Table 2. Clinical and radiological course**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Reason to start MMF</th>
<th>Clinical coursea with MMF</th>
<th>Significant improvement in PFT parameter</th>
<th>Change in dyspnea</th>
<th>Radiological course</th>
<th>Treatment time with MMF, months</th>
<th>Long-term follow up after stopping MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AE with cyclosporine: anemia</td>
<td>stable</td>
<td>none</td>
<td>none</td>
<td>improvement</td>
<td>53</td>
<td>lost to follow-up</td>
</tr>
<tr>
<td>2</td>
<td>UR to azathioprine</td>
<td>stable</td>
<td>FVC, TLC</td>
<td>improvement</td>
<td>improvement</td>
<td>35</td>
<td>lost to follow-up</td>
</tr>
<tr>
<td>3</td>
<td>UR to infliximab</td>
<td>improved</td>
<td>FEV$_1$, TLC</td>
<td>improvement</td>
<td>improvement</td>
<td>27</td>
<td>stable on MMF and low-dose CS</td>
</tr>
<tr>
<td>4</td>
<td>UR to azathioprine</td>
<td>improved</td>
<td>FVC, FEV$_1$, PaO$_2$</td>
<td>none</td>
<td>deterioration</td>
<td>36</td>
<td>died</td>
</tr>
<tr>
<td>5</td>
<td>AE with azathioprine: pancytopenia, elevation of transaminases</td>
<td>stable</td>
<td>none</td>
<td>none</td>
<td>stable</td>
<td>18</td>
<td>relapse, restart of MMF and CS</td>
</tr>
<tr>
<td>6</td>
<td>UR to high-dose CS monotherapy, multi-organ involvement, TPMT deficit</td>
<td>improved</td>
<td>FVC, FEV$_1$</td>
<td>improvement</td>
<td>improvement</td>
<td>36</td>
<td>relapse, restart of CS</td>
</tr>
<tr>
<td>7</td>
<td>AE with azathioprine: nausea, diarrhea</td>
<td>improved</td>
<td>FEV$_1$</td>
<td>improvement</td>
<td>stable</td>
<td>27</td>
<td>stable on low-dose CS</td>
</tr>
<tr>
<td>8</td>
<td>AE with azathioprine: nausea, diarrhea</td>
<td>stable</td>
<td>none</td>
<td>none</td>
<td>stable</td>
<td>8</td>
<td>changed to infliximab and improved</td>
</tr>
<tr>
<td>9</td>
<td>UR to azathioprine</td>
<td>stable</td>
<td>none</td>
<td>improvement</td>
<td>improvement</td>
<td>15</td>
<td>stable on low-dose CS</td>
</tr>
<tr>
<td>10</td>
<td>AE with azathioprine: nausea, diarrhea</td>
<td>stable</td>
<td>none</td>
<td>improvement</td>
<td>stable</td>
<td>66</td>
<td>relapse, restart of MMF and CS</td>
</tr>
</tbody>
</table>

AE = Adverse event; TPMT = thiopurin methyltransferase; UR = unsatisfactory response.

*a Overall clinical course using the algorithm of change in lung function parameter and dyspnea.*

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**Table 3.** Changes in pulmonary function parameters, radiological stages and dyspnea scores

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>6 months before MMF</th>
<th>Start of MMF</th>
<th>At 12 months of MMF</th>
<th>p value*</th>
<th>End of MMF</th>
<th>p value*</th>
<th>Median change in % (range)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$, % pred</td>
<td>10</td>
<td>10</td>
<td>9$^a$</td>
<td>10</td>
<td></td>
<td></td>
<td>$^+$8.5 (–2 to 16)</td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>68.5 ± 12.8</td>
<td>66.6 ± 15.1</td>
<td>72.6 ± 13.7</td>
<td>0.035</td>
<td>71.2 ± 11.1</td>
<td>0.016</td>
<td>+8.5 (–2 to 16)</td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>82.0 ± 14.7</td>
<td>78.8 ± 11.9</td>
<td>85 ± 9.6</td>
<td>0.057</td>
<td>84.2 ± 9.0</td>
<td>0.028</td>
<td>+7 (–6 to 24)</td>
</tr>
<tr>
<td>DLco, % pred</td>
<td>78.4 ± 10.2</td>
<td>81.5 ± 9.1</td>
<td>85.2 ± 11.6</td>
<td>0.285</td>
<td>83.3 ± 9.5</td>
<td>0.357</td>
<td>+1 (–6 to 15)</td>
</tr>
<tr>
<td>Chest X-ray stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>II</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
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<tr>
<td>III</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
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<tr>
<td>Dyspnea level (ATS)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>None (0)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mild (I–II)</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Moderate/severe (III–IV)</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented in numbers or mean ± SD. * Level of significance compared to at the start of MMF.

$^a$ One patient was changed on infliximab after 8 months. $^b$ Change in % between the start and end of treatment with MMF.

**Fig. 2.** Change of FVC over time. a FVC in % predicted 6 months prior to the start of MMF treatment, and at the start and end of treatment in the subgroup of patients whose treatment regimen was changed due to an insufficient response to the prior treatment. b FVC in % predicted for the same time points in the subgroup of patients who started MMF due to intolerable side effects to the preceding therapeutic regimen.
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Radiological Changes

Five of 10 patients showed radiological improvement. Three stage-II patients and 1 stage-IV patient showed a partial resolution of the reticulonodular pattern. In 1 patient, the chest X-ray normalized (i.e. changed from stage III to stage 0). The chest X-rays of 1 stage-II and 2 stage-IV patients remained unchanged. One stage-IV patient had progressive fibrotic changes. For details, see tables 2 and 3.

Discussion

In this study, we show that the addition of MMF to CS in CPS allows for a significant reduction in the dosage of CS while keeping lung function parameters (FVC, FEV1) stable. In the patients studied, MMF was safe and well tolerated.

Patients who develop CPS and require long-term treatment still represent a challenge with regard to effective and safe therapy [24]. Once the decision is made to start a steroid-sparing agent, there are little data to guide the treatment, especially if the patient does not respond or does not tolerate first- or second-line immunosuppressive therapies. The results of our study suggest that MMF in combination with CS is an effective and safe alternative therapeutic option in patients with CPS.

MMF inhibits lymphocyte proliferation and the expression of adhesion molecules. The rationale to use this drug in the treatment of pulmonary sarcoidosis is to inhibit the compartmentalization of T lymphocytes and the release of proinflammatory mediators within granulomas [25]. Its rapid onset of action and more selective inhibition of lymphocytes are important advantages over other immunosuppressive agents [25].

The patients were pretreated with other steroid-sparing agents and CS dose was already tapered before introducing MMF. Thus, the mean dose of CS at baseline was lower than in patients starting treatment for new-onset pulmonary sarcoidosis or relapse. Nevertheless, adding MMF led to a further and significant reduction of CS to a daily dose of below 10 mg prednisolone, paralleled by the improvement or stabilization of pulmonary function, indicating its steroid-sparing quality.

In patients with CPS, it is crucial to prevent or at least reduce the formation of irreversible fibrotic changes that may result in disabling restrictive ventilatory defects and finally respiratory failure. FVC may be used as a surrogate marker for progressive pulmonary restriction, and a decrease in FVC in patients with CPS may be an indicator of the activity and progression of the disease.

Our study shows a statistically significant improvement of FVC of +8.5% (median). The group of patients that was started on MMF because of the intolerable side effects of the prior treatment had already shown an improvement in lung function before starting MMF. This might explain why there was less PFT improvement in this group of patients than in the subjects that did not respond to prior treatment (median change in FVC +2 vs. +11%). The overall increase in FVC is comparable to the improvements found with other immunosuppressive agents in CPS treatment. A randomized, placebo-controlled study [8], investigating infliximab in patients with stable sarcoidosis and a FVC of 68% predicted, showed an improvement of +2.5% in FVC after 24 weeks of treatment in the combined infliximab group. Only patients with stable disease were included in this study, probably leading to an underestimation of PFT response to the treatment. Another study, adding azathioprine [7] to initially high-dose CS, resulted in a significant improvement of FVC from 74.8 ± 12.4% predicted to 89.2 ± 15.2% (n = 11). The effect of the concomitant initially high dose CS cannot be distinguished from the effect of azathioprine. Studies using other immunosuppressive agents demonstrated only slight improvements in lung function, i.e. a mean change of FVC of +200 ml in a retrospective study with leflunomide [26], an improvement in FVC of +3.3% in 18 patients treated with pentoxifylline [6] and no change in lung function in a case series with adalimumab [27].

As a relevant clinical improvement is difficult to assess with a single PFT parameter, we also applied a clinical algorithm for outcome evaluation, confirming the stabilization or improvement of the clinical course in our subjects. Furthermore, we found a significant increase in FEV1 and a trend towards improvement in TLC and DLCO, although these changes missed significance, probably due to the small sample size.

In 4 patients, the long-term course after stopping MMF could not be assessed (1 died, 2 were lost to follow-up and 1 switched to infliximab). In the remaining 6 patients, a stabilization or improvement of the disease could be documented. After cessation of MMF therapy, there was a tendency to relapse, indicating that MMF was efficient to control inflammation during treatment, but did not have a lasting effect on the disease.
MMF was generally well tolerated; no severe adverse events were reported. This is in line with previous case reports of MMF treatment for extrapulmonary sarcoidosis and of large cohorts of patients receiving MMF after single organ transplantation [28, 29] or for dermatological disease [25]. Although no standardized prospective attempt was applied to record all adverse events, patients were monitored closely, including clinical visits every 4–12 weeks. Therefore, the possibility of missing relevant adverse events is negligible.

Our study has some limitations that need to be addressed. This is a retrospective cohort study with all the limitations that come with this design, including selection bias, lack of a control group and no randomization. In addition, the number of treated patients is very small. Sarcoidosis is a disease with a high rate of spontaneous remission, even after several years [30–32]. However, it is difficult to extrapolate these data on patients with severe or progressive pulmonary disease that is active for several years. If sarcoidosis persists for more than 2 years, the likelihood of spontaneous resolution becomes low and end-stage pulmonary sarcoidosis may develop over 1 or 2 decades [30, 32]. With the lack of a control group in our study and keeping in mind the possibility of spontaneous improvement, we could not definitively conclude that the observed improvements or stabilization in PFT and clinical course can be attributed solely to MMF treatment. All of our patients had a long history of CPS (table 1) and had required continuous treatment before the introduction of MMF. Therefore, spontaneous improvement of the disease in our patients seems very unlikely. Furthermore, 5 patients did not respond sufficiently to previous treatment and improved or stabilized under MMF treatment. In addition, 3 out of 8 patients relapsed after MMF cessation, indicating the disease’s activity and the need for ongoing therapy before and after treatment with MMF.

In conclusion, our study indicates that MMF is an effective and safe steroid-sparing agent in patients with CPS that allows stabilization of lung function despite CS reduction. Larger prospective randomized controlled trials are warranted to confirm the clinical value of MMF in the treatment of CPS. As long as these data are missing, our data suggest that MMF may be considered as an alternative treatment option.

Financial Disclosure and Conflicts of Interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the manuscript.

References

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