CLINICAL REPORT

Use of Mycophenolate Mofetil in Patients with Severe Localized Scleroderma Resistant or Intolerant to Methotrexate

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To assess the efficacy and safety of mycophenolate mofetil (MMF) in patients with localized scleroderma (LoS) resistant or intolerant to previous treatment with methotrexate (MTX). A case series of patients with LoS treated with MMF. Outcome was assessed through clinical examination. Adverse events were documented. Seven patients with LoS were treated with MMF. Median age at MMF initiation was 15 years (range 7–74 years). Three patients received MMF due to MTX ineffectiveness and 4 due to MTX intolerance. Disease remission was achieved in 4 patients and maintained in one patient. One patient showed a favourable response, but had to discontinue treatment due to elevated liver enzymes. The remaining patient experienced disease progression. MMF was shown to improve the clinical condition of patients with refractory LoS and may be a relatively safe alternative in patients who are intolerant to MTX. Key words: localized scleroderma; morphea; mycophenolate mofetil; methotrexate.

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Localized scleroderma (LoS), also known as morphea, encompasses a spectrum of sclerotic skin diseases primarily affecting the dermis, but may also affect underlying tissues such as subcutaneous fat, fascia, muscle and underlying bone (1). The different subtypes of LoS may vary in severity and are classified into morphea en plaque, linear LoS, generalized LoS, deep LoS, pansclerotic morphea and the mixed subtype (2). Morphea en plaque is the most common variant in adults. Linear LoS is the most frequently observed subtype in children and is usually accompanied by fibrosis of the underlying tissues of the limbs and face. In severe cases the disease results in muscle atrophy, growth restrictions of the limbs and joint contractures, leading to discomfort, dysfunctional use and psychological distress (3–5). In LoS, treatment consists of topical corticosteroids, vitamin D analogues or calcineurin inhibitors, low-dose methotrexate (MTX), systemic corticosteroids and ultraviolet A1 (UV A1) phototherapy (6, 7). For some patients with severe debilitating deformities these treatments are not sufficient, due to progressive disease and/or intolerance to treatment. In these refractory cases of LoS, mycophenolate mofetil (MMF) may be beneficial. However, literature supporting this evidence is scarce, with only one article reporting beneficial results of this treatment option in LoS (8). The aim of this concise report is to provide more evidence of the efficacy and safety of MMF therapy in patients with severe LoS.

MATERIALS AND METHODS

A retrospective chart review was performed of patients with LoS treated with MMF, at the Radboud University Medical Centre, Nijmegen, The Netherlands. Disease subtype classification was based on the classification system proposed by Zulian et al. (9). The diagnosis was made by clinical inspection and confirmed with skin biopsies if necessary. Treatment with MMF was initiated when treatment with MTX as a treatment for LoS, in combination with systemic corticosteroid therapy, did not result in disease remission or stabilization, or when intolerance to MTX occurred. Active disease was defined as the presence of one of the following items: an erythematous border (“lilac ring”) surrounding a lesion, or disease progression (development of new lesions, expansion of existing lesions, expansion of sclerosis, decrease in the range of motion (RoM) of an affected limb, or imaging studies showing signs of disease activity). Inactive disease was defined as the absence of the above-mentioned items for disease activity. Disease remission was defined as 6 consecutive months of inactive disease. A favourable response to treatment with MMF was defined as disease remission or absence of disease recurrence during follow-up. All patients were evaluated by both a dermatologist and a rheumatologist, with extensive experience in the treatment of LoS in paediatric and adult patients, respectively. Extracutaneous manifestations (ECMs) were recorded as previously reported by Zulian et al. (9)

RESULTS

Patients

Clinical characteristics are described in Table I. Seven patients with LoS, 6 females and 1 male, were treated with MMF at our centre. The median age at MMF initiation was 15 years (range 7–73 years). LoS subtypes...
included were deep (n = 2), linear (n = 1), generalized (n = 2) and mixed subtypes (n = 2). Two patients, both classified with generalized subtype of LoS, had an overlap diagnosis with systemic sclerosis (SSc). One of these patients was diagnosed with a diffuse cutaneous SSc (dcSSc), based on the presence of Raynaud’s phenomenon, sclerodactyly, positive ANA, positive anti-topoisomerase-I, abnormal nail-fold capillaries and a diffuse pattern of thickening of the skin. The other patient was diagnosed with a limited cutaneous SSc (lcSSc), based on the presence of Raynaud’s phenomenon, digital ulcers, sclerodactyly, positive ANA and anti-centromeres and oesophageal dysmotility. In the 2 patients diagnosed with SSc, MMF treatment was initiated due to progression of the LoS lesions. The remaining 5 patients were solely diagnosed with LoS. One patient (#1) was diagnosed with mild pulmonary restriction at the initial presentation of LoS, which remained stable during the 6 years of follow-up. This patient also experienced a decreased RoM of the wrist and knee. No other ECMs, especially no arthritis, were reported in the patients.

**Treatment**

All patients were treated with systemic corticosteroids and MTX, with maximum doses up to 25 mg administered orally and subcutaneously, prior to starting treatment with MMF (Table II). Two patients (# 6 and 7) had a history of treatment with azathioprine. The patient with dcSSc had received cyclophosphamide because of progressive skin disease, with good response of dcSSc, but not of LoS. In addition, she was treated with rituximab previous to MMF initiation. Four patients had experienced MTX intolerance (nausea, abdominal discomfort, elevated liver enzymes), which was the incentive to start MMF therapy. In 3 patients MMF therapy was started because of ineffective prior treatment with MTX. Median duration of disease at the start of MMF therapy was 46 months (range 21–194 months). Six out of 7 patients showed signs of disease activity at the start of MMF treatment. In the remaining paediatric patient, MMF was started as a treatment to maintain disease remission. All patients discontinued MTX treatment, ranging from 1 week to 3 years, prior to MMF initiation. Five patients (#1, 3, 4, 6 and 7) were treated concomitantly with prednisone treatment. Two of these 5 patients were already being treated with 10 mg prednisone daily for several years prior to MMF initiation and no dose alterations were made during the treatment episode of MMF. One patient (# 3) received 7.5 mg prednisone daily for 6 weeks at the same time as the MMF dose was increased. Another patient (# 1) was being treated with up to 30 mg prednisone daily for the first 6 months of MMF treatment. The remaining patient (#4) received 20 mg prednisone for the first 2 months of MMF treatment. The starting dose of MMF ranged from 500 to 2,000 mg daily and the maximum dose prescribed was 2,500 mg daily. Median duration of MMF treatment at data lock was 15 months (range 9–40).

**Outcome: disease course**

As described in Table II, 6 patients had a favourable response to MMF treatment. Of the patients who started MMF treatment, while having active disease, 4 patients (#1, 3, 4 and 6) achieved disease remission. After initial disease remission during MMF treatment, patient #1 had a disease recurrence, which responded favourably after dose increase of MMF. In addition, the RoM returned to normal during treatment. Patient #3 also experienced disease remission after dose increase. Patient #4 experienced disease remission without dose increase. One patient with generalized LoS (#6) experienced clinical improvement of the LoS, but progression of the systemic manifestations of SSc. Patient #7 experienced clinical improvement, but had to discontinue MMF treatment after 3 months due to elevated liver enzymes. One patient (#2) already had disease remission prior to starting treatment with MMF; therapy with MMF was started due to MTX intolerance and the aim of the treatment was to maintain disease remission. Only one patient (#5) was reported to show progression of disease during 12 months of treatment with MMF.

**Outcome: MMF discontinuation and safety**

Of the 7 patients, 3 (#1, 2 and 6) were still being treated with MMF at the data lock. Patient #3 stopped on his

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**Table I. Overview of patients’ characteristics**

<table>
<thead>
<tr>
<th>Pat. No./Sex</th>
<th>Clinical subtype</th>
<th>Affected areas</th>
<th>Autoimmune-serology</th>
<th>Follow-up months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>Deep LoS</td>
<td>Anterior and posterior trunk, left arm and left leg</td>
<td>1+ ANA (homogeneous), + Anithiston</td>
<td>81</td>
</tr>
<tr>
<td>2/F</td>
<td>Linear LoS</td>
<td>Right leg</td>
<td>Not available</td>
<td>26</td>
</tr>
<tr>
<td>3/F</td>
<td>Linear LoS</td>
<td>Right leg</td>
<td>Negative</td>
<td>37</td>
</tr>
<tr>
<td>4/F</td>
<td>Mixed</td>
<td>Head, anterior trunk, left arm and left leg</td>
<td>Weak positive ANA (homogeneous), ENA –</td>
<td>40</td>
</tr>
<tr>
<td>5/F</td>
<td>Generalized LoS and dcSSc</td>
<td>Anterior and posterior trunk, left and right arm</td>
<td>3+ ANA (nucleolar), + Anti-topoisomerase I</td>
<td>61</td>
</tr>
<tr>
<td>6/F</td>
<td>Generalized LoS and lcSSc</td>
<td>Left and right leg</td>
<td>3+ ANA (centromeric), + Anti-Centromere</td>
<td>118</td>
</tr>
<tr>
<td>7/F</td>
<td>Deep LoS</td>
<td>Left and right leg</td>
<td>Negative</td>
<td>40</td>
</tr>
</tbody>
</table>

own initiative at the time of disease remission. There was no report of adverse events in this patient. In patient #4, MMF was discontinued after disease remission was present for one year. In patient #5, MMF was ineffective and treatment was therefore discontinued after 12 months. This patient also experienced diarrhoea at MMF doses greater than 1,000 mg daily. Lastly, patient #7 developed elevated liver enzymes after 3 months of MMF treatment, leading to discontinuation of treatment.

**DISCUSSION**

The current paucity of evidence about MMF treatment in patients with LoS motivated us to analyse the efficacy and safety of MMF in these patients from our hospital. Our findings indicate that MMF may be a suitable alternative to MTX in patients who experience MTX-intolerance or insufficient disease control, considering that the majority of our patients achieved disease remission when using MMF. One patient with an extensive history of LoS refractory to various medications showed disease progression under MMF treatment.

MMF is an ester derivative of mycophenolic acid (MPA), which selectively and non-competitively inhibits an important enzyme, inosine monophosphate dehydrogenase, required for the proliferation of lymphocytes. Therefore, blocking this enzyme may specifically inhibit multiple functions of lymphocytes. MMF was initially used for prevention of organ transplant rejection and, several years later, use of MMF for dermatological conditions ensued. In addition, in vitro studies have shown that MMF also inhibits proliferation of smooth muscle cells and fibroblasts, making it a potentially promising treatment for sclerodermatous conditions as well (10, 11). A previous case series described stabilization of lung disease in patients with dcSSc treated with MMF (12). Furthermore, one prospective observational study of MMF reported a marked improvement in skin involvement in patients with progressive dcSSc (13). A review by Cappelli et al. (14) describes several observational studies with encouraging results of MMF on the modified Rodnan Skin Score in patients with SSc. SSc and LoS probably share a common pathway, given that the same cytokines and chemokines are activated, leading to increased collagen and extracellular matrix deposition (4). These findings further support that MMF could also be efficacious in patients with LoS.

Compared with other immunosuppressant medications, including MTX, MMF has a favourable side-effect profile (15). Common side-effects of MMF are gastrointestinal symptoms, such as diarrhoea and nausea. Haematological abnormalities, most frequently leucopaenia, and increased susceptibility to infections, such as urinary tract infections, are also commonly observed (11). In this case series, one patient developed elevated liver enzymes after 3 months of treatment with MMF, and another

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**Table II. Treatment history.** Mycophenolate mofetil (MMF) treatment characteristics, response to treatment and reason for treatment discontinuation of methotrexate (MTX) and MMF, respectively.

<table>
<thead>
<tr>
<th>Pat. No.</th>
<th>Treatment previous to MMFa</th>
<th>Reason to start MMF</th>
<th>Disease duration (months)</th>
<th>Activity at start</th>
<th>MMF dose (mg) and duration (months)</th>
<th>Concomitant treatment</th>
<th>Course of disease following MMF treatment</th>
<th>Reason for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SC 25 mg, prednisone 1,750</td>
<td>Intolerance</td>
<td>40</td>
<td>Active</td>
<td>1,000, 1,750</td>
<td>Prednisone up to 30 mg first 6 months of MMF treatment</td>
<td>Disease remission</td>
<td>Still being treated</td>
</tr>
<tr>
<td>2</td>
<td>SC 20 mg, prednisone 1,200</td>
<td>Intolerance</td>
<td>20</td>
<td>Inactive</td>
<td>1,200, 1,200</td>
<td>Prednisone up to 30 mg first 6 months of MMF treatment</td>
<td>Disease remission</td>
<td>Still being treated</td>
</tr>
<tr>
<td>3</td>
<td>SC 25 mg, prednisone 2,500</td>
<td>Ineffective</td>
<td>9</td>
<td>Active</td>
<td>2,000, 2,500</td>
<td>Prednisone 7.5 mg 6 weeks</td>
<td>Disease remission</td>
<td>Disease remission</td>
</tr>
<tr>
<td>4</td>
<td>SC 20 mg, oral</td>
<td>Inactive</td>
<td>15</td>
<td>Active</td>
<td>1,000, 1,000</td>
<td>Prednisone up to 20 mg first 2 months of MMF treatment</td>
<td>Disease remission</td>
<td>Prednisone 10 mg, 7.5 mg 6 weeks of MMF treatment</td>
</tr>
<tr>
<td>5</td>
<td>SC 20 mg, oral</td>
<td>Ineffective</td>
<td>12</td>
<td>Active</td>
<td>1,000, 1,000</td>
<td>Prednisone up to 20 mg first 2 months of MMF treatment</td>
<td>Disease remission</td>
<td>Prednisone up to 20 mg first 2 months of MMF treatment</td>
</tr>
<tr>
<td>6</td>
<td>SC 25 mg, oral</td>
<td>Intolerant</td>
<td>28</td>
<td>Active</td>
<td>1,000, 1,000</td>
<td>Prednisone 7.5 mg 6 weeks</td>
<td>Disease remission</td>
<td>Prednisone 10 mg, 7.5 mg 6 weeks of MMF treatment</td>
</tr>
<tr>
<td>7</td>
<td>SC 12.5 mg, oral</td>
<td>Intolerant</td>
<td>3</td>
<td>Active</td>
<td>1,000, 1,000</td>
<td>Prednisone up to 20 mg first 2 months of MMF treatment</td>
<td>Disease remission</td>
<td>Prednisone 10 mg, 7.5 mg 6 weeks of MMF treatment</td>
</tr>
</tbody>
</table>

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*aAll have received systemic corticosteroids. *bPrevious to MMF.

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$\text{AE: adverse events.}$
patient experienced diarrhoea at MMF doses exceeding 1,000 mg daily. No other side-effects were reported.

One of the limits of the current study is that the effect of previous treatment, such as MTX, in LoS lasts for an unknown period of time. Six out of 7 patients were treated with MMF for at least 9 months, most likely dissipating an MTX effect. Another possibility is that the disease remission is due to the natural course of disease, given that an unknown percentage of lesions tend to slowly soften over a period of 3–5 years (4). However, all cases had a history of difficult-to-treat LoS with refractoriness to systemic treatments, which makes spontaneous remission less probable. It is also important to note that 5 out of 7 patients received concomitant treatment with prednisone. Two of these patients were already being treated with low-dose prednisone for multiple years prior to MMF initiation and no dose alterations were made during the treatment episode of MMF. In the remaining 3 patients, prednisone was either prescribed at the initiation or during the course of MMF treatment, making it difficult to attribute the favourable therapeutic effect solely to MMF. In addition, this study is limited by its retrospective design and small sample size. Lastly, validated clinical scores, such as the LoScat (16, 17) or media RSS, were not routinely performed, as these patients were treated in daily practice care.

Reviews of LoS treatment mention the use of MMF in patients with LoS intolerant or refractory to MTX (1, 18, 19). However, to date, only one case series by Martini et al. (8) has described the effect of MMF in LoS patients, emphasizing the need for additional evidence to support this proposition. Martini et al. describe continuation of MTX treatment, concomitantly with MMF in 6 patients. In our study, all patients discontinued treatment with MTX at the start of MMF. Hence, our description of case series provides additional evidence for the efficacy and safety of MMF in patients with LoS and facilitates the decision to opt for MMF in LoS. However, further randomized controlled studies are warranted to further evaluate the efficacy of MMF in patients with LoS.

In conclusion, MMF may be a safe alternative in severe MTX-refractory or MTX-intolerant patients with LoS and may be an efficacious alternative to MTX in patients with severe LoS. More evidence is needed to compare MMF with MTX in patients with severe LoS.

The authors declare no conflicts of interest.

REFERENCES