Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil

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Objective. To evaluate the efficacy of mycophenolate mofetil (MMF) in the treatment of severe refractory juvenile localized scleroderma (JLS).

Methods. A retrospective chart review was performed in patients with JLS who had been treated with MMF after the failure of a combination of MTX and corticosteroids for at least 4 months, or whose JLS had concomitant severe extracutaneous manifestations. Outcome was assessed through clinical examination and thermography. Adverse events were recorded.

Results. Ten patients (six females and four males) were enrolled in the study. JLS clinical subtypes were deep morphoea (two patients with disabling pansclerotic morphoea), generalized morphoea (three patients), linear scleroderma (five patients) affecting the limbs in two and face in three patients (en coup de sabre). The age at onset of disease was 8 (range 2–16) years, and the disease duration at the time of treatment with MMF was 18 (range 8–62) months. All MMF-treated patients experienced clinical improvement that allowed withdrawal or reduction of doses of corticosteroids and MTX. Over a follow-up of 27 (range 6–56) months, mild abdominal discomfort was reported in only one patient.

Conclusions. MMF appears to be effective in arresting disease progression in severe or MTX-refractory JLS and is generally well tolerated. Further controlled studies are needed to confirm these data.

Key words: Localized scleroderma, Treatment, Methotrexate, Mycophenolate mofetil, Child.

Introduction

Juvenile localized scleroderma (JLS) includes a number of conditions characterized by the presence of areas of skin thickening with varying severity such as plaque morphoea, linear scleroderma and the ‘en coup de sabre’ (ECDS) which characteristically occurs on the face. The most frequent subtype is linear scleroderma affecting limbs or face, which accounts for around two-thirds of patients, followed by plaque morphoea (25%) and generalized morphoea, whereas other subtypes, such as deep and bullous morphoea, are very rare [1]. Although JLS may be relatively benign, many patients develop both cosmetic and functionally deforming effects due to the involvement of deeper subcutaneous tissue, muscle and bone. Many children, particularly those with the linear subtype, develop severe deformities, joint limitation and limb length discrepancy. In the ECDS variety, hemiatrophy of the face may develop with consequent cosmetic problems as well as involvement of eyes and brain, which may lead to serious complications [2].

Many treatments have been tried so far with variable success. These include D-penicillamine, cyclosporin, ultraviolet light therapy and vitamin D analogues [3–7]. During the last several years, various investigators, in uncontrolled studies, have reported efficacy using a combination of low-dose MTX and corticosteroids [8–10]. Although a large number of patients with JLS respond to this treatment, for some patients it is ineffective or not well tolerated. In addition, ~25% of the patients with JLS have extracutaneous manifestations, such as cerebral involvement, which may require additional therapeutic agents.

In this study, we investigated the efficacy of mycophenolate mofetil (MMF), an agent which not only inhibits proliferation of lymphocytes, but also of smooth muscle cells and fibroblasts [11], in a cohort of patients with severe JLS.

Materials and methods

Patients with JLS followed at five Paediatric Rheumatology Units (Padova and Florence, Italy; Würzburg, Germany; Bristol, UK; and Philadelphia, PA, USA) were included in the study. The diagnosis and classification of JLS was made clinically by experienced paediatric rheumatologists, according to the Mayo Clinic classification which include: (i) plaque morphoea, (ii) generalized morphoea, (iii) bullous morphoea, (iv) linear scleroderma including ECDS and Parry–Romberg disease and (v) deep morphoea including the four subtypes: subcutaneous morphoea, morphoea profunda, disabling pansclerotic morphoea and eosinophilic fasciitis [12]. In six patients, the diagnosis was confirmed by skin biopsy.

MMF was introduced when JLS was judged to be persistently active despite therapy with i.v. and/or oral steroids and MTX for at least 4 months. In one patient (No. 6) with ECDS, MMF was chosen first because of reactivation of skin lesion and concomitant severe extracutaneous manifestations such as cerebral and ocular vasculitis. Moreover, parents had refused any other proposed immunosuppressive agents. This patient has been described previously as a case report [13].

The disease was defined as active by the appearance of new lesions or an increasing size of previous lesions, clinical signs of active inflammation such as erythema and/or by detection of disease activity by thermography. Thermography was performed solely in the Italian cohort of patients at the Paediatric Rheumatology Unit of Padova, by the same thermographer (G.M.) using the infrared camera FLIR P695 Thermacam.
(Flir Systems, Stockholm, Sweden). Patients were scanned undressed, 15 min after acclimatation. Lesions were defined as ‘active’ on thermography when the affected area was >0.5°C warmer than the contralateral area or the surrounding skin depending on the site of the lesion itself.

A favourable response to treatment was defined as the absence of extension of the lesions and improvement in at least one of the following: signs of inflammation, softening and/or lightening of the skin by clinical examination and/or absence of activity by thermography.

Relevant laboratory tests results during the disease course were recorded and included acute phase reactants such as ESR and CRP, total white blood cell count (WBC), eosinophil count, creatine kinase, aldolase, ANAs and anti-ENA antibodies.

**Results**

**Patients**

Ten patients, six females and four males, were included. The mean age at onset of the disease was 8 (range 2–16) years and the mean duration of disease at the time of diagnosis of JLS was 14.5 (range 2–47) months. Three patients had generalized morphoea; two had deep morphoea (disabling pansclerotic morphoea subtype) affecting lower limbs (one of them also having one plaque of morphoea on the trunk); and five had linear scleroderma, of which three had that affecting the upper limbs and two had ECDS (Table 1). In 6/10 patients, a skin biopsy confirmed the clinical diagnosis of scleroderma. Four patients (Nos 1–4) were treated with both regimens at different times. The initial dose of oral prednisone ranged from 0.8 to 1 mg/kg/day, and this was administered for a mean of 13.8 (range 3–34) months. IVMP was given as monthly pulses in four patients (5, 6, 7 and 8 times, respectively), whereas the other four received a series of three daily pulses as initial therapy prior to starting oral prednisone.

Indeed, in 8/10 patients the first treatment was a combination of steroids and MTX and the duration of disease at the start of MTX therapy was 13.7 (range 2–47) months. The dose of MTX was 15 mg/m² in 7/8 patients and 25 mg/m² in one (Patient 5). Side effects associated with steroids and MTX included Cushing syndrome in two patients, abdominal pain in one, ocular hypertension and mood changes in one.

MMF was introduced because of MTX resistance in eight patients and for corticosteroids side effects in one patient. In one patient with ECDS, MMF was chosen as the first therapy because beside skin lesion activation, concomitant cerebral and ocular vasculitis was present. The MMF dose ranged from

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at onset, years</th>
<th>Disease duration at diagnosis, months</th>
<th>Clinical subtype</th>
<th>Associated morbidity</th>
<th>Previous treatment</th>
<th>Disease duration at MMF start, months</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>3.5</td>
<td>18</td>
<td>Pansclerotic + plaque</td>
<td>Right leg, abdomen</td>
<td>IVMP pulses (3), PDN, MTX</td>
<td>11</td>
<td>Arrest of disease progression, erythema reduction, softening</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>4</td>
<td>48</td>
<td>Generalized morphoea</td>
<td>Trunk, left leg, face</td>
<td>IVMP pulses (3), PDN, MTX</td>
<td>62</td>
<td>Arrest of disease progression, erythema reduction, softening</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>16</td>
<td>2</td>
<td>Linear + plaque</td>
<td>Left arm, trunk</td>
<td>PDN, MTX</td>
<td>22</td>
<td>Arrest of disease progression, softening, erythema and joint contractures reduction</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>9.2</td>
<td>5</td>
<td>Linear + plaque</td>
<td>Right arm and shoulder, right leg, trunk</td>
<td>IVMP pulses (3), PDN, MTX</td>
<td>8</td>
<td>Arrest of disease progression, softening, erythema and joint contractures reduction</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>12.9</td>
<td>21</td>
<td>Pansclerotic morphoea</td>
<td>Legs, arms</td>
<td>IVMP pulses (3), PDN, MTX</td>
<td>21</td>
<td>Arrest of disease progression, softening, erythema and joint contractures reduction</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>3</td>
<td>24</td>
<td>ECDS</td>
<td>Left forehead</td>
<td>None</td>
<td>8</td>
<td>Arrest of disease progression</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>9</td>
<td>3</td>
<td>Generalized morphoea</td>
<td>Trunk, legs</td>
<td>IVMP pulses (8), PDN</td>
<td>12</td>
<td>Softening, joint contractures reduction</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>14</td>
<td>8</td>
<td>Generalized morphoea</td>
<td>Both lower and upper limbs</td>
<td>IVMP pulses (6), MTX</td>
<td>12</td>
<td>Arrest of disease progression, regression of old lesions, softening</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>6.5</td>
<td>3</td>
<td>ECDS</td>
<td>Left side of face and scalp</td>
<td>IVMP pulses (7), PDN, MTX</td>
<td>12</td>
<td>Arrest of disease progression, softening, erythema reduction, softening</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>2</td>
<td>14</td>
<td>Linear</td>
<td>Left arm</td>
<td>IVMP pulses (5), MTX</td>
<td>11</td>
<td>Arrest of disease progression, softening, erythema reduction, softening</td>
</tr>
</tbody>
</table>

PDN: oral prednisone.
600 to 1200 mg/m²/day twice daily. The mean duration of MTX treatment before the start of MMF was 6.6 (range 4–15, median 7.5) months. When MMF was started, the mean disease duration was 18 (range 8–62) months. In six patients, both immunosuppressants were administered, whereas in two patients MTX was discontinued at MMF introduction. The mean duration of treatment with MMF, at last follow-up evaluation, was 20 (range 6–40) months. No patients dropped out, whereas in one (Patient 2) patient MMF was tapered and then definitely discontinued after 36 months by the treating physician because of a persistent disease remission.

Outcome

As shown in Table 1, all patients treated with MMF presented a favourable response defined as the absence of extension of the lesions and improvement in at least one of the following: signs of inflammation, softening and/or lightening of the skin by clinical examination and/or absence of activity by thermography. In 7/10 patients erythema disappeared and in 9/10 softening of the skin was noticed and none of the patients developed any new lesions during treatment (Fig. 1). Moreover, in three patients an improvement of the restriction of joint movement was recorded. The patient with ECDS associated with ocular and cerebral vasculitis exhibited markedly improved ophthalmological examination and an arrest of progression of cerebral vasculitis as shown by MRI.

Thermography detected significant improvement, consistent with clinical assessment, in all the four patients monitored by this technique; in particular, in Patients 2, 3 and 4 there was a complete resolution of the hyperthermia noted at the start of MMF after 3 months and beyond (Fig. 2). In Patient 1, a significant decrease of disease activity was noticed (a difference of 3.2°C in the affected area when compared with the contralateral region, decreasing to 1.2°C after 6 months of treatment).

Corticosteroids and MTX were significantly reduced in five patients and completely withdrawn in one. The mean time interval needed to achieve definite clinical improvement was 3.5 (range 3–6) months. During the follow-up period, only mild abdominal discomfort in one patient was reported. No haematological or biochemical abnormalities were noted.

Discussion

Our results suggest that MMF was effective and well tolerated in patients with severe JLS with or without extracutaneous manifestations. Indeed, the clinical response was quite rapid with substantial improvement after an average of 3.5 months from the start of treatment.

MMF is a selective inhibitor of de novo purine biosynthesis and exerts a relatively specific inhibitory effect on T- and B-lymphocyte proliferation [11, 14]. It is currently utilized mostly for the prophylaxis of renal, cardiac and hepatic transplant rejection and is increasingly being used in the management of autoimmune diseases such as lupus nephritis in adults and children [15, 16]. In dermatological conditions such as psoriasis, pemphigus lichen planus and pyoderma gangrenosum, MMF also has been found to be both effective and well tolerated [17–20].

Recent in vitro studies show that MMF inhibits proliferation of not only lymphocytes but also of other cell types, including smooth muscle cells and fibroblasts [11]. Moreover, MMF has been shown to directly inhibit several fibroblast functions that are amplified in fibrotic disorders, such as scleroderma, chronic GVHD and chronic allograft nephropathy [21]. In particular, MMF has been shown to inhibit type I collagen expression, to enhance the expression of MMP-1, which is reduced in fibrotic processes such as liver and cardiac fibrosis [22, 23], and to alter both the migratory and contractile functions of fibroblasts. Thus, it has been hypothesized that MMF has direct anti-fibrotic properties in addition to its well-known immunosuppressive effects.

Several clinical studies demonstrated the efficacy of MMF in systemic scleroderma-related lung disease, and in two studies the cutaneous response to MMF in SSc was assessed [24, 25]. The first study evaluated the response of 13 patients treated initially with anti-thymocyte globulin for 5 days followed by 12 months of MMF as maintenance therapy [24]. MMF was very well tolerated and resulted in a significant decrease in the skin score. In the second study, a retrospective comparison between 109 patients with SSc treated with MMF and 63 who received other immunosuppressive agents showed that there was no significant difference between the two groups of treatment [25]. Recently, treatment with MMF was successfully used to induce partial or complete and lasting remission in another fibrotic autoimmune disorder, retroperitoneal fibrosis [26].

To date no previous study measured the effect of MMF in localized scleroderma. In the present study, we found that...
MMF resulted in significant clinical improvement that allowed a decrease of corticosteroids and MTX dose and even discontinuation. In particular, the beneficial effect of MMF was evident in the eight patients who, after a reasonably long period of treatment with MTX, did not obtain a significant control of the disease.

In the last 8 years, since the first observations of Uziel et al. [8] the treatment of choice for JLS has been a combination therapy with low-dose MTX and corticosteroids. Since then, other two additional case series documented favourable results with this regimen [9, 10]. In our personal experience, 70–80% of the patients respond to corticosteroids and MTX, as reported by other groups [10, 27]. However, all studies on MTX are retrospective, non-randomized and include small cohorts of patients. Therefore, they are subject to multiple limitations such as absence of blinded observers, lack of standardized methods for disease activity assessment and bias due to physicians’, patients’ and families’ judgement.

Our present study, although with the limits of being small sized and retrospective, suggests that MMF may represent a valid alternative to MTX, particularly in severe cases, when extracutaneous manifestations or deformities and growth impairment are present, such as disabling pansclerotic morphea and generalized morphea. Indeed, as MMF is more expensive than MTX and corticosteroids, it would be prudent to use it only after documented failure of these other agents. Based on our preliminary but encouraging results of this study, further larger controlled studies of MMF are warranted to optimize the therapeutic approach to this rare condition.

**Rheumatology key messages**

- MMF may represent a valid alternative to MTX in JLS.
- MMF may be helpful in MTX-refractory cases or when deformities and growth impairment are present.

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**References**


