# Mycophenolate mofetil for localized scleroderma

**Evaluation of: Martini G, Ramanan AV, Falcini F *et al.*: Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. *Rheumatology (Oxford)* 48, 1410–1413 (2009).** This retrospective study reports the outcome of mycophenolate mofetil (MMF) treatment in ten juvenile patients with severe or methotrexate-resistant localized scleroderma (two with pansclerotic morphea, five with linear scleroderma and three with generalized morphea). The clinical efficacy of MMF was assessed by clinical examination and thermography. The authors demonstrated efficacy of MMF in reducing the signs of inflammation, softening or lightening of skin lesions, which allowed reduction in dosage or withdrawal of corticosteroids and methotrexate in all patients. MMF was well tolerated and the investigators concluded that MMF is a valid alternative to methotrexate in arresting disease progression in juvenile localized scleroderma.

**KEYWORDS: antifibrotic ▪ clinical trial ▪ linear scleroderma ▪ morphea ▪ mycophenolic acid ▪ systemic sclerosis**

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## Commentary

Systemic sclerosis is one of the rheumatic diseases that is associated with the worst prognosis. Systemic sclerosis is divided into localized and systemic forms. Localized scleroderma comprises four subtypes, namely morphea, generalized morphea, linear scleroderma and en coup de saber, and is more commonly encountered in children. Although conversion into systemic sclerosis is very uncommon [1], localized scleroderma can be extremely disabling owing to formation of mutilating contractures and deformities, and cosmetic disfigurement, as well as the increased susceptibility of the sclerodermatous tissue to ulceration and malignant transformation.

There are many treatment options of localized scleroderma, but their efficacy have not been confirmed by controlled trials. These include ultraviolet-A phototherapy, highly potent topical glucocorticoids, calcipotriol, D-penicillamine, hydroxychloroquine, methotrexate (MTX) and cyclosporin A [2–4]. A recent, open-label, prospective study has reported efficacy and safety of monthly intravenous pulse methylprednisolone and oral MTX (15 mg/week) in the treatment of severe localized scleroderma [5]. Combined high-dose methylprednisolone, cyclosporin A and antithymocyte globulin has also been reported to be effective in a patient with refractory pansclerotic morphea [6]. However, these treatment regimens are not universally effective and may be associated with potentially serious side effects. Thus, there is a need to explore safer and more effective treatment for localized scleroderma.

Mycophenolate mofetil (MMF) is an immunosuppressive agent commonly used in transplant medicine and autoimmune diseases owing to its inhibitory effects on lymphocyte functions. Recent *in vitro* studies have also revealed that MMF suppresses the functions of smooth muscle cells and fibroblasts [7]. Martini *et al.* recently reported good response of ten juvenile patients with severe or refractory localized scleroderma to MMF treatment [8]. Although the findings of this retrospective study are anecdotal and have to be confirmed by larger scale, placebo-controlled trials, they suggest that MMF exerts both anti-inflammatory and antifibrotic actions on skin lesions of scleroderma.

## Methods

This is a retrospective study carried out in five pediatric rheumatology units in Europe. Patients with severe or MTX refractory active juvenile localized scleroderma who were treated with MMF were included. Juvenile localized scleroderma was diagnosed clinically by experienced pediatric rheumatologists with or without confirmation by skin biopsy, and classified according to the proposal of the Mayo Clinic (MN, USA) [9]. Active disease was defined as increasing size of pre-existing lesions or appearance of new lesions, with clinical signs of active inflammation, such as erythema and/or evidence

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from thermography. Refractoriness to treatment referred to persistently active skin lesions, despite therapy by corticosteroids and MTX for at least 4 months. A favorable response to treatment was defined as the absence of extension of lesions and improvement in at least one of the following: signs of inflammation, softening and/or lightening of skin by clinical examination and/or absence of activity by thermography.

## Results

Ten patients were studied (six females and four males) and the mean age of onset of localized scleroderma was 8 years (range: 2–16 years). The subtypes of localized scleroderma were generalized morphea (three patients), pansclerotic morphea (two patients) and linear scleroderma (five patients). All except one patient had been treated with high-dose corticosteroids. Eight patients had been treated with a combination of corticosteroids and MTX (15 mg/m$^2$ in seven patients and 25 mg/m$^2$ in one patient for a median duration of treatment of 7.5 months). MMF was introduced in eight patients owing to resistance to MTX and one patient owing to side effects to corticosteroids. In the remaining patient, MMF was used as first-line treatment owing to concomitant cerebral and ocular vasculitis.

Mycophenolate mofetil was administered at doses ranging from 600 to 1200 mg/m$^2$/day. The mean duration of treatment was 20 months (range: 6–40 months). No patients withdrew from MMF treatment but one patient was discontinued MMF owing to persistent disease remission for 36 months.

All MMF-treated patients had improvement in their skin lesions. Skin erythema disappeared in seven patients and softening of skin lesions occurred in nine patients. None of the patients had worsening of existing skin lesions or development of new skin lesions. Thermography documented significant reduction or complete resolution of hyperthermia in four patients. The mean time interval for improvement was 3.5 months (range: 3–6 months). Corticosteroids and MTX doses could be significantly reduced or withdrawn in six patients. MMF was well tolerated. The authors suggested that MMF is a valid alternative therapy to MTX, particularly in severe cases of localized scleroderma.

## Discussion & future perspective

Mycophenolate mofetil is a prodrug with very good oral bioavailability that undergoes rapid hepatic hydrolyzation to produce mycophenolic acid (MPA). MPA is a noncompetitive inhibitor of inosine 5-monophosphate dehydrogenase, the rate-limiting enzyme in *de novo* purine biosynthesis. Compared with other eukaryotic cells, T and B lymphocytes are more dependent on this *de novo* pathway of purine synthesis. As a result, MMF inhibits functions of activated lymphocytes [10] through inhibition of DNA synthesis. Compared with azathioprine, another purine antagonist, and cyclophosphamide, a conventional alkylating agent, the actions of MMF are more lymphocyte selective. In transplant studies, MMF is more potent than azathioprine in suppressing antibody responses [11]. Moreover, *in vitro* studies have demonstrated that MPA induces apoptosis of polyclonally activated human T lymphocytes and downregulates expression of adhesion molecules on endothelial cells [12].

In addition to its inhibitory effects on lymphocyte functions and cellular chemotaxis, MMF has been demonstrated to inhibit proliferation of other cell types, which include renal mesangial cells, fibroblasts and smooth muscle cells [7,13]. Of interest are the inhibitory actions of MMF on several functions of fibroblasts, such as motility and migration, contractility, synthesis and expression of type I collagen expression [7]. On the other hand, MMF enhances the expression and synthesis of interstitial collagenase (matrix metalloproteinase-1), which is involved in fibrotic processes, such as liver and cardiac fibrosis [14]. In a murine model, MMF was demonstrated to reduce the TGF-β1 gene expression and protein synthesis in lung tissues [15]. These properties of MMF make it attractive as a therapeutic agent for the treatment of fibrotic diseases, such as scleroderma, interstitial lung diseases, graft-versus-host disease and retroperitoneal fibrosis.

The pathogenesis of systemic sclerosis is still enigmatic [16]. In the early inflammatory/edematous stage, activation of the immune system occurs with T-cell activation, production of autoantibodies, cytokines and growth factors, that in turn contribute to fibroblast activation and deposition of collagen in various organ systems, as well as vascular pathologies. The initial immune activation could create autocrine loops that require no further stimulus to perpetuate the fibrotic and vascular lesions. Thus, the anti-inflammatory and antifibrotic properties of MMF justify clinical trials of this agent in early scleroderma.

Indeed, several case series or open-label studies have reported efficacy of MMF, with and without concomitant corticosteroids, in early

scleroderma lung disease, with stabilization or improvement in vital capacity and diffusion capacity [17–19]. Two uncontrolled studies assessed the change in skin scores after MMF treatment in systemic sclerosis [20,21]. In the pilot study by Stratton *et al.*, 13 patients with recent onset of diffuse scleroderma were treated with 5 days of antithymocyte globulin, followed by MMF for 12 months [20]. Significant improvement in scleroderma skin scores was observed. In a second study from the same group of investigators, the clinical records of 109 scleroderma patients treated with MMF and 63 control subjects receiving other immunosuppressive drugs were reviewed [21]. Treatment with MMF was well tolerated up to 5 years. Overall, 12% of patients experienced adverse reactions with gastrointestinal intolerance and infections being most frequent. There was a significantly lower frequency of clinically significant pulmonary fibrosis in MMF-treated patients, which was associated with a significantly better 5-year survival from disease onset and commencement of MMF. However, no significant difference between the two groups in terms of changes in modified Rodnan skin score and forced vital capacity was observed.

To date, there has not been any published study on the efficacy of MMF in localized scleroderma. Although the pilot experience of Martini *et al.* appears to be encouraging [8], some cautions should be exhibited in the interpretation of the results. First, this is a retrospective and uncontrolled study. Spontaneous improvement of skin lesions remains a possibility. Second, the sample size is small and selection bias is unavoidable. Third, the delayed effects of previous treatment, such as high-dose corticosteroids and MTX, cannot be totally ignored. Fourth, owing to the small sample size, analysis of the degree of improvement of subtypes of localized scleroderma is not possible. Finally, biomarkers of collagen turnover and lymphocyte activation are not studied, and neither are the changes in expression of TGF-β1 on skin biopsy samples before and after treatment.

Despite these caveats, the results of the study by Martini *et al.* suggest antifibrotic and anti-inflammatory properties of MMF [8]. Larger scale, multicenter, placebo-controlled trials should be arranged for proper evaluation of the efficacy of MMF in the treatment of skin lesions of localized scleroderma and systemic sclerosis.

**Financial & competing interests disclosure**

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**Executive summary**

- *In vitro* and animal studies have revealed antifibrotic properties of mycophenolate mofetil (MMF).
- Preliminary evidence demonstrates that MMF is effective in halting the progression of sclerotic skin lesions in juvenile localized scleroderma.
- The role of MMF in the treatment of scleroderma skin lesions and major organ manifestations, such as interstitial lung disease, has to be tested in larger scale, placebo-controlled trials.

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