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Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: Poor results with mycophenolate mofetil

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ABSTRACT

Objective. *Skin disease can be one of the most refractory clinical manifestations of systemic lupus erythematosus (SLE). The standard therapy consists of sunscreens, topical corticosteroids and antimalarials. However in difficult cases a variety of other drugs have been tried. Here we describe our clinical experience with mycophenolate mofetil (MMF) in patients with cutaneous manifestations of SLE.*

Methods. *Seven patients with SLE and skin involvement (including acute cutaneous lupus, subacute cutaneous lupus, discoid lupus erythematosus, vasculitis, urticarial rash and chilblain lupus) who had received treatment with MMF were included. The clinical characteristics, serological findings and response to treatment were recalled from retrospective review of the files.*

Results. *Our results showed no response in 5 patients, partial response in 1 patient and initial response but skin flare whilst on MMF in 1 patient. The median dose of MMF was 2 g (range 2-3 g). Adverse events on MMF were mild, mainly gastrointestinal and occurred in 5 patients. No patients discontinued MMF due to adverse events.*

Conclusions. *MMF appears not to be particularly effective in the treatment of skin disease in SLE. It should be noted that our group of patients had previously failed to respond to a median of 4 (range 2-10) different drugs used to treat SLE skin disease. Thus, the patients in the study could be considered at the severe end of skin disease spectrum.*

Introduction

Skin disease represents an important clinical manifestation of systemic lupus erythematosus (SLE) with a large spectrum of different presentations, and affects 70% of patients during the course of the disease (1). Cutaneous lupus erythematosus (LE) can also present as a skin eruption without systemic disease and includes a variety of LE specific skin lesions. The skin lesions seen in patients with lupus can be classified into those that are lupus-specific histologically, and those that are lupus-nonspecific. The lupus-specific lesions may be further divided into those that are acute, subacute cutaneous lupus erythematosus (SCLE), and chronic LE (2).

The acute lesions include the 'butterfly' rash, pathologically, the lesions may show only non-specific inflammation, although by immunofluorescence the classic immune deposits at the dermal–epidermal junction may be seen. Other acute lesions include generalized erythema, which may or may not be photosensitive and bullous lesions. SCLE refers to a distinct cutaneous lesion which is nonfixed, nonscarring, exacerbating and remitting. The lesions originate as erythematous papules or small plaques with a slight scale and may evolve further into a plaque and scale, the papulosquamous variant, which mimics psoriasis or lichen planus, or merge and form polycyclic or annular lesions which may mimic erythema annular centrifugum. The most common manifestation of chronic lupus is discoid lupus (DLE). The lesions may occur in the absence of any systemic manifestations, as discoid lupus, or may be a manifestation of SLE. These lesions often begin as erythematous papules or plaques, with scaling which may become thick and adherent with a hypopigmented central area. As the lesion progresses follicular plugging occurs, with the development of scarring with central atrophy. Discoid lupus may be localized or generalized.

The standard therapy consists of sunscreens with UVA and UVB filters, topical corticosteroids and antimalarials. However in refractory cases a variety of other drugs have been tried, including dapsone, thalidomide, retinoids, topical tacrolimus, gold methotrexate, azathioprine, cyclophosphamide, cyclosporin A, methylprednisolone pulses, intravenous immunoglobulin (IVIg) (3-7). Limitations of these agents include variable efficacy and toxicity. For example, while thalidomide is very effective it causes neuropathy even at low doses (8). Hence, there is a need for further effective agents with low toxicity.

Mycophenolate mofetil (MMF) is an immunosuppressive agent, which has been used very effectively in organ

transplantation. Reports of its use have been favourable in a number of autoimmune diseases including SLE (9). The major experience in SLE has focused on proliferative lupus nephritis whilst details on its efficacy for other organ involvement are less well described. MMF is effective in the treatment of various autoimmune bullous skin diseases such as pemphigus vulgaris, bullous, pemphigoid, epidermolysis bullosa acquisita and psoriasis (9).

MMF has also been used with good results to treat cutaneous manifestations of systemic autoimmune diseases such as SCLE, DLE, chilblain lupus and skin manifestations of dematomyositis (10-14). Here we describe our clinical experience with MMF in 7 patients with refractory cutaneous manifestations of SLE.

Patients and methods

Seven patients fulfilling at least four criteria for the classification of SLE (15) and skin manifestations who had received treatment with MMF were retrospectively studied. Four patients attended the Lupus Unit at St Thomas' Hospital within the last five years and 3 patients attended the autoimmune skin disease clinic at the Clinical Department of Dermatology and Venerology, Innsbruck Medical University, Austria. Four patients received MMF specifically to treat skin involvement and 3 patients were treated with MMF for renal and skin involvement.

Patient records were studied for response to previous treatments, details of MMF therapy and clinical outcome. For data collection related to MMF treatment, patient records were reviewed from commencement of the drug until the final time point, defined as last follow-up or withdrawal of the drug. Starting dose, maximum dose and duration of treatment with MMF were available. All prior treatments for skin disease were documented including immunosuppressive, antimalarial and other therapies.

Outcome measures were not formally assessed at outset. Assessment of the degree of improvement in rash was not systematic, being based on the joint overall impression of patient and treating physician. Treatment response was considered as complete remission when clearance of rash occurred, partial remission defined retrospectively as good to very good but less complete improvement in rash, no response as no changes in skin rash and or initial response with subsequent flare.

Adverse event information and reasons for MMF discontinuation were obtained from physician evaluation noted in the records from baseline to final time point.

Clinical features

Six of 7 patients were female. Median age at diagnosis was 35 years (range 18-53). The median duration of SLE was 6 years (range 3-13).

The following types of cutaneous lesions were observed: acute cutaneous lupus erythematosus (ACLE) 4 patients, SCLE 1 patient, DLE 3 patients, vasculitis 2 patients and chilblain-lupus in 1 patient. Three patients displayed more than one type of rash. Further clinical details are given in Table I.

Skin biopsy was performed in 5 patients. It was usually not performed in patients with clinically characteristic LE lesions like DLE or chilblain lupus. Biopsy showed cutaneous leukocytoclastic vasculitis in 2 patients (with the clinical appearance of urticarial vasculitis and cutaneous necrotizing vasculitis, patients number 5 and 6 in Table I). One patient, who had long-term psoriasis vulgaris, developed SCLE, with biopsy displaying characteristic interface dermatitis and mucin deposits (patient number 2 in Table I). DLE was confirmed with biopsy in 1 patient (number 3 in Table I). In one patient with SLE presenting with extensive erythematosus rash, biopsy showed granular deposits of IgM and C3 at the dermoepidermal junction (Patient number 1 in Table I).

Results

Previous treatments

Patients had received a median of 4

Table I. Clinical characteristics.

Patient	Age	Sex	Race	Dx	Year Dx Skin	Other organs	Skin	Biopsy	Antibody
1	22	F	Caucasian	SLE	1996	Joints/cerebral/renal	ACLE	Yes	ANA/dsDNA
2	53	F	Caucasian	SLE	1998	Joints/heart	SCLE	Yes	ANA, Ro
3	42	F	Caucasian	SLE	1987	Renal/serositis	DLE/malar rash (ACLE)	Yes	ANA/dsDNA/Ro
4	29	F	Caucasian	SLE	2000	Joints/CNS	DLE of mucous membrane (mouth), ACLE	No	ANA/Ro/La/Sm/ RNP
5	35	M	Black	SLE	1996	Renal	DLE/ACLE/leucocytoclastic vasculitis	Yes	ANA/dsDNA/Ro/ RNP/Sm
6	50	F	Caucasian	SLE	1995	Joints/serositis	urticarial vasculitis	Yes	ANA/Ro/La
7	18	F	Caucasian	SLE	1999	Renal/ joints	Chilblain lupus	No	ANA

Dx: diagnosis; ACLE: acute cutaneous lupus; SCLE: subacute cutaneous lupus erythematosus; SLE: systemic lupus erythematosus; F: female; M: male; CNS: central nervous system; DLE: discoid lupus erythematosus.

Table II. Previous treatments.

Patient	Previous therapy	Number of previous drugs	Drug with good response	Reason to stop drug with good response
1	Chloroquine/AZA/Quinacrine/Cyclosporin A/ iv Cyp/ Thalidomide/ MTX/Prednisolone	8	Thalidomide	Thalidomide: amenorrhoea and flare
2	MP/AZA/HCQ/ MTX	4	No	No
3	Prednisolone/AZA/MTX/HCQ/mepacrine/ MPpulses/ thalidomide/ acitretin/ auronafin	10	Thalidomide/AZA	Thalidomide: neuropathy AZA: flare
4	Prednisolone/MTX/Cyclosporin A/iv Cyp	4	No	No
5	Prednisolone/HCQ	2	Mepacrine after MMF	Continue
6	Prednisolone/dapsone/AZA/ thalidomide/MTX	5	AZA	AZA: flare
7	Prednisolone/ iv Cyp/AZA	3	Iv Cyp	Achieved renal remission

HCQ: hydroxychloroquine; iv Cyp: intravenous cyclophosphamide; MTX: methotrexate; MP: methylprednisolone; AZA: azathioprine; MMF: mycophenolate mofetil.

Table III. Treatment with MMF.

Patient	Time on MMF (months)	MMF (Max dose)	Adverse events	Response	Stop MMF
1	2	2	No	No	Lack of efficacy
2	2	2	GI	No	Lack of efficacy
3	24	2	No	No	MMF continued (renal)
4	2	3	GI, effluvium	Initial/flare	Lack of efficacy
5	42	2	Flu-like symptoms	No	Lack of efficacy (renal and skin)
6	32	2	No	Partial	MMF continued (renal)
7	11	2	GI, anxiety	No	Lack of efficacy

GI: gastrointestinal.

drugs (range of 2 to 10 drugs) to treat skin manifestations of SLE, including the following: hydroxychloroquine, chloroquine, mepacrine, thalidomide, dapsone, acitretin, oral gold, prednisolone, intravenous methylprednisolone pulses, azathioprine, methotrexate, cyclosporin A, and intravenous cyclophosphamide pulse therapy. Further details are given in Table II. Two patients had a good previous response with thalidomide, 2 with azathioprine, 1 with cyclophosphamide. The two patients that achieved a good response with thalidomide had stopped the drug due to adverse events (neuropathy and amenorrhea).

MMF treatment

The median dose of MMF was 2 g (range 2-3 g); the median treatment duration was 11 months (range 2-42 months). No clinical improvement of skin disease was seen in 5 patients, 1 patient had a partial response (achieved in 2 months) and 1 had an initial response (achieved at 6 weeks) and then flared again while still on MMF treatment. No patient had a complete remission.

Adverse events on MMF were mild and occurred in 4 patients (Table III).

Discussion

A minority of patients with predominantly cutaneous manifestations of SLE may be refractory to conventional treatment (sunscreens, topical steroids and antimalarials). Therapeutic failure could be due to drug intolerance, adverse events or inability to induce remission or disease flare while being treated with the drug.

MMF is an immunosuppressive drug that is becoming a commonly used drug in lupus nephritis and more recently is being used for other clinical manifestations. It is a reversible inhibitor of inosine monophosphate dehydrogenase, which catalyses a rate-limiting step in the novo synthesis of purine nucleotides. MMF causes inhibition of T- and B-lymphocyte proliferation, decreases antibody production and adhesion molecule expression (9). The rationale of using MMF to treat LE skin lesions might include a reduction of leukocyte migration to skin (as a result of inhibition of adhesion molecules expression), and inhibition of T- and B-

cell proliferation which constitute the bulk of inflammatory infiltrate in LE skin (10).

This study describes our observations regarding the use of MMF in SLE patients with resistant skin lesions. Because of the retrospective nature of the study, assessment of treatment response was not systematic and was based mainly on physician and patient assessment. Rashes in SLE can either be or not associated with systemic disease flares making assessment of individual treatment response even more difficult. Our results showed no response in 5 patients, partial response in 1 patient and initial response but skin flare while being on MMF in 1 patient. All the patients received an adequate dose and were treated for 2 months or more (range 2-42 months) with MMF. Overall, MMF was well tolerated, with no patient stopping the drug due to adverse events. Three patients had gastrointestinal symptoms, 1 patient flu-like symptoms, 1 patient had anxiety and 1 patient effluvium.

Our results contrast with previous reports of successful treatment of cutaneous LE and skin rash in dermatomyositis with MMF. Boehm & Bieber reported the use of MMF in a patient with refractory chilblain lupus who had previously failed on azathioprine, dapsone, combination of antimalarials and prednisone. Their patient improved substantially after 6 weeks on MMF (10). Hanjani & Nousari reported a patient with discoid LE and lupus profundus previously treated with prednisone, hydroxychloroquine, quinacrine and azathioprine with complete remission of skin disease in a few weeks with MMF (11). Shanz *et al*. reported 2 patients with SCLE, 1 previously treated with hydroxychloroquine and prednisone and the other with antimalarials, prednisone and azathioprine with good response to MMF in 3 weeks and stable disease on maintenance (12). Goyal & Nousari reported 2 cases of resistant palmoplantar lesions successfully treated with MMF, one of the patients requiring 3 g (13). A report of effective treatment with MMF in the skin rash of 4 dermatomyositis patients was published by Gelber *et al*. (14).

It should be noted that our group of patients had previously failed to respond to a median of 4 (range 2-10) different drugs used to treat LE skin disease while in the other reports patients had used a range 2 to 5 drugs. Thus, our group should be considered as resistant skin disease, which probably accounts for a minority of the overall skin disease burden in SLE. Another reason for the lack of response in our patients may be dose and time related. In our group, we used a median dose of 2 g (range 2-3); one of the two patients that responded received 3 g of MMF. However, it is worth noting that in the case reports mentioned earlier with positive results, the dose range was usually 2 g, with the exception of Goyal *et al*. who used 3 g daily. In proliferative lupus nephritis, Chan *et al*. used a starting dose of 2 g daily for induction therapy (16), and 2-3 g has been used in renal transplantation. In our experience MMF at a dose of 2 g was effective in other SLE related manifestations (17).

In conclusion, MMF appeared not to be particularly effective in the treatment of severe and unresponsive to previous treatments skin disease in patients with SLE.

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