Rheumatol Int (1998) 18: 59–62

ORIGINAL ARTICLE

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Management of cutaneous lupus erythematosus with low-dose methotrexate: indication for modulation of inflammatory mechanisms

Received: 20 November 1997 / Accepted 15 June 1998

Abstract There is no consensus about an effective and safe treatment for patients with cutaneous lupus erythematosus (LE) who are refractory to antimalarials and/or low-dose oral glucocorticosteroids. Therefore, we retrospectively analyzed the clinical data and laboratory findings of 12 patients who received weekly administrations of 10–25 mg methotrexate (MTX). Previous treatment with antimalarials and/or glucocorticosteroids was not effective or had to be withdrawn because of side effects. Of 12 patients, ten showed improvement of their skin lesions; two patients did not respond to low-dose MTX; two patients cleared rapidly, and five other patients had long-lasting remissions of 5–24 months after stopping MTX treatment. A reduction of circulating autoantibodies was detected in five patients. In all patients, MTX was well tolerated subjectively and objectively. Weekly low-dose MTX is useful for the treatment of cutaneous LE, particularly in those cases which need long-term treatment and/or do not respond to standard therapeutic regimens.

Key words Cutaneous lupus erythematosus · Immunomodulatory activity · Low-dose methotrexate

Introduction

When patients with cutaneous lupus erythematosus (LE) do not respond to glucocorticosteroids, systemic antimalarials, or an association thereof, more toxic alternatives, e.g., thalidomide, cyclosporine A, and high-dose pulse treatment with methylprednisolone should usually be envisaged. With respect to long-standing disease activity, deciding on a regimen with an acceptable efficacy/risk profile is difficult. For patients with autoimmune diseases, especially for those with rheumatoid arthritis (RA), it became evident that the use of low-dose methotrexate (MTX) provides an interesting therapeutic tool. Consequently, much clinical information and experimental results exist on MTX therapy of this disease. In contrast, clinical data on MTX treatment in LE patients are sparse. Most reports dealing with this subject present cases of systemic LE (SLE) [1–8], and only few patients with cutaneous LE have been described [9–11]. Here we present our experience with low-dose MTX in the treatment of 12 patients with various subsets of cutaneous LE.

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Patients and methods

We retrospectively checked the records of patients with a diagnosis of cutaneous LE who had been admitted to our department between January 1991 and October 1996. Only those cases treated with low-dose methotrexate because of ineffective therapeutic modalities with antimalarials and/or systemic corticosteroids were included. Twelve patients met these inclusion criteria.

The diagnosis of LE was biopsy-proven in all patients. Systemic involvement was excluded by detailed examinations, including chest X-ray, sonography of the abdomen, kidney function analysis, neurologic and ophthalmologic examination, heart sonography and computed tomography of the abdomen, thorax, and/or cerebrum.

After careful checks for contraindications to MTX, i.e., liver disease, elevated liver enzymes, alcohol abuse, altered liver and/or kidney function, anemia, and immunosuppression as detected by flow cytometric analysis of peripheral blood mononuclear cells, the patients received 10–25 mg MTX intravenously or orally weekly. The pa-

Table 1 Clinical data and autoantibodies of 12 patients with different lupus erythematosus (LE) subsets who received low-dose MTX treatment

Patient	Sex/age (years)	LE subset	dsDNA-antibody	Ro/La	ANA (Hep2)	Other auto-Abs	Associated symptoms
1	F/35	DLE	∅	–/–	1:1280[a]	RNP-Sm	Diarrhea
2	F/65	SCLE	∅	+/–	1:160[a]	∅	Vomitus
3	F/38	SCLE	534 IU/ml	+/+	1:2560[b]	U1-sn-RNP, RNP-Sm, cardiolipin Abs	Arthralgia, nephrolithiasis, cephalgia
4	F/48	DLE	∅	–/–	∅	Anti-parietal-cell Abs	Mucocutaneous lesions, Raynaud's phenomenon
5	M/51	SCLE	326 IU/ml	–/–	1:320[a]	Cardiolipin Abs	Arthralgia
6	M/43	SCLE	∅	+/+	1:160[a]	∅	B-CLL, diabetes insipidus
7	M/28	DLE	∅	–/–	∅	Cardiolipin Abs	
8	M/58	SCLE	∅	+/+	1:160[a]	∅	Recurrent thromboses of the legs, livedo reticularis, helicobacter pylori infection
9	F/85	CLE	∅	+/+	1:320[a]	RNP-Sm, Sm	Myalgia, Raynaud's phenomenon
10	M/59	LEP	84 IU/ml	–/–	1:40[a]	∅	
11	F/86	SCLE	101 IU/ml	–/–	1:320[b] homogen	Cardiolipin Abs	
12	M/55	DLE	∅	–/–	∅	∅	Diabetes mellitus

[a] Speckled immunofluorescence pattern
[b] Homogeneous immunofluorescence pattern
DLE, discoid LE; SCLE, subacute-cutaneous LE; CLE, chilblain LE; LEP, LE profundus

tients were instructed to maintain a topical sunblock. Six patients were concomittantly treated with systemic low-dose corticosteroids and three cases with local applied steroids. During low-dose MTX treatment, routine laboratory tests and lymphocyte subsets, as detected by flow cytometry, were analyzed weekly. The clinical outcome was documented as: Complete response (CR), partial response (PR, >75%), minimal response (MR, 25%–75% of skin lesions cleared), and no change (NC). Concomittantly-applied corticosteroids were tapered off and possibly withdrawn when the skin lesions had started to improve. When a complete resolution of the cutaneous lesions had been achieved, MTX applications were either stopped or the application intervals were lengthened from weekly to every other week or the single dose applied was reduced. Liver biopsy was not necessary since none of the patients reached a cumulative MTX dose of more than 1.5 g.

Results

The patients' clinical characteristics and autoantibody profiles are shown in Table 1. The mean age of the patients was 53 years (range, 28–86 years). The patients' clinical outcome, the weekly applied doses, and the duration of MTX therapy are shown in Table 2.

Ten patients improved (CR, $n = 6$; PR, $n = 4$). In two patients, the skin lesions cleared quickly: they were almost free of cutaneous LE after 2 and 4 weeks of MTX treatment, respectively. The other patients cleared after an average of 6 weeks. In two patients, MTX administration was stopped because of ineffectiveness. A concomittant temporary or permanent treatment with systemic corticosteroids was necessary in six patients. Only one patient showed an exacerbation under MTX which could be improved by a low-dose corticosteroid co-medication. Five patients showed long-term remissions of 5–24 months. In one patient, MTX treatment lasted for nearly 1 year. During this period, a cessation of MTX treatment was impossible since even stretching the injection interval to an every-other-week rhythm led to deterioration of the disease. Following this period, however, the patient had a long-term remission of 21 months. The remaining cases relapsed quickly when MTX injections were discontinued.

A decrease in elevated circulating autoantibodies was observed in five patients under MTX treatment. All patients tolerated low-dose MTX treatment very well. Only mild and temporary elevations in liver enzymes was observed in three patients. We documented neither a decrease of leukocytes, nor of lymphocyte subsets. No withdrawal due to side effects was necessary.

Discussion

In six cases, the cutaneous LE disappeared completely and in four partially under low-dose MTX treatment. Of these, two improved quickly and five other cases had long-lasting remission phases; thus we confirm the previous positive reports of MTX therapy in cutaneous LE [9–11].

Table 2 Overview of the previous treatments and the efficacy of low-dose MTX

Patient	Previous treatment	Single weekly MTX dose	Duration of MTX cycle(s)	Clinical outcome	Comment
1	Systemic corticosteroids	25 mg	9 Weeks 6 Weeks 7 Weeks	CR	Disappearance of gigantic hyperkeratotic lesions on palms and soles; duration of MTX-induced remissions: 5, 9, and 24 months
2	Chloroquine, systemic corticosteroids	12.5–25 mg	6 Weeks 23 Weeks 15 Weeks	CR	
3	Corticosteroids	12.5–25 mg	12 Weeks	CR	Improvement after 2 weeks; duration of MTX-induced remission: 15 months
4	Chloroquine, topical steroids	10–25 mg	50 Weeks	PR	Skin scarring after healing of deep inflammatory LE lesions; MTX-induced remission: 21 months
5	Chloroquine, systemic corticosteroids	25 mg	12 Weeks	NC	
6	Chloroquine, systemic corticosteroids	25 mg	18 Weeks 21 Weeks	CR	Decrease in elevated circulating B-cells
7	Chloroquine	15–25 mg	6 Weeks 6 Weeks	PR	MTX administered orally produced no improvement, whereas i.v. did
8	Systemic corticosteroids plus azathioprin	12.5–25 mg	18 Weeks	PR	Exacerbation during MTX monotherapy, improvement after addition of steroids
9	Topical steroids	12.5–25 mg	14 Weeks	NC	Monotherapy with steroids improved LE lesions
10	Systemic corticosteroids	25 mg	7 Weeks	CR	After withdrawal of MTX, 6 months relapse-free
11	Systemic corticosteroids	10 mg	5 Weeks	PR	
12	Systemic corticosteroids	10–15 mg	7 Weeks	CR	Improvement after 6 weeks

CR, complete response; PR, partial response; NC, no change

The mode of action by which the clinical success is induced is largely unclear. While some authors propose immunosuppressant effects [4], we [12] and others [13] favor immunomodifying activities of the low-dose regimen. This is based on the fact that: (a) Even long-term low-dose MTX treatment does not induce immunosuppression [14] as detected by monitoring of hematologic parameters and lymphocyte subsets; (b) in some cases very low cumulative doses are able to improve the disease [9].

Segal and colleagues [15] were the first to show that MTX inhibits the activity of interleukin-1b (IL-1b), whereas its synthesis and secretion was not affected. We found that MTX blocks the binding of IL-1b to its cell surface receptor in vitro [16]. IL-1 is a proinflammatory mediator which plays a role in many diseases and also seems to be relevant to the pathogenesis of LE [17]. For example, IL-1 up-regulates adhesion molecules on endothelial cells, a crucial step for the invasion of cells from the circulating blood into tissue to form the inflammatory infiltrate. Moreover, LE patients seem to have a defective IL-1 receptor antagonist synthesis [18].

Furthermore, in five patients we were able to demonstrate a decrease in elevated autoantibodies. Previously, O'Meara and coworkers showed that MTX is able to reduce all classes of immunoglobulins in vitro [19]. Interestingly, IL-1, IL-6, and tumor necrosis factor α (TNF-α) are necessary for spontaneous immunoglobulin production in SLE patients [20]. Experimentally, it has been shown that the functional alteration of one or all of these cytokines results in a reduction in antibody production. Moreover, B-cells seem to be a target for IL-1. Patients with SLE have spontaneous IL-1-producing B-cells influencing precursor B-cells to differentiate into immunoglobulin-producing cells as an autocrine mechanism [21]. Therefore, IgG synthesis could be experimentally down-regulated in the presence of antibodies against IL-1 and may possibly be decreased in vivo by agents blocking the release or biological activity of IL-1.

The reason for the unresponsiveness of two of the 12 patients is unclear. Neither age, sex, autoantibody profile, nor LE subset (possibly excepting the chilblain LE) seemed to be responsible for the clinical outcome. We are aware that the patient group treated in this report is too small to draw global conclusions. However, our experience suggests that in the case of unresponsiveness to MTX after 6–8 weeks, further administration of MTX will not improve the disease. When a patient is taking MTX po without clinical improvement, the route should be changed to iv injection, which could lead to therapeutic success (Tables 1 and 2, patient no. 7).

Although we did observe only minor side effects with transiently elevated liver enzymes, the use of MTX carries the risk of other common mild side effects, such as nausea, vomiting, and malaise, and serious side effects, such as hepatotoxicity, hematotoxicity, pulmonary complications, and teratogenesis [12]. Therefore, careful patient selection is recommended in order to avoid or minimize side effects. Patients with increased risk of developing MTX-

induced side effects should be excluded by careful pretreatment examinations. Careful documentation of the MTX dose administered is necessary. Furthermore, during treatment, the patient should be monitored in order to recognize the onset of unwanted effects as early as possible. If the guidelines for MTX treatment [22] are closely respected, the risk of side effects can be reduced.

We conclude from our experiences that low-dose MTX is an useful second-line drug in the treatment of various cutaneous LE subsets. While some cases additionally require low-dose corticosteroids as temporary or permanent co-medication, other LE patients resolve with low-dose MTX monotherapy. Nevertheless, about 16% of LE patients showed no improvement. The individual factor(s) responsible for clinical outcome, speed of resolving the skin lesions, and duration of remission remain(s) to be elucidated in larger patient groups.

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