Cutaneous lupus erythematosus: Update of therapeutic options

Part II

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In the first part of the review, topical agents and first-line systemic treatment options for cutaneous lupus erythematosus were discussed whereas in the second part, recent information on efficacy, dosage, and side effects for further systemic treatment options are described in detail. In contrast to other immunosuppressive agents, such as azathioprine, cyclophosphamide, and cyclosporine, methotrexate has recently received more attention in the treatment of the disease. Further second-line treatment includes retinoids, dapsone, and mycophenolate mofetil. Because of severe side effects or high costs, other agents, such as thalidomide or high-dose intravenous immunoglobulins, are reserved for severe recalcitrant CLE. Biologics, ie, rituximab, have been used to treat systemic lupus erythematosus; however, in CLE, most biologics have only been applied in single cases. In addition to successful treatment, induction of CLE subtypes by biologics has been reported. In conclusion, many treatment options exist for CLE, but not many are supported by evidence from randomized controlled trials. (J Am Acad Dermatol 2011;65:e195-213.)

Key words: biologics; dapsone; lupus erythematosus; methotrexate; mycophenolate mofetil; retinoids; second-line treatment; skin.

Topical agents and first-line systemic treatment options for patients with cutaneous lupus erythematosus (CLE) were discussed in the first part of this review. A structured overview of further systemic treatment options is given in this second part of the review, by summarizing recent information on therapeutic strategies and substances available for the treatment of the different disease subtypes. However, no medication has been approved particularly for the treatment of CLE, although several agents are licensed for systemic lupus erythematosus (SLE) and other immunologic diseases. Moreover, only a few randomized, double-blind, placebo-controlled multicenter trials are available and in most cases, off-label-use of systemic agents is applied in CLE. In this review, we have included a treatment algorithm for practicing dermatologists (Fig 1).

Abbreviations used:

ACLE:	acute cutaneous lupus erythematosus
CHLE:	chilblain lupus erythematosus
CLE:	cutaneous lupus erythematosus
DILE:	drug-induced lupus erythematosus
DLE:	discoid lupus erythematosus
dsDNA:	double-stranded DNA
EC-MPS:	mycophenolate sodium
ECP:	extracorporeal photopheresis
IL:	interleukin
IV:	intravenous
IVIG:	intravenous immunoglobulins
LE:	lupus erythematosus
LEP:	lupus erythematosus panniculitis
LET:	lupus erythematosus tumidus
MMF:	mycophenolate mofetil
MTX:	methotrexate
sc:	subcutaneous
SCLE:	subacute cutaneous lupus erythematosus
SLE:	systemic lupus erythematosus
TNF:	tumor necrosis factor
TPMT:	thiopurine methyltransferase

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SECOND-LINE SYSTEMIC TREATMENT

Methotrexate

Methotrexate (MTX), a folic acid analog, inhibits dihydrofolate reductase responsible for conversion of

dihydrofolate to tetrahydrofolate, which is necessary for several key enzymes involved in the synthesis of pyrimidine and purine nucleotides. The folic acid pathway explains the antineoplastic effects of MTX, whereas it has been supposed that the anti-inflammatory effects of MTX are mediated via the inhibition of lymphocyte proliferation.[1] Recent studies have linked the anti-inflammatory properties of MTX to the effects on adenosine, a purine nucleoside that has potent anti-inflammatory effects on different target cells (inhibition of the oxidative burst in neutrophils and monocytes; prevention of leukocyte chemotaxis; inhibition of monocyte and macrophage secretion of multiple cytokines, eg, tumor necrosis factor [TNF]-alfa, interferon-gamma, and interleukin [IL]-12 and -6). Furthermore, MTX selectively induces apoptosis in activated, proliferating $CD4^+$ T cells and has also been shown to inhibit IL-1 activity.

CAPSULE SUMMARY

- Second-line treatment of cutaneous lupus erythematosus includes methotrexate, retinoids, dapsone, and mycophenolate mofetil.
- Because of severe side effects or high costs, other agents, such as thalidomide or high-dose intravenous immunoglobulins, are reserved for patients with severe recalcitrant cutaneous lupus erythematosus.
- Biologics have been used to treat systemic lupus erythematosus; however, in cutaneous lupus erythematosus, most biologics have only been applied in single cases and induction of the disease by biologics has also been reported.

MTX has been used for the treatment of therapy-refractory subacute CLE (SCLE)[2-5] and discoid lupus erythematosus (DLE).[5-8] In a retrospective study from 1998, 12 patients with different subtypes of CLE (6 SCLE, 4 DLE, 1 lupus erythematosus [LE] panniculitis [LEP], and 1 chilblain LE [CHLE]) were analyzed. All patients received weekly low-dose administration of 10 to 25 mg MTX orally or intravenously (IV), and 10 patients improved.[5] In 6 of these 10 patients, CLE disappeared completely, and 4 patients showed partial remission; in two patients, MTX administration was ineffective. Of the 10, 5 patients showed long-term remission of 5 to 24 months.

In a study of 43 patients with various subtypes of recalcitrant CLE (16 SCLE, 12 DLE, 3 LE tumidus [LET], 1 LEP, 4 CHLE, and 7 SLE with cutaneous manifestations), low-dose MTX was administered either orally or IV.[4] Nearly all patients (98%) showed improvement of skin lesions; the best clinical improvement was seen in patients with SCLE and localized DLE, whereas treatment of disseminated DLE was less effective. Discontinuation of treatment after significant side effects, such as extraordinary increase in liver enzymes (n = 4), nausea (n = 2), and panleukocytopenia (n = 1), was recorded in 7 patients; however, side effects resolved after cessation of MTX. In this study, IV application was tolerated better than oral administration. In 15 of these 43 patients with CLE, who had received MTX IV, the administration was changed to subcutaneous (sc) application in a follow-up study.[9] This sc route of MTX was well tolerated, and it was appreciated by the patients because of easier and self-administered application, while maintaining a similar efficacy.

In addition to the recommended sc injection of 7.5 to 25 mg MTX once weekly, folic acid supplementation is given up to 5 days a week, excluding the day of MTX application and the day thereafter. This can alleviate gastrointestinal side effects; however, many different schemes of protective folic acid supplementation exist. For example, one-time administration 24 hours after MTX application is advised by many rheumatologists.[10] MTX is further known for its bone-marrow toxicity, which calls for regular hemograms, but also for nephrotoxicity and hepatotoxicity. Moreover, it is important to rule out tuberculosis and hepatitis before MTX treatment. Long-term application of MTX can lead to liver fibrosis, cirrhosis, or both. Therefore, liver and kidney function tests should be carried out before and during MTX treatment; however, the risk of liver disease in patients with LE seems less than in patients with psoriasis. In patients with psoriasis, it has been suggested that serial destinations of the aminoterminal propeptide of type III procollagen may decrease the need for liver biopsies.[11] Signs of mucositis appear rarely with low-dose MTX therapy. MTX-induced interstitial pneumonitis (acute hypersensitivity reaction) is a potentially fatal but reversible complication. Therefore, MTX treatment is to be discontinued at signs of dry nonproductive cough, dyspnea, fever, and peripheral eosinophilia, and a chest x-ray should be arranged immediately. The recommended therapeutic approach includes administration of high-dose corticosteroid (CS) therapy and respiratory support together with broad-spectrum antibiotics until an infectious cause is excluded.[12] However, MTX pneumonitis is an extremely rare side effect in dermatologic diseases. In conclusion, we consider MTX a second-line treatment for patients with CLE who are refractory to antimalarials, especially those patients with SCLE and localized DLE,