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).

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. Recent studies have linked the anti-inflammatory properties of MTX to the effects on adenine, 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]-alpha, 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.

MTX has been used for the treatment of therapy-refractory subacute CLE (SCLE)5-8 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. 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. 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 panleukopenia (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. 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. 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. 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. 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.
or those who cannot tolerate antimalarials (Table I). Moreover, a combination of MTX with antimalarials is possible.

Retinoids

Retinoids comprise a family of compounds with structures and mechanisms of action that resemble those of vitamin A (retinol), an essential nutrient that plays a role in cell growth and differentiation. The aromatic retinoid etretinate (no longer available) and its major metabolite acitretin are used for psoriasis and keratinization disorders. Meanwhile, acitretin has replaced etretinate because of its shorter serum half-life. Isotretinoin is approved for the treatment of acne. In addition, acitretin and isotretinoin are listed as second-line substances for CLE in the American Academy of Dermatology guidelines, because of their relatively innocuous side-effect profile (Table I). Etretinate was first used in 1985 in an open prospective trial by Ruzicka et al in 19 patients with localized and disseminated DLE, SCLE, and one patient with cutaneous manifestations.

Fig 1. Algorithm of treatment for cutaneous lupus erythematosus (CLE). If there is partial response with quinacrine, methotrexate (MTX) may be added; if there is no response with antimalarials, these drugs are discontinued and MTX is started. Retinoids are primarily used in hypertrophic discoid lupus erythematosus (LE), refractory subacute CLE (SCLE), and CLE/lichen planus overlap (discontinue MTX). Thalidomide should only be applied in severe refractory CLE as remission-inducing agent (discontinue MTX). Dapsone is recommended for urticarial vasculitis, LE panniculitis, SCLE, and oral ulcers (discontinue MTX). Mycophenolate mofetil (MMF) or mycophenolate sodium (EC-MPS) are primarily indicated in refractory SCLE (discontinue MTX). Note that “maintain” only refers to a certain period of time depending on agent, efficacy, and CLE subtype. After clearing of skin lesions, agents should be reduced to minimum effective dose or discontinued; however, sunscreens should be used for prevention of skin lesions. CI, Calcineurin inhibitors; CS, Corticosteroids.
of SLE. The dose of etretinate was 50 mg per day given in two separate oral doses. A complete or almost complete clearing of CLE skin lesions was seen in 11 patients within 2 to 6 weeks of treatment; moderate response or treatment failure was observed in 8 patients. The best treatment results with etretinate were obtained in male patients with DLE. In 1988, acitretin was administered to 20 patients with CLE; 5 showed unsatisfactory results, whereas the rest demonstrated complete clearing or marked improvement of all lesions.15 A further study conducted by Ruzicka et al16 in 1992 was a double-blind, randomized, multicenter trial, comparing efficacy of acitretin (50 mg per day) with hydroxychloroquine (400 mg per day) in 28 and 30 patients with CLE, respectively. Up to now, this is the only randomized controlled trial in CLE using two systemic drugs. Overall improvement occurred in 13 of the 28 patients (46%) treated with acitretin and 15 of the 30 patients (50%) treated with hydroxychloroquine. In the following years, isotretinoin was applied in approximately 50 patients, particularly with DLE and SCLE, in open studies and case reports; favorable responses were documented in up to 86.9% of the patients.17-21 Acitretin was especially useful in treating hyperkeratotic verrucous forms of DLE on hands, feet, and legs.22

In CLE, the recommended dose for acitretin and isotretinoin is 0.2 to 1.0 mg/kg body weight per day. Both retinoids are teratogenic; therefore, effective contraception is essential during and after treatment (isotretinoin: 1 month; acitretin: 2 years). Therefore, isotretinoin is preferable in female patients of child-bearing potential because of the shorter half-life. Most common side effects of retinoids include dryness of skin and mucous membranes (xerophthalmia, xerostomia), less common are gastrointestinal disturbances and skeletal toxicity, as well as muscle pain and arthralgia.23 Because of pre-existing keratoconjunctivitis sicca, treatment with retinoids is a relative contraindication in SCLE-associated Sjögren syndrome. Retinoid therapy may cause hyperlipidemia and alter liver function tests, but severe hepatotoxic reactions are rare. Reversible hair loss can be recorded in up to 50% of patients, mainly during treatment with acitretin. Psychiatric disorders such as depression have been reported in patients during and after isotretinoin therapy. Despite the known side effects, retinoids are part of second-line treatment for CLE refractory to antimalarials.

**Dapsone**

In addition to its known antibacterial activity, dapsone, which inhibits the synthesis of dihydrofolic acid through competition with para-aminobenzoate, exhibits significant anti-inflammatory activity and has been used in many neutrophilic dermatoses. It protects cells from neutrophil-mediated auto-oxidative tissue injury by converting myeloperoxidase to an inactive compound, thus suppressing the formation of toxic oxygen intermediates; it has been shown to block neutrophil chemotaxis.24 Dapsone has been reported to be effective in SCLE, LEP, urticarial vasculitis, oral ulcerations, and bullous eruptions complicating SLE.23,25 Seven patients (4 with DLE, 3 with widespread rash of SLE) were treated with dapsone, resulting in resolution of urticarial vasculitis in SLE, discoid lesions, and oral ulcerations in DLE. However, widespread eruptions of SLE and disseminated DLE were unresponsive to dapsone.26

In 1982, 11 patients with DLE received dapsone with moderate effect in 4 and appreciable improvement in another 4 patients.27 Lindskov and Reymann28 treated 33 patients with DLE and dapsone showing excellent results in 8 patients (24%), some effect in 8 patients (24%), and no response in 17 patients (52%). Of the 6 patients who received a combination of dapsone and hydroxychloroquine, two responded well and no effect was seen in the one patient with hypertrophic lesions. Six patients terminated dapsone because of side effects, such as dyspepsia (n = 3), exanthema (n = 2), fever (n = 2), methemoglobinemia (n = 1), and vertigo (n = 1). The authors suggested that dapsone might be an alternative or supplement to antimalarials in the treatment of DLE, when the latter cause adverse reactions or fail to be effective. Single case reports of successful treatment of SCLE and LEP with dapsone have also been described in the literature.29-33 Ujiie et al34

**Table I. Second-line systemic treatment in cutaneous lupus erythematosus**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>7.5-25 mg (0.2 mg/kg body weight) once weekly per os, sc, IV, or IM</td>
</tr>
<tr>
<td>Acitretin</td>
<td>0.2-1.0 mg/kg body weight per day</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>0.5-1.0 mg/kg body weight per day</td>
</tr>
<tr>
<td>Dapsone</td>
<td>50-150 (maximum 200) mg per day</td>
</tr>
<tr>
<td>MMF/EC-MPS</td>
<td>2 × 1000 mg MMF per day</td>
</tr>
<tr>
<td></td>
<td>2 × 720 mg EC-MPS per day</td>
</tr>
</tbody>
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Agents for first-line treatment can be combined with agents for second-line treatment.

reported a further case of LEP successfully treated with dapsone and reviewed 10 previously published Japanese cases with LEP. The initial dose of dapsone was between 25 and 75 mg per day, and disease remission was obtained in all patients between 1 and 8 weeks (mean 4.6 weeks).

Therapeutic dosages of dapsone range from 25 to 150 (maximum 200) mg per day; it is recommended to start with a low dose and to increase the dose gradually (Table I). A maintenance dose of 25 to 50 mg per day may be necessary, the lowest effective dose should be applied to minimize possible side effects. Because hemolysis and methemoglobinemia are known dose-dependent side effects of dapsone, glucose-6-phosphate dehydrogenase deficiency must be excluded before therapy. During the first month of dapsone treatment blood cell counts need to be obtained weekly, and, if stable, every 2 weeks for 2 months thereafter, along with liver function tests. After the initial 3 months of treatment with dapsone, blood cell counts and liver function tests should be obtained every 3 months. Methemoglobin levels should be monitored in case of severe anemia and clinical symptoms of cyanosis and dyspnea, especially in patients with cardiopulmonary disease. Oxygen radicals are thought to be involved in dapsone-induced hemolytic anemia. Antioxidants, such as vitamins C and E, or cimetidine have been described to reduce methemoglobin levels and are therefore protective against this adverse event. A severe side effect is the dapsone hypersensitivity syndrome, which usually occurs 1 to 6 weeks (on average 27 days) after the start of therapy and shows an infectious mononucleosis-like picture with fever, malaise, rash (ie, exfoliative dermatitis), lymphadenopathy, jaundice with hepatic dysfunction, atypical lymphocytosis, and eosinophilia. Another rare, severe, and unpredictable idiosyncratic reaction is dapsone-mediated potentially fatal agranulocytosis; the risk is highest within the first 3 months of treatment. If symptoms, such as fever and stomatitis, occur, dapsone must be discontinued and blood cell count checked immediately.

**Mycophenolate mofetil and mycophenolate sodium**

Another immunosuppressive drug not approved for treatment of LE is mycophenolate mofetil (MMF), a mycophenolic acid ester, which is reabsorbed quickly and transformed to mycophenolic acid after oral administration. Mycophenolic acid is a specific, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase, a key enzyme of the guanosine nucleotide synthesis specifically within T and B lymphocytes. Beyond inhibition of lymphocyte proliferation, MMF is able to directly induce apoptosis of activated T lymphocytes; in addition, antibody production by activated B cells is also inhibited by MMF. MMF has multiple effects on other cell types of the immune system, such as dendritic cells. In addition, MMF affects the expression and processing of various adhesion molecules and appears to have a role in limiting oxidative stress associated with immunologic driven inflammatory reactions by suppressing the production of the inducible nitric oxide synthase.

MMF should be administered in doses between 1 and 3 g per day (Table I). The best clinical results are achieved with 2 to 3 g per day; however, it can take 1 to 2 months for clinical effects to become visible. Recently, MMF has shown good efficacy in bullous autoimmune dermatoses in two prospective multicenter, randomized, nonblinded clinical trials. In patients with SLE, lupus nephritis has been successfully treated with MMF. In single case reports, MMF also proved successful in one patient with CHLE, two patients with refractory palmoplantar DLE, and 4 patients with SCLE. Moreover, Hanjani and Nousari reported the treatment of MMF in 4 patients with various manifestations of CLE (LEP, DLE, “lupus perniosis,” SCLE, and LET) and smoldering systemic involvement resistant to conventional therapy. All patients achieved a complete remission within 3 months of starting MMF; it is noteworthy that 3 of the patients were treated with 3 g per day. In contrast, the lack of a response was reported in 5 of 7 patients with various LE-specific and nonspecific skin diseases in the context of SLE including acute CLE (ACLE), SCLE, DLE, CHLE, vasculitis, and urticarial rash.

In general, MMF is well tolerated. Typical side effects include gastrointestinal symptoms, such as diarrhea, nausea, and vomiting, as well as infections of the urinary system and viral infections, such as herpes simplex and herpes zoster. Before therapy, chronic infections should be ruled out, and liver and kidney function tests as well as regular hemograms are to be performed and continued during therapy. With the common dose of 2 g of MMF, hematologic side effects are extremely rare and less common than with azathioprine. The enteric-coated form of MMF, mycophenolate sodium (EC-MPS), is associated with fewer gastrointestinal side effects. EC-MPS was recently used in a nonrandomized, open-pilot study to treat 10 patients with active SCLE resistant to at least one standard therapy (Table I). The substance led to significant improvement of the skin lesions, while no serious side effects were recorded. However, randomized
controlled trials with a larger number of patients are needed to further evaluate efficacy and safety of MMF or EC-MPS in CLE.

**SYSTEMIC TREATMENT OPTIONS FOR PATIENTS WITH REFRACTORY DISEASE**

**Thalidomide and lenalidomide**

Thalidomide (alpha-N-phthalimido-glutarimide) is thought to inhibit synthesis of TNF-alfa and to modify the expression of TNF-alfa—induced adhesion molecules on endothelial cells and human leukocytes. It has further been demonstrated in a murine system that thalidomide inhibits ultraviolet (UV) B—induced keratinocyte apoptosis; moreover, these observations were extended to patients with CLE and SLE, suggesting that inhibition of UVB—induced inflammation may, in part, explain the therapeutic benefits of this agent on photosensitive disease. In addition, thalidomide may have several other modes of action. In 1953, thalidomide was synthesized in Germany and was commonly used as a mild sedative to treat insomnia, until it was phased out in 1961 because of its teratogenic effect. Hence, thalidomide should only be prescribed to women of childbearing potential (appropriate contraception), and effective contraceptive measures. Particularly in patients with DLE, successful therapy with a high number of cases has been reported as a result of the agent’s immunomodulatory and anti-inflammatory characteristics.

The first large series of thalidomide in DLE was a study of 60 patients treated initially with 400 mg per day subdivided in two equal doses. After marked clinical response, the dosage was reduced every month until a maintenance dosage of 50 to 100 mg per day was reached. This dosage was maintained for 3 to 5 months or longer, resulting in a 90% complete or marked response. Thirty of 41 patients (71%) relapsed after stopping thalidomide; however, most of the skin lesions were not as severe as they were before thalidomide treatment. Sixteen of the relapsing patients again responded well while undergoing a second course of treatment with thalidomide. Various side effects were reported; all patients reported drowsiness, 31.6% constipation, and 11.6% rash, which resulted in discontinuation in one patient with DLE. Other side effects included edema and xerostomia; however, most importantly, peripheral polyneuropathy appeared in 25% of the patients (Table II). This side effect, which may be irreversible, makes close neurologic monitoring absolutely mandatory; baseline nerve conduction studies should be performed before therapy and periodically thereafter. In addition to neurologic symptoms, electromyogram abnormalities may occur during thalidomide treatment, as may signs of muscle weakness and changes. The characteristic neurologic presentation is a sensory rather than a motor axonal polyneuropathy that presents with symmetric painful distal paresthesias or numbness. Electrophysiologic alterations may persist and even worsen after thalidomide discontinuation, suggesting a prolonged neurotoxic effect. Aside from strict precautions for the use of this drug in women of childbearing potential (appropriate contraception), polyneuropathy is the major limiting toxicity of thalidomide. The manufacturer has developed a comprehensive program to control prescribing, dispensing, and use of this drug, known as the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.). Aside from thrombotic events, secondary amenorrhea is a well-recognized side effect in patients with CLE treated with thalidomide, beginning 4 to 5 months after onset of the drug and resolving 2 to 3 months after withdrawal. This emphasizes the importance of performing pregnancy tests regularly.

Recently, Cuadrado et al demonstrated in a retrospective study of 48 patients with therapy-refractory CLE (18 DLE, 4 SCLE, 2 LEP, 24 SLE with skin involvement) an overall clinical response rate of 81%. However, there were no clear dose-dependent effects of thalidomide, as determined by administering 3 different dosages (100, 50, and 50 mg/d on alternate days). The relapse rate after discontinuation of the drug was 67% in the 39 patients who received remission. In patients with SLE, no changes were noticed in other clinical features, such as arthralgia, Raynaud phenomenon, renal function, leukopenia, anti-double-stranded DNA (dsDNA) antibody level, or thrombocytopenia. The high incidence (27%) of polyneuropathy, even at low doses, suggests that it may be most useful as a remission-inducing agent—if applicable in combination with antimalarials—to minimize the high incidence of relapse observed after stopping thalidomide. Recent studies of approximately 100 patients with CLE (mostly DLE, but also SCLE and LEP) and SLE

| Table II. Further systemic treatment options for refractory cutaneous lupus erythematous |
|---------------------------------|-----------------------------------------------|
| **Thalidomide**                | High risk of polyneuropathy                   |
| 50-200 mg per day             |                                               |
| **IVIG**                       | High costs                                     |
| 1-2 g/kg body weight monthly  |                                               |
| **Clofazimine**               | Only one recent study                          |
| 100-200 mg per day            |                                               |

**IVIG,** Intravenous immunoglobulins.
with cutaneous manifestations treated with thalidomide confirmed the efficacy of this drug, but also the high relapse rate, the known side effects, and most importantly the high risk of potential irreversible polyneuropathy. Therefore, thalidomide should only be used to treat severe refractory CLE, and the lowest dose possible is advised; however, even at low doses, there is a high incidence of neurotoxicity. Notwithstanding its great efficacy in refractory DLE, thalidomide should only be applied in appropriately selected patients after intensive consideration of the risk-benefit ratio.

Lenalidomide is a structural derivative of thalidomide introduced in 2004; it was initially intended as a treatment for multiple myeloma, but has also shown efficacy in the class of hematologic disorders known as myelodysplastic syndromes. Similar to thalidomide, lenalidomide has complex immunomodulatory, antiangiogenic, antiproliferative, and proapoptotic effects. Recently, two patients with severe refractory disseminated DLE were treated with lenalidomide, 5 to 10 mg per day. In one patient, improvement of skin lesions was noted within 1 month at a dosage of 5 mg per day. This dosage was maintained for 10 months before it was doubled to 10 mg per day for another 12 months because of a slight worsening of symptoms. The patients showed a good clinical response and the dosage of 60 mg of prednisolone per day was tapered and discontinued. The second patient failed to show clinical improvement on 5 mg per day of lenalidomide, which was stopped after 6 months. Both patients had failed to respond to several therapies including topical corticosteroids, antimalarials, dapsone, MTX, azathioprine, MMF, rituximab, IV immunoglobulins (IVIG), and cyclosporine. The first patient was previously treated successfully with thalidomide, which had to be discontinued secondary to neuropathy. Interestingly, in this patient thalidomide-induced peripheral neuropathy symptoms resolved during lenalidomide therapy. The second patient had previously failed to respond to thalidomide.

The same strict precautions used for thalidomide have to be applied for lenalidomide; the risk of neurotoxicity seems to be lower for lenalidomide. A prospective noncontrolled, open-labeled pilot study is being conducted to evaluate the safety and effectiveness of lenalidomide in patients with CLE (clinicaltrials.gov).

**IV Immunoglobulins**

The mechanism of action of IVIG is complex and not fully understood, although numerous immunomodulatory mechanisms have been suggested. Clinical efficacy has been shown in the treatment of skin diseases, despite the lack of evidence from randomized, double-blind, placebo-controlled trials. Therapy with IVIG has been reported to show beneficial effects in a 2-day course (1 g/kg per day) every 4 weeks in 5 patients with refractory extensive long-lasting DLE with major face involvement. IVIG failed in two patients; in 3 others, all active skin lesions disappeared between 3 weeks and 3 months after institution of IVIG. Relapses occurred 2 to 10 months after IVIG withdrawal and skin lesions were controlled again with IVIG in one patient with DLE. In another case report, one patient with both antimalarial-resistant SCLE and ACLE was treated with IVIG (2 g/kg per month) and showed dramatic improvement within 3 months and almost complete resolution after 6 months. More recently, 3 patients with SCLE unresponsive to previous antimalarial and immunosuppressive therapy were treated with IVIG, which achieved good response of their skin lesions. Twelve patients with histologically confirmed CLE of various subtypes were given IVIG with starting doses of 1 g/kg per day on 2 consecutive days, followed by 400 mg/kg per month for 6 months or until disease resolution. Five patients had complete or near complete clearing of their skin disease (>75% clearing), two had partial improvement (>50% clearing), and 3 had limited response (<50% clearing). Two patients received no further treatment because of pregnancy and development of acute cutaneous vasculitis, respectively. In 2005, Kreuter et al reported a female patient with highly recalcitrant SCLE who responded very well to treatment with IVIG (1 g/kg per day on 3 consecutive days per month). Amelioration was observed after the first cycle and an almost complete clearing of skin lesions was achieved after 3 cycles of IVIG. At this time, IVIG was reduced to 0.5 g/kg per month. In 1997, de Pita et al described 5 female patients with SLE and two with SCLE treated with IVIG at a dosage of 300 mg/kg per day for 5 consecutive days each month for a 12-month period. Although some clinical symptoms, such as asthenia, arthralgias, and fever, disappeared in the patients with SLE and immunologic parameters improved (eg, decrease of antinuclear antibodies, negativity of anti-dsDNA antibodies, slight increase of C3, and reduction of immunoglobulin sediments in the dermal papillae analyzed by direct immunofluorescence), IVIG was not able to improve the cutaneous manifestations. Moreover, skin lesions in SCLE worsened. Recently, a case of LEP successfully treated with IVIG was reported after other therapy modalities failed. The majority of adverse reactions with IVIG are mild; of these, headache is most common. Rare serious side effects include urticarial rash and
cutaneous vasculitis with vascular occlusion, proteinuria, acute renal failure, deep venous thrombosis, embolism, myocardial infarction, stroke, and anaphylactic reactions in IgA-deficient patients. Overall, although IVIG may be a useful and promising therapy for highly resistant and severe CLE, it is very expensive, and additional controlled clinical trials are needed to investigate its efficacy in this disease (Table II).

Clofazimine

Clofazimine is a lipophilic rimino-phenazine dye with antimicrobial, anti-inflammatory, and immunosuppressive activity, which is not only taken up by macrophages but is also deposited in the subcutaneous fat. The resulting reddish-brown discoloration of the skin and body secretions is the most frequent but reversible side effect and more marked with high dosages. Other side effects include dry skin, occasional nausea and diarrhea, and in rare cases, eosinophilic enteritis and splenic infarction (only after high-dose and long-term use of clofazimine).

In 1974, clofazimine was first used in different dosages for the treatment of 26 patients with long-standing DLE (3 months-27 years, mean: 8.6 years) by Mackey and Barnes. The dose of 200 mg per day was more effective than 100 mg per day, and 17 of the 26 patients with DLE, many of whom had failed to respond to chloroquine and other treatments, went into remission. In the following years, only a few case reports were published describing the treatment of CLE (mostly DLE) with clofazimine. In 2005, a randomized, double-blind, controlled trial compared clofazimine (100 mg per day) with chloroquine (250 mg per day) in 33 patients with SLE and active skin lesions (ACLE, SCLE, localized and disseminated DLE). At the end of the 6-month study, a complete response was seen in 18.8% of patients treated with clofazimine as compared with 41.2% of patients treated with chloroquine, but the difference was not significant. A good response was observed in 12 of 16 patients (75%) from the clofazimine group and in 14 of 17 patients (82.4%) from the chloroquine group. These findings suggest that clofazimine is equally effective as chloroquine in controlling cutaneous lesions in patients with SLE; however, 5 patients who were treated with clofazimine and one who was treated with chloroquine were withdrawn from the study because of development of a serious flare. The authors could not exclude the possibility that clofazimine itself could have been the cause of these flares or that the difference in frequency of flares between the groups might have been a result of the known effect of chloroquine in reducing disease activity. Clofazimine should therefore only be recommended for patients who have exclusively cutaneous manifestations of the disease (Table II).

FURTHER TREATMENT OPTIONS

Azathioprine

The mechanism of azathioprine, a prodrug of 6-mercaptopurine, is still not fully understood although it was introduced approximately 50 years ago. Azathioprine is a purine antimetabolite and classically has been described as a cell-cycle specific drug, an s-phase inhibitor. The active metabolites of azathioprine disrupt the function of endogenous purines; the generally accepted mechanism of its cytotoxic and immunosuppressive activity is the disruption of nucleic acids. Lymphocytes rely on de novo synthesis of purines, and accordingly, azathioprine is thought to be relatively specific for lymphocytes. It is more selective for T lymphocytes than for B lymphocytes. Before initiation of azathioprine therapy the activity of the enzyme thiopurine methyltransferase (TPMT) should be determined, as TPMT deficiency results in significant accumulation of thioguanine nucleotides with increased hematopoietic toxicity. Interestingly, one of 300 individuals are homozygous for very low TPMT activity. In a recent report, one of 220 individuals had no detectable activity. Therefore, testing for TPMT levels would be helpful to achieve proper dosing.

The dosage of azathioprine should range between 1 and 2.5 mg/kg body weight per day, usually around 100 to 150 mg, and clinical effects can be expected 1 to 2 months after starting therapy. This immunosuppressive drug has been used since the early 1960s to treat SLE, eg, lupus nephritis. In 1991, 6 patients with different subtypes of refractory CLE (4 SCLE, 2 DLE) were treated with 100 to 150 mg of azathioprine and 20 to 30 mg of prednisone per day. The 4 patients with SCLE exhibited partial or complete clearing of skin lesions and the prednisone dose could be decreased; but one of these patients had to discontinue therapy secondary to pancreatitis. One patient with erosive palmar DLE did not respond to azathioprine and the other patient with DLE had a short duration of therapy as a result of development of drug-induced fever. In 1988, Ashinoff et al also reported successful treatment of two patients with resistant DLE on the palms and soles. Two further reports in the literature showed successful treatment of generalized discoid lesions, unresponsive to conventional therapies. Moreover, skin lesions in a patient given the diagnosis of so-called Rowell syndrome (SCLE with erythema multiforme-like eruption) were successfully treated with prednisolone and azathioprine.
The main side effects of azathioprine include bone-marrow toxicity, hepatotoxicity, and gastrointestinal symptoms; rarely, a hypersensitivity reaction with fever, nausea, vomiting, diarrhea, rash, and occasionally shock occurs. Considering the side effects of azathioprine and the drug’s inconclusive efficacy in the treatment of CLE, this immunosuppressive drug should be primarily reserved for patients with SLE.

**Cyclophosphamide**

Cyclophosphamide is an inactive mechlorethamine derivative, which is metabolized by mitochondrial cytochrome P-450 enzymes in the liver to a variety of active metabolites with both therapeutic and toxic actions. Aside from the liver, other tissues such as transitional epithelial cells in the bladder and lymphocytes, may metabolize the drug, resulting in local toxicity, immunosuppression, or both. Direct effects of cyclophosphamide on DNA resulting in cell death have been identified as being the major effect of this drug. The onset of therapeutic efficacy is rapid (within 2–4 days) in contrast to azathioprine.

Cyclophosphamide is used in lupus nephritis in conjunction with IV prednisolone, particularly as pulse IV therapy, which has significantly less toxicity than continuous oral application. In a study from 2003, high-dose IV cyclophosphamide (50 mg/kg) for 4 consecutive days without stem cell transplantation and without pulse prednisolone was used in refractory SLE. Among these patients, two were successfully treated for severe skin lesions, one with severe refractory “cutaneous lupus” and one with pyoderma gangrenosum. In an explorative trial with 9 patients, DLE and “subacute LE” were treated with cyclophosphamide at a dosage of 50 to 200 mg per day. Clinical improvement was excellent in 5 patients, moderate in 3 patients, and negligible in one patient; in two patients, in whom cyclophosphamide has been stopped, there was no recurrence after 6 and 23 months, respectively.

Close monitoring of blood cell counts and liver enzymes is mandatory during therapy with cyclophosphamide. Because of its impact on reproduction (ovarian failure), the risk of hemorrhagic cystitis/urothelial toxicity, and secondary malignancies (bladder cancer, myeloproliferative disorders, eg, leukemia, especially after a cumulative dose >80 g), cyclophosphamide can no longer be recommended for treatment of CLE.

**Cyclosporine**

Cyclosporine is derived from a soil fungus, Tolypocladium inflatum, and is a prodrug that becomes active after forming complexes with an intracytoplasmatic protein called cyclophilin. This binding results in inhibition of T-cell function by preventing the dephosphorylation of nuclear factors and blocking this path to gene transcription.

Oral doses of 2.5 to 5 mg/kg body weight per day are usually applied to achieve clinical effects and can be tapered after 4 weeks to the minimal effective maintenance dose. Application of cyclosporine in SLE has been the subject of only a few reports, and large multicenter controlled trials in this area are lacking; however, a steroid-sparing effect is evident. Although skin disease was not a primary outcome measure of many studies in SLE, malar rash and LE-nonspecific manifestations, such as vasculitis, have been reported to improve with cyclosporine.

Treatment of a patient with coexisting SCLE and extensive generalized lichen planus with hydroxychloroquine (200 mg per day) and cyclosporine (2.5 mg/kg per day) led to significant remission of skin lesions. In this patient, only marginal improvement had been observed after treatment with 400 mg of hydroxychloroquine per day for 10 weeks as single therapy. In a young female patient with SLE and recurrent lesions of LEP, which were therapy refractory to various drugs such as dapsone, low-dose corticosteroids, azathioprine, and cyclophosphamide, only 4 mg/kg of cyclosporine per day maintained remission of LEP. A 27-year-old female patient with severe mutilating, progressive, therapy-refractory DLE relapsed repeatedly after decrease of prednisone to less than 40 mg per day. However, addition of 5.3 mg/kg of cyclosporine per day did not improve the skin lesions despite reliable therapeutic trough blood concentrations. Cyclosporine at 4 to 5 mg/kg per day was also not effective in the treatment of two patients with long-standing recalcitrant DLE. In two patients with psoriasis and in a patient with liver transplantation for primary biliary cirrhosis, the first manifestation of DLE developed despite treatment with cyclosporine at a dose of 3 mg/kg per day. Because of contradictory reports, its poor efficacy, and the well-known side effects, especially nephrotoxicity, hypertension, and the risk of malignancy, cyclosporine should not be regarded as treatment for CLE.

**Antibiotics**

Sulfasalazine is used for the treatment of inflammatory bowel disease and different forms of arthritis; however, the mode of action remains unclear. It is suggested that the anti-inflammatory activity of sulfasalazine may rely on inhibition of the transcription factor nuclear factor-κB. Aside from two single case reports of DLE responsive to sulfasalazine,
one small open-label case series with 11 patients with DLE exists. In this study, sulfasalazine at a dose of 2 mg per day was administered and showed complete response in 7 patients, partial response in one patient, and 3 failures. Efficacy in these patients could be explained by drug metabolism because all responders except one were rapid acetylators whereas nonresponders were of the slow acetylator phenotype. Although there were no serious side effects in this case series, Callen cited a study (abstract only) of 6 patients treated with sulfasalazine that showed beneficial effects in only two patients; remarkably, 5 of these patients experienced a drug eruption. Moreover, drug-induced lupus by sulfasalazine has been reported.

Danazol is a heterocyclic steroid hormone, has shown favorable effects in 7 randomized controlled trials involving 842 patients with SLE; however, no reports of dehydroepiandrosterone exist in the therapy of CLE. In addition, cyproterone acetate, which is a synthetic hydroxyprogesterone derivative, has also been shown to reduce the frequency of SLE flares as well as the frequency and severity of oral and vulva ulcerations.

**Extracorporeal photopheresis**

Extracorporeal photopheresis (ECP) is a leukapheresis-based therapy that uses 8-methoxypsoralen and ultraviolet-A irradiation. In advanced cutaneous T-cell lymphoma, ECP is an established and effective therapy and has shown promising efficacy in a number of other severe and difficult-to-treat conditions, such as systemic sclerosis, graft-versus-host disease, and prevention and treatment of rejection in solid organ transplantation. In a single patient with disseminated DLE, who did not respond to conventional therapy, monthly cycles of ECP showed nearly complete regression of the discoid lesions within a period of 3 to 14 months. In another case report, a female patient with refractory SCLE first responded dramatically to ECP, but after 9 months of ECP, the cutaneous lesions relapsed and treatment was discontinued. Two female patients with therapy-resistant CLE, one with SCLE and the other with DLE, were treated with ECP; after 6 and 8 cycles of ECP, patients went into prolonged remission of 18 and 11 months, respectively. In a recent report, a patient with Sjögren syndrome and anti-Ro/SSA and anti-La/SSB antibodies developed a terbinafine-induced flare of widespread SCLE. Despite topical steroids and 100 mg per day of chloroquine, the rash progressed within 2 months and ECP was started. Three days after each cycle of ECP the patient noted improvement and complete clearance occurred after 4 cycles without relapse.

Therapeutic plasmapheresis in combination with dexamethasone and azathioprine has been successfully used in one case report for the prevention of congenital complete heart block associated with anti-Ro/SSA and anti-La/SSB antibodies.

**EXPERIMENTAL THERAPIES WITHOUT PROVEN EFFICACY AND/OR UNFAVORABLE RISK-BENEFIT RATIO**

**Anti-CD4 antibody**

The recombinant chimeric CD4 monoclonal antibody binds specifically to a conformational epitope in the extracellular V1/V2 domains of the CD4 receptor protein and blocks in vitro helper T-cell functions. One report describes successful treatment of 5 patients with severe cutaneous manifestations of...
DLE, SCLE, and SLE with monoclonal anti-CD4 antibodies. After receiving total doses of 275, 400, or 475 mg in single administrations of 20 to 50 mg during a period of 5 to 8 weeks, patients showed lasting decreases in disease activity and healing of LE skin lesions. As an immediate response, all patients showed a nearly complete loss of cutaneous inflammatory activity, and as a long-term effect anti-CD4 antibody treatment restored the responsiveness to conventional therapies. No further reports exist on treatment with anti-CD4 antibodies, possibly because of the high costs of this therapy.

**Interferon alfa**

Interferon alfa has antiviral, antiproliferative, and immunomodulating properties and is used for the treatment of tumors, viral infections, and inflammatory conditions. In one study, 6 patients with DLE and 4 patients with SCLE received recombinant interferon alfa-2a. Patients had been pretreated with hydroxychloroquine, systemic or topical corticosteroids, or thalidomide, with or without clinical improvement. In DLE, average treatment duration was 5.6 weeks at a mean dose of $35 \times 10^6$ IU per week. Improvement was experienced in 5 patients with DLE, whereas 3 patients with SCLE obtained similar improvement but required longer time until remission (10 weeks) and a higher mean weekly dose of $80 \times 10^6$ IU of recombinant interferon alfa-2a. However, the response to interferon alfa-2a was only temporary with a rapid relapse a few weeks after withdrawal of therapy in all patients who were improved or cleared. Exacerbation of skin lesions was observed in one patient with SCLE, and one patient with DLE was unchanged after 4 weeks of therapy. In 1992, Tebbe et al described a 43-year-old female patient with SCLE resistant to several standard therapies. In one study, 6 patients with DLE were observed in one patient with SCLE, and one patient with DLE was unchanged after 4 weeks of therapy. In 1992, Tebbe et al described a 43-year-old female patient with SCLE resistant to several standard therapies, who was treated with recombinant interferon alfa-2a ($3 \times 9 \times 10^6$ IU weekly). Prednisolone was initially continued at 25 mg per day. After some weeks the prednisolone dose was tapered down to 7.5 mg per day as a result of partial remission. Ten months after starting therapy with interferon alfa-2a the patient demonstrated more than 90% improvement of the skin lesions and maintained a clinically stable condition. However, induction of an SLE-like syndrome in a patient receiving interferon alfa treatment has been reported. Recently, 5 cases of cutaneous reactions at the injection site of interferon beta-1b with histologic findings mimicking CLE were reported. Side effects of interferon therapy include flu-like syndrome, headache, fever, depression, and hair loss.

Martinez et al reported on intraleSIONal injection of interferon alfa in 3 patients with refractory DLE on the face and scalp (two patients with $6 \times 10^6$ IU interferon alfa-2b twice weekly, one patient with $5 \times 10^6$ IU interferon alfa—not further specified—twice weekly). An excellent improvement was seen after repeated injections in all 3 patients with DLE, and follow-up was reported in two of these patients with no recurrence within 12 months after withdrawal of interferon therapy.

**Leflunomide**

The active metabolite of leflunomide, A771726, is an inhibitor of dihydroorotate dehydrogenase, a key mitochondrial enzyme of the de novo pyrimidine synthesis in immune cells, particularly in activated T and B lymphocytes. It has been suggested to be effective in the management of SLE; in a double-blind, placebo-controlled pilot study of 12 patients with SLE and mild to moderate disease activity, leflunomide was more effective than placebo and was safe and well tolerated. Furthermore, leflunomide was efficacious and safe after 2 to 3 months of therapy in an open-label pilot study of a cohort of 18 female patients with SLE. However, in 3 patients taking leflunomide for rheumatoid arthritis SCLE occurred, resolving several months after discontinuation of the drug. Goeb et al reported induction of SCLE with leflunomide in two other patients with rheumatoid arthritis. In one patient, skin lesions completely cleared after 3 weeks of discontinuation of leflunomide and anti-Ro/SSA antibodies reverted to normal after 2 years, supporting more clearly the induction of SCLE by the drug. Furthermore, SCLE did not reappear within a follow-up period of 2 and 3 years in either patient. In a female patient with ankylosing spondylitis, a drug reaction to leflunomide was recently described, consistent with an erythematous annular/bullous variant of SCLE over the trunk in association with a malar rash and erythema multiforme-like lesions involving hands and feet as well as conjunctival, oral, and genital mucous membranes. Induction of SCLE by leflunomide was reported in a female patient with primary Sjögren syndrome; the skin lesions showed resolution when leflunomide was stopped and reappeared with reintroduction of the drug. This outcome might have been favored by the genetic disease background (HLA-B8, -DR3 predisposition) in Sjögren syndrome, which is identical to that observed in patients with SCLE. A recent case report describes two patients with pre-existing SCLE. The female patient with a history of rheumatoid arthritis and SCLE experienced rapid improvement of arthritis, but severe deterioration of her cutaneous disease. In contrast, the second male patient experienced a complete clinical remission of
arthralgia and SCLE lesions with leflunomide. In conclusion, the data in the literature demonstrate a higher risk of CLE induction by leflunomide (8 patients) than warranted by the level of disease improvement (one patient with SCLE). The most prominent side effects of leflunomide include gastrointestinal symptoms, such as nausea, rash, transient elevation of transaminases, and leukopenia.

**TNF-alfa antagonists**

TNF-alfa is a mediator of inflammation and is involved in many cutaneous and systemic inflammatory diseases. The development of biologics that block the effects of TNF-alfa has increased therapeutic possibilities for treatment of several autoimmune diseases, such as rheumatoid arthritis and psoriasis. However, final conclusions about the efficacy and safety of TNF-alfa antagonists can only be made with growing experience and after conduction of randomized controlled multicenter trials. Although the similarity of biologics compared with human proteins results in good compatibility, severe infections can appear when applying TNF-alfa antagonists. Cytokines play a significant role in immune defense and, therefore, application of these agents in patients with apparent infections is contraindicated. Since the introduction of TNF-alfa antagonists, an increase in the incidence of tuberculosis has been observed. Therefore, a chest x-ray and an intracutaneous tuberculin skin test (also called PPD or Mantoux test) is required in every patient before therapy with TNF-alfa antagonists. If the patient has a positive PPD test result and has never been treated for tuberculosis or shows signs of previous infection of tuberculosis on chest x-ray, therapy with isoniazid should be initiated at least 1 month before therapy with TNF-alfa antagonists. In cases where BCG vaccination is not documented, the same therapeutic procedure is indicated. Recent blood tests based on antigen-specific T-cell response measuring production of interferon-gamma, so called interferongamma release assays (eg, enzyme linked immunospot technique [ELISPOT]), are a major advantage in screening for tuberculosis. These assays seem to be more sensitive and specific than the tuberculin skin test and are unaffected by BCG vaccination.

Furthermore, it is well-known that TNF-alfa blockade leads to the formation of antinuclear antibodies including anti-dsDNA antibodies, which are usually of the IgM- and not of the pathogenic IgG-isotype. However, drug-induced LE (DILE) is relatively rare. In a recent review, 33 cases of DILE secondary to anti-TNF-alfa therapy have been summarized and compared with classic DILE. In contrast to classic DILE induced by more traditional agents such as hydralazine and procainamide, DILE secondary to TNF-alfa antagonist therapy shows a high incidence of skin lesions (72%), nephritis (9%), antinuclear antibodies (100%), and hypocomplementemia (59%). In most cases, the symptoms are reversible after discontinuation of the drug. Less frequent cutaneous findings (malar rash, discoid rash, or photosensitivity) (29%) and more frequent arthritis (93%) were seen in 14 patients with Crohn disease or rheumatoid arthritis, who developed a lupuslike syndrome after treatment with infliximab (n = 13) or adalimumab (n = 1). In a MEDLINE search of articles published between January 1990 and December 2006, 233 patients with autoimmune diseases induced by TNF-targeted therapies were analyzed (including 92 cases of LE induced by infliximab in 40, etanercept in 37, and adalimumab in 15 cases).

**Infliximab.** Infliximab is a chimeric monoclonal antibody against TNF-alfa, which blocks and inactivates soluble and possibly membrane-bound TNF-alfa by creating stable antigen-antibody complexes. To date, there are no reports on the treatment of CLE with infliximab; however, TNF-alfa antagonists have been successfully used in the treatment of 6 patients with SLE and kidney involvement. Disease activity of arthritis and lupus nephritis decreased significantly during therapy; anti-dsDNA antibodies and anticardiolipin antibodies increased in 4 patients, but the increase of these autoantibodies was transient and not associated with a decrease in serum complement levels, with vascular events, or with disease flares. However, induction of CLE subtypes (SCLE- and DLE-like eruption, CHLE) and worsening of SCLE through infliximab have been reported.

Moreover, in a patient with rheumatoid arthritis, induction of LET by infliximab has recently been described. LET completely resolved after discontinuing therapy and, interestingly, did not relapse after administering another TNF-alfa antagonist (etanercept). In another study, 4 of 5 patients with infliximab-induced lupus-like syndrome tolerated an alternative TNF-alfa inhibitor (5 patients, adalimumab; 1 patient, etanercept).

**Etanercept.** Etanercept is a fully human dimeric fusion protein composed of a TNF-alfa type II receptor and the Fc portion of IgG-1. In contrast to the monoclonal antibodies infliximab and adalimumab, the receptor blocker etanercept has a single binding site for TNF-alfa. In 2002, Fautrel et al described a complete resolution of SCLE in a patient treated with etanercept for rheumatoid arthritis. After 6 months of therapy the rheumatoid arthritis remained controlled and there were no signs of SCLE lesions. In a recent report, a 42-year-old patient with
SCLE failed to respond to other therapeutic options (MTX, hydroxychloroquine, prednisone) and was treated with 25 mg of etanercept sc twice a week.\textsuperscript{164} After 3 doses of etanercept, flaring of the cutaneous lesions was noted and therapy was discontinued. However, the patient reported that flaring had already occurred before etanercept treatment. Etanercept was restarted without adverse events, leading to clearing of SCLE after 3 months and to discontinuation of other therapies.

There is also one case report about the induction of SCLE by etanercept in a 54-year-old woman with rheumatoid arthritis.\textsuperscript{162} The patient was treated with betamethasone cream and, at the time of the last follow-up 5 months later, the skin lesions of SCLE had resolved despite continuation of etanercept. In this article, the authors documented reports of the Dutch Inspectorate for Healthcare including 3 other cases of etanercept-induced CLE (2 “acute DLE,” 1 SCLE), which resolved after discontinuation of the TNF-alfa antagonist.

Adalimumab. Adalimumab is a fully human monoclonal antibody composed of the constant and variable regions of human IgG-1 targeted toward TNF-alfa. So far, there are no reports on the treatment of CLE with adalimumab in the literature. However, 10 days after starting adalimumab for rheumatoid arthritis, a 51-year-old Caucasian woman developed SCLE in a photosensitive distribution with positive antinuclear antibodies in a homogeneous pattern.\textsuperscript{163} Two weeks after stopping adalimumab the rash resolved without treatment and antinuclear antibodies became negative again. Seven days after a second injection of adalimumab for rheumatoid arthritis, a 40-year-old African American woman presented with DLE lesions on the scalp and later on the eyebrow and forehead.\textsuperscript{164} After discontinuation of adalimumab and topical therapy with high-potency steroids the DLE lesions resolved after 4 weeks and did not reoccur despite the initiation of treatment with etanercept. A further case of “acute lupus-like skin rash” (edematous and annular skin lesions, clinical picture not typical for ACLE) was presented with DLE lesions on the scalp and later on the forehead.\textsuperscript{165} After discontinuation of adalimumab and treatment with 30 mg of prednisone per day, the lesions faded over the following 3 weeks (with continued leflunomide administration).

Three case reports of DLE caused by adalimumab have been published; in two of these cases, the development of SLE followed treatment conversion of infliximab to adalimumab in patients with rheumatoid arthritis.\textsuperscript{164,166} Therefore, caution may have to be taken when anti-dsDNA antibodies are present after infliximab therapy (even without clinical signs of SLE) and before conversion to adalimumab. The third 52-year-old female patient with rheumatoid arthritis and previously negative antinuclear and anti-dsDNA antibodies and normal serum creatinine developed class III focal proliferative lupus nephritis 1 week after receiving her third monthly dose of adalimumab.\textsuperscript{167}

In summary, because of the reported inductions of SLE and different subtypes of CLE, therapy with TNF-alfa antagonists cannot be recommended in the treatment of CLE up to now.

Other biologics

Other biologics, such as rituximab and efalizumab, have been used in SLE treatment. However, in CLE most biologics have only been applied in single cases.

Rituximab is a chimeric monoclonal antibody that selectively depletes B cells for a median of 6 months by targeting CD20, a surface molecule expressed exclusively on B cells.\textsuperscript{168} Rituximab has been used successfully in adults and children for refractory SLE, usually in conjunction with corticosteroids, other immunosuppressive agents, antimalarials, or a combination of these.\textsuperscript{169} In a case report, two patients with SLE and cutaneous lesions (urticarial vasculitis and diffuse generalized rash with painful erythema on feet and hands) were treated with 2 $\times$ 1000 mg/m$^2$ IV rituximab in combination with 100 mg IV methylprednisolone at an interval of 2 weeks.\textsuperscript{170} The patients had previously been treated with various combinations of therapeutic agents, such as antimalarials, thalidomide, immunosuppressive drugs, and high-dose IVIG, with no significant impact or serious adverse events; however, skin lesions cleared completely and persistently in both patients with rituximab treatment. Recently, a 44-year-old male patient with therapy-resistant SLE, who presented with pso-riasisform SCLE skin lesions and bullous lesions on the palms, was successfully treated with rituximab (two doses of IV rituximab, 1000 mg each, 1 week apart).\textsuperscript{171} The patient had already failed on hydroxychloroquine in addition to 60 mg per day prednisone and azathioprine, which was later substituted by MMF. The skin lesions improved partially, but prednisone could not be lowered under 40 mg per day. After initiation of treatment with rituximab, prednisone could be discontinued 6 weeks after the second infusion and follow-up after 6 months showed only minimal residual lesions.

A recent case report described a 44-year-old patient with refractory SCLE who was successfully treated with IV rituximab (375 mg/m$^2$) weekly for 4 weeks, remaining on oral hydroxychloroquine at
Efalizumab is a recombinant monoclonal antibody that binds to CD11a, a subunit of leukocyte function antigen-1. The agent blocks the interaction between leukocyte function antigen-1 and intercellular adhesion molecule-1 (inhibiting the firm attachment of lymphocytes to endothelial cells and impeding the recruitment of lymphocytes to the skin). Efalizumab is administered sc once weekly. It has been reported to be effective in a single case report in a patient with extremely therapy-refractory SCLE (including a high number of first- to third-line treatments) at a dose of 1 to 1.25 mg/kg sc per week. The cutaneous lesions improved dramatically within 6 weeks, while efalizumab was well tolerated and side effects were not observed. In a recent retrospective study, 13 patients with severe recalcitrant DLE were treated with efalizumab (1 mg/kg sc weekly; initialization dose 0.7 mg/kg) and 12 of them showed good to excellent results. All patients had severe DLE, which had failed to respond to a wide range of systemic therapies. The mean time of treatment response to efalizumab was 5.5 weeks (mean treatment duration 14.1 months). In this case series, adverse events were noted in 9 patients, such as superficial erosions, generalized rash, arthralgia, and gastrointestinal symptoms. Furthermore, two patients experienced a mild flare of DLE 2 months after starting treatment. There was a decrease in the titer of antinuclear antibodies in some patients with DLE; however, an increase of the antinuclear antibody titer was seen in other patients. Hamprecht et al reported successful treatment of recalcitrant malar rash in a patient with a 10-year history of a biopsy-proven LET with positive anti-Ro/SSA antibodies and marginally raised anti-dsDNA antibodies. Six weeks after the initiation of treatment with efalizumab (0.7 mg/kg per week) in addition to 5 mg of prednisolone per day, the patient developed systemic exacerbation of the disease with high anti-dsDNA antibodies and biopsy-proven lupus nephritis, despite substantial improvement of the skin lesions. Obviously, this patient had mild SLE before therapy with efalizumab.

Furthermore, a 65-year-old woman, who was treated for oral and cutaneous lichen planus with efalizumab, developed photodistributed SCLE 8 weeks after the initial injection. Aside from antinuclear antibodies (titer 1:160) with speckled pattern and anti-Ro/SSA antibodies, anti-dsDNA antibodies were positive without clinical symptoms of SLE; however, the test for anti-dsDNA antibodies was not specified (in case of positive anti-dsDNA antibodies the antinuclear antibodies usually show a homogeneous pattern; possibly, the anti-dsDNA antibodies in this patient were not of the pathogenic IgG-isotype). In a recent case report, two cases of recalcitrant SCLE were treated with efalizumab at a dose of 100 mg per week sc. In one patient, complete response was seen after 16 weeks; however, in the second patient the response was incomplete with initial dramatic improvement but a flare after 2 months.

Efalizumab was approved for plaque psoriasis; however, the European Medicines Agency recommended withdrawal of its marketing authorization and by June 8, 2009, efalizumab was no longer available in the United States because of the increased risk of progressive multifocal leukoencephalopathy. It has been concluded that the benefits of efalizumab no longer outweigh its risks.

### HISTORICAL MEDICATIONS

#### Phenytoin

Phenytoin (diphenylhydantoin) is a highly effective and widely prescribed anticonvulsant agent used in the treatment of grand mal and psychomotor epilepsy. In a single open trial from Mexico, phenytoin has been applied for the treatment of 93 patients with DLE (76 women and 17 men). In 74 patients (79.5%), DLE was localized, and in 19 cases (20.5%) the lesions were disseminated. The treatment consisted exclusively of 100 mg of phenytoin administered orally 3 times per day the mean time of treatment was 4 to 5 months (range 2-12 months). The response was excellent in 90% of patients with disseminated DLE and in 87.5% of patients with localized DLE. Improvement was visible after 4 to 6 weeks of treatment; 8.3% of patients discontinued phenytoin because of adverse events, such as erethema multiforme, urticaria reactions, muscle weakness, or paresthesia. Within a follow-up period of 6 to 12 months, 32.9% of the patients remained without relapse, 15.7% had a relapse, and in the remaining patients, follow-up data were not available before publication. The mechanism of action with phenytoin in the treatment of DLE is unclear. Phenytoin can induce a variety of generalized eruptions and systemic complications, such as erethema multiforme/Stevens-Johnson syndrome; toxic epidermal necrolysis; generalized exfoliative dermatitis; vasculitis; and a hypersensitivity syndrome with fever, rash, lymphadenopathy, hepatitis with elevated liver enzymes, eosinophilia, and other organ involvement. Similar to several other anticonvulsants phenytoin is associated with a low but significant incidence of DILE (SLE-like). One case of phenytoin-induced
SCLE has been described in a 73-year-old woman with detectable antibodies to Ro/SSA, La/SSB, and histones. Despite the promising data from a single study, no further trials with phenytoin in CLE have been published since 1995, which might be a result of the growing evidence of severe side effects.

**Gold**

Auranofin, an oral form of gold, was developed for the treatment of rheumatoid arthritis and has also been used in DLE at a dose of 3 mg per day. If there was little or no beneficial response after 3 months, the dose was elevated to a maximum of 9 mg per day. In 25 patients with severe long-standing DLE unresponsive to conventional treatment, auranofin showed improvement in 15 patients and resolution of skin lesions in 4 patients; one patient worsened and in 3 patients DLE was unchanged. In another study, 8 patients with long-standing disfiguring refractory DLE were treated with auranofin (3 mg twice daily). Three patients improved and in one of these a complete resolution of skin lesions occurred. However, the potential toxicity of gold compounds limits their use. Side effects, such as diarrhea, nausea, headache, pruritus, rash, and hematologic and renal abnormalities can appear so that monitoring with regular complete blood cell counts and urinalysis is mandatory. Treatment with gold is historic and no longer used in DLE because of its wide spectrum of side effects.

**CONCLUSION**

In conclusion, many treatment options exist for CLE, but most are not supported by evidence from randomized controlled trials. This is also the case for antimalarials, although long-term experience shows high efficacy of these agents, which are still considered first-line therapy in the different subtypes of CLE. However, new molecules, such as chemokines (ie, CXCR3), will possibly provide new therapeutic alternatives based on recent research activities in CLE.

**REFERENCES**


143. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN. Assessment of antibodies to double-stranded DNA induced by...


