Guideline

DOI: 10.1111/ddg.14491

S2k guideline: Diagnosis and management of cutaneous lupus erythematosus – Part 2: Therapy, risk factors and other special topics

AWMF registry no.: 013-060

Validity of this guideline: The guideline is valid until 24.03.2023.

Professional Societies involved:
- German Dermatological Society (Deutsche Dermatologische Gesellschaf, DDG)
- German Society for Rheumatology (Deutsche Gesellschaft für Rheumatologie e.V. DGRh)
- German Society for Pediatric Rheumatology (Gesellschaft für Kinder- und Jugendrheumatologie e.V., GKJR)

Margitta Worm[1], Miriam Zidane[2], Lisa Eisert[3], Rebecca Fischer-Betz[4], Ivan Foeldvari[5], Claudia Günther[6], Christof Iking-Konert[7], Alexander Kreuter[8], Ulf Müller-Ladner[9], Alexander Nast[2], Falk Ochsendorf[10], Matthias Schneider[4], Michael Sticherling[11], Klaus Tenbrock[12], Jörg Wenzel[13], Annegret Kuhn[14]

(1) Allergology and Immunology, Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health
(2) Division of Evidence-Based Medicine (dEBM), Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health
(3) Department of Dermatology and Venereology, Vivantes Klinikum Neukölln, Berlin
(4) Clinic and Functional Division for Rheumatology, University Hospital Düsseldorf
(5) Hamburg Center for Pediatric and Adolescent Rheumatology, Hamburg
(6) Department and Clinic of Dermatology, University Hospital Carl Gustav Carus, Dresden
(7) Center for Internal Medicine at the IIIrd Medical Department and Clinic, University Hospital Hamburg-Eppendorf
(8) Dermatology, Venereology and Allergology, Helios St. Elisabeth Klinik Oberhausen
(9) Department of Rheumatology and Clinical Immunology, Kerckhoff-Klinik GmbH, Bad Nauheim
(10) Department of Dermatology, Venereology and Allergology, University Hospital Frankfurt am Main
(11) Dermatological Department, University Hospital Erlangen
(12) Department of Pediatrics and Adolescent Medicine, University Hospital RWTH Aachen
(13) Dermatological Department, University Hospital Bonn
(14) Medical Director, Klinikum Passau, Passau

Treatment

Topical treatment

Topical glucocorticoids

Class 2–4 topical glucocorticoids are the treatment of choice for cutaneous lupus erythematosus (CLE). A randomized, controlled study has shown that fluocinonide 0.05 % is more effective than hydrocortisone 1 % [1]. Class 4 topical glucocorticoids are indicated for lesions on the capillitium, the palms of the hands/soles of the feet, and for hyperkeratotic lesions, covered by a foil/hydrocolloid dressing where required. Strictly intralesional injections of triamcinolone acetonide may be considered in individual cases, and this may be repeated after 4-6 weeks as needed. Side effects with use over longer periods of time are a limiting factor, so either short-term use over a period of several weeks, or interval treatment is recommended.

Recommendation	Strength	Agreement
Topical glucocorticoids are recommended for treating circumscribed CLE lesions.	↑↑	91 %
Considering the side effect profile of topical glucocorticoids and the location of the skin lesions, it is recommended to limit the duration of use to the shortest possible time.	↑↑	100 %
For extensive lesions, an inclination to scarring, or insufficient response, combination with a systemic treatment (antimalarial drug) is recommended.	↑↑	100 %

Topical calcineurin inhibitors

A randomized, controlled trial showed that tacrolimus 0.1 % ointment was significantly more effective than a placebo cream [2]. Tacrolimus 0.1 % ointment was most effective in patients with lupus erythematosus tumidus (LET), followed by SCLE patients. Facial lesions responded better than lesions on the body, especially when the lesions had been present for < 6 months. This treatment was not effective for scaling, hypertrophy, and subjective symptoms such as dysesthesia. Another randomized controlled trial found that tacrolimus 0.1 % ointment (once a day) was as effective as clobetasol 0.05 % but did not result in skin atrophy [3]. A side-by-side comparison (tacrolimus 0.1 % twice a day versus clobetasol 0.05 % once a day) in discoid lupus erythematosus (DLE) on the trunk showed superior efficacy of clobetasol after six weeks [4]. For labial DLE, tacrolimus 0.03 % was just as effective as triamcinolone cream 0.1 % [5]. Yet another randomized controlled trial in patients with DLE showed no difference in efficacy between pimecrolimus (twice a day) and betamethasone valerate 0.1 % [6]. This confirmed the findings of previous case series [7]. Since they present no risk of skin atrophy, topical calcineurin inhibitors are particularly suited for use on the face (under a foil dressing if indicated). The current EULAR recommendations also state that topical calcineurin inhibitors should be considered a treatment of first choice for cutaneous lesons in patients with systemic lupus erythematosus (SLE) [8].

Recommendation	Strength	Agreement
Topical calcineurin inhibitors are recommended predominantly for treating facial lesions, but also as an alternative to topical glucocorticoids.	↑↑	100 %
For extensive lesions, an inclination to scarring, or insufficient response, combination with a systemic treatment (antimalarial drug) is recommended.	↑↑	100 %

Topical retinoids and other topical compounds

Individual patients with hypertrophic DLE lesions have been treated successfully with tazarotene gel 0.05 % (not currently available in Germany), tretinoin gel 0.025 %, tretinoin cream 0.05 %, and tocoretinate 0.25 % [9–11]. R-salbutamol 0.5 % (twice a day) for DLE significantly improved scaling/hypertrophy, induration, pain, pruritus, and overall response when compared with placebo [12].

Individual cases of successful treatment with imiquimod have been reported (for example Gül 2006 [13]), but on the other hand there have been reports that imiquimod use led to the appearance of LE lesions (for example Chan and Zimarowski [14]). Topical clindamycin was effective in one case report [15].

Recommendation	Strength	Agreement
Topical retinoids may be considered for hypertrophic LE lesions.	0	100 %
Imiquimod is not recommended for treating CLE.	↓	100 %

UV therapy, cryotherapy, and laser treatment

The abovementioned physical procedures have been used in individual patients with treatment refractory CLE. There are no randomized controlled trials, so the value and differential indications for these procedures cannot be properly assessed at this point in time.

Cryotherapy

Treatment refractory lesions have been successfully treated with cryotherapy [16, 17]; however, the side effect profile and the risk of provoking lesions in DLE patients (Köbner's phenomenon) must be considered.

Laser treatment

There have been reports of successful treatment in individual patients with various laser treatments including pulsed dye laser [18], flash lamps (IPL) [19], and the 1.064-nm long pulse Nd:YAG-Laser to improve their appearance [20, 21]. Defined parameters, indications, and criteria for success are not available, and there are no controlled studies.

UV therapy

UVA1 phototherapy has been used successfully for treating SLE (evidence level Ib, [22]). For DLE, there are some case reports with varying response [23]. An open, non-controlled pilot study sought to improve light tolerance via UVB hardening. This worked in 35/44 patients, and skin findings improved in five patients [24]. However, UV therapy is not recommended since UV rays frequently induce skin lesions.

PDT

Some patients with cutaneous lesions responded to PDT, others did not [25, 26].

Extracorporeal photochemotherapy

There are currently three reports of successful use of extracorporeal photochemotherapy [27].

The value of UVA1, PDT, extracorporeal photopheresis, or cryotherapy for treating CLE cannot be properly assessed at this point in time.

Recommendation	Strength	Agreement
Therapeutic UV irradiation is not recommended for treating CLE.	↓	100 %
Cryotherapy may be considered in selected cases for treatment refractory lesions.	0	91 %
Selective lasers/IPL may be considered in selected cases for treatment refractory lesions (teleangiectasies).	0	100 %

Systemic treatment

Recommendation	Strength	Agreement
It is recommended to evaluate the efficacy of systemic treatment for CLE after a minimum of three months and a maximum of six months (except for glucocorticoids).	↑↑	100 %

Antimalarial drugs are the most important basic medications for treatmentof CLE and in the first-line treatment of SLE [8, 28]. In SLE, antimalarials result in a higher remission rate, fewer relapses, or fewer organ complications such as lupus nephritis [29]. Though randomized controlled trials are still lacking, this treatment is now also recommended for pediatric patients [30, 31].

Antimalarial drugs

Of the antimalarial drugs (AM) hydroxychloroquine (HCQ) and chloroquine (CQ), only HCQ is currently available in Germany. Although it is known that the antimalarials can improve skin lesions, there are currently only a small number of randomized controlled trials in CLE and/or SLE. In CLE patients, for example, skin was 'improved/remarkably improved' more frequently with HCQ than with placebo after 16 weeks of treatment (51 % versus 9 %) [32]. Another randomized, controlled, multicenter study showed that HCQ improved the skin lesions in 50 % of patients with various CLE subtypes (compared to acitretine in 46 %, with more side effects) [33]. In 33 patients with SLE and active skin lesions, full remission was achieved in 41 % of those treated with CQ and in 19 % of those treated with clofazimine. Partial remission was seen in 82 % (CQ) and in 72 % (clofazimine) [34]. In an analysis of patients in the EUSCLE database [35, 36], HCQ and CQ were assessed in 57 % and 31 % respectively of the 1002 patients with response rates of 82 % and 87 % respectively. In SLE, as well, HCQ and CQ have been proven to be very effective with few side effects. The side effect profile of HCQ is slightly better than that of CQ [8, 29, 37].

The most important side effect of HCQ and CQ from a clinical point of view is irreversible retinopathy [37]. Regular screening is indicated to detect initial but still reversible changes of the retina (premaculopathy). If present, antimalarial treatment must be discontinued. Intervals and examination procedures should follow the guidelines issued, for example, by the American Academy of Ophthalmology [38]. This side effect can mostly be avoided by adhering to a maximum daily dose of 3.5 (–4) mg/kg body weight [BW] (ideal BW or actual BW, respectively, whichever is lower) for CQ and

6 (–6.5) mg/kg ideal BW or actual BW respectively, whichever is lower, for HCQ. When adhering to these maximum doses, retinopathy need not be anticipated even after several years of continuous treatment [39–41]. Pre-existing maculopathy, renal failure (GFR < 50 mL/min), accompanying treatment with tamoxifen, or daily doses of > 5 mg/kg BW HCQ indicate an increased risk for AM-induced retinopathy. These patients should be examined by an ophthalmologist once a year from the time AM treatment is initiated.

Special attention is required for patients with an actual or ideal body weight of less than 63 kg. Even one daily tablet containing the usual dose of 250 mg CQ or 400 mg HCQ (= equivalent doses) will be too much in the long term [41].

If the patient shows no response to HCQ/CQ, treatment adherence needs to be verified before considering changes in the treatment regime. In treatment refractory patients, investigation of HCQ or CQ blood levels should be considered.

Various studies have shown that smoking as well as pronounced DLE are associated with reduced responses to antimalarial drugs [42–47]. It needs to be mentioned, however, that the literature on a connection between smoking and treatment with antimalarial drugs is controversial. In accordance with the publication by Khoo et al., clinical observations have shown that hemolysis in patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency is only rarely induced by antimalarial drugs [48]. Routine assessment of G6PD activity is therefore not recommended, based on current data. Use of antimalarial drugs before and during pregnancy and during lactation is covered in a separate chapter (see below).

Despite a lack of controlled studies, HCQ is also recommended for pediatric patients. Case series confirm that the dose recommendations are the same as for adult patients [49, 50]. This has also been included in the European recommendations issued by the SHARE initiative [30].

Mepacrine

Mepacrine (= Atabrine, Atebrine, Quinacrine) was widely used as a prophylactic antimalarial drug during the Second World War. More than three million soldiers took this drug for up to four years. Case series (> 750 CLE patients) between 1940 and 1961 found average improvements of 73 %. Today, mepacrine is usually combined with CQ/HCQ since it acts synergistically with these drugs and does not increase the risk of retinopathy. In exceptional cases, such as intolerance of HCQ or CQ, mepacrine may also be used as monotherapy [51, 52]. The current EULAR recommendations also include mepacrine as first-line therapy for cutaneous lesions in SLE patients [8, 51, 53–55].

Mepacrine dosage: A daily dose of 100 mg mepacrine should ideally not be exceeded, although doses of 200 mg per day may be administered for short periods of time. Skin lesions will improve within three to four weeks; maximum effects are seen after six to eight weeks. If no improvement is evident after three months of treatment, this drug is ineffective and should be discontinued. In case of diarrhea or other side effects, the dose may be reduced to 25–50 mg per day. Such low doses will take longer to achieve an effect. In cases of good response, the dose should be slowly reduced after three to six months (reduce by one tablet per week every two months) until a maintenance dose of one to three tablets per weeks has been reached [54].

Mepacrine side effects: Mepacrine does not have any ophthalmological side effects but displays non-specific side effects such as headaches or gastrointestinal complaints (diarrhea, anorexia, nausea, abdominal cramps) in about one-third of patients. These side effects are mild and will usually resolve spontaneously or after dose reduction. Low doses may act as a psychological stimulant. Reversible agitation, sleeplessness or psychotic episodes have been observed in the first 2–3 weeks after discontinuation of higher doses [54]. Mepacrine may cause reversible yellow skin discolorations as well as hyperpigmentation of the skin, mucous membranes, and nails. This is dose-dependent and will resolve or at least decrease significantly after dose reduction to less than 50 mg per day. The most important side effect, however, is aplastic anemia. When adhering to the abovementioned recommendation, this will occur in about one in 500,000 patients and also depends on dosage and duration of treatment. In most cases, aplastic anemia is preceded by a lichen planus eruption. Rhabdomyolysis has also been observed as a very rare side effect. Mepacrine can pass the placental barrier, so its use during pregnancy and lactation is discouraged in spite of individual reports of uneventful pregnancies [54].

Monitoring: Before initiating mepacrine treatment, a differential blood count should be performed. This needs to be monitored every 2–3 months (in patients with long-term treatment every six months). A decrease of hemoglobin or reticulocytes is a sign that treatment must be discontinued [54].

Procurement: In Germany, mepacrine is available only via Pharmavertrieb Heinze in Lörrach (https://www.pharmavertrieb-heinze.de/) as a British import (BCM Specials at http://www.bcm-specials.co.uk).

Recommendation	Strength	Agreement
Antimalarial drugs are recommended as first-line treatments, also for long-term therapy, in all CLE patients with severe and disseminated skin lesions; in particular for patients with a risk of scarring.	↑↑	100 %

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For calculating the daily dose of antimalarial drugs, it is recommended to use the so-called "ideal weight" (height in cm minus 100, then subtracting 10 % for men or 15 % for women). If the patient's current weight is below the "ideal weight", it is recommended to use the actual weight. CQ dosage ist 3.5 (– max. 4) mg/kg BW, HCQ dosage is 6 (– max. 6.5) mg/kg BW.	↑↑	100 %
Opthalmological evaluation is recommended for all CLE patients during the first year of treatment with antimalarial drugs, and every year after five years of treatment. In cases of pre-existing ocular disease, ophthalmological evaluation is recommended before initiating treatment with antimalarial drugs. In patients with risk factors (especially renal failure), yearly ophthalmological monitoring is generally recommended.	↑↑	100 %
Routine assessment of G6PD activity is not recommended based on current data.	↓	100 %
In treatment refractory cases, or in cases of intolerance or retinopathy, systemic treatment with mepacrine is suggested either instead of or in combination with HCQ or CQ.	↑	100 %

Systemic glucocorticoids

A prospective, multicenter, cross-sectional study showed that systemic glucocorticoids were the most effective of any systemic drugs used for CLE treatment. 94 % out of a total of 413 patients responded to systemic glucocorticoids. In addition, systemic glucocorticoids were most frequently (in 58 %) and most successfully (in 97 %) used in patients with acute CLE (ACLE) [36]. The most frequently used dose of oral systemic glucocorticoids was 0.5 to 1.0 mg prednisolone equivalent per kg body weight per day over a period of about two to four weeks, followed by dose reduction to ≤ 7.5 mg/day. If this reduction is unsuccessful due to high disease activity, the drug can be combined with other medications (see treatment algorithm, Figure 1). In individual patients with persisting CLE who had not responded to conventional therapy, a three-day intravenous pulsed treatment regimen with 250 mg to 1 g methylprednisolone per day was successful [56]. The current EULAR recommendations also allow for glucocorticoids as first-line therapy in SLE patients with cutaneous affection [8].

Please refer to the chapter on pregnancy and lactation for recommendations on the use of systemic glucocorticoids in pregnant and lactating women.

Glucocorticoids have long been used in childhood SLE. Since these drugs have a range of well-known side effects, they should only be used for a limited time. There is no consensus on the dosage of glucocorticoids in childhood CLE or on dose reduction [57, 58]. However, some studies have shown that a more restrive use of systemic glucocorticoids is not a disadvantage and has fewer side effects [59].

Recommendation	Strength	Agreement
For severe or disseminated CLE lesions, systemic glucocorticoids are recommended as first-line treatment in addition to antimalarial drugs, for a limited period of time. Systemic glucocorticoids should be tapered off as soon as possible.	↑↑	100 %

Methotrexate

Methotrexate (MTX) has been successfully used as a second-line treatment in patients with treatment-refractory SCLE and DLE [60, 61]. A retrospective study evaluated 43 patients with various CLE subtypes [62] who were treated with methotrexate, some of them intravenously (15–25 mg once a week). Ninety-eight percent of these patients showed a significant improvement of disease activity. The best clinical improvement was observed in DLE and SCLE patients, but seven patients discontinued treatment due to side effects. In a follow-up study, 15 out of the previous 43 CLE patients who had been treated with intravenous MTX switched to subcutaneous application, with comparable efficacy. There is currently no evidence-based study on how long MTX can or should be used for CLE patients. Experience with other dermatological diseases (such as psoriasis) however suggests that MTX can be used as long as it is effective and well tolerated. Weekly doses of 15 mg and above are usually tolerated better if applied subcutaneously. During MTX treatment, a single

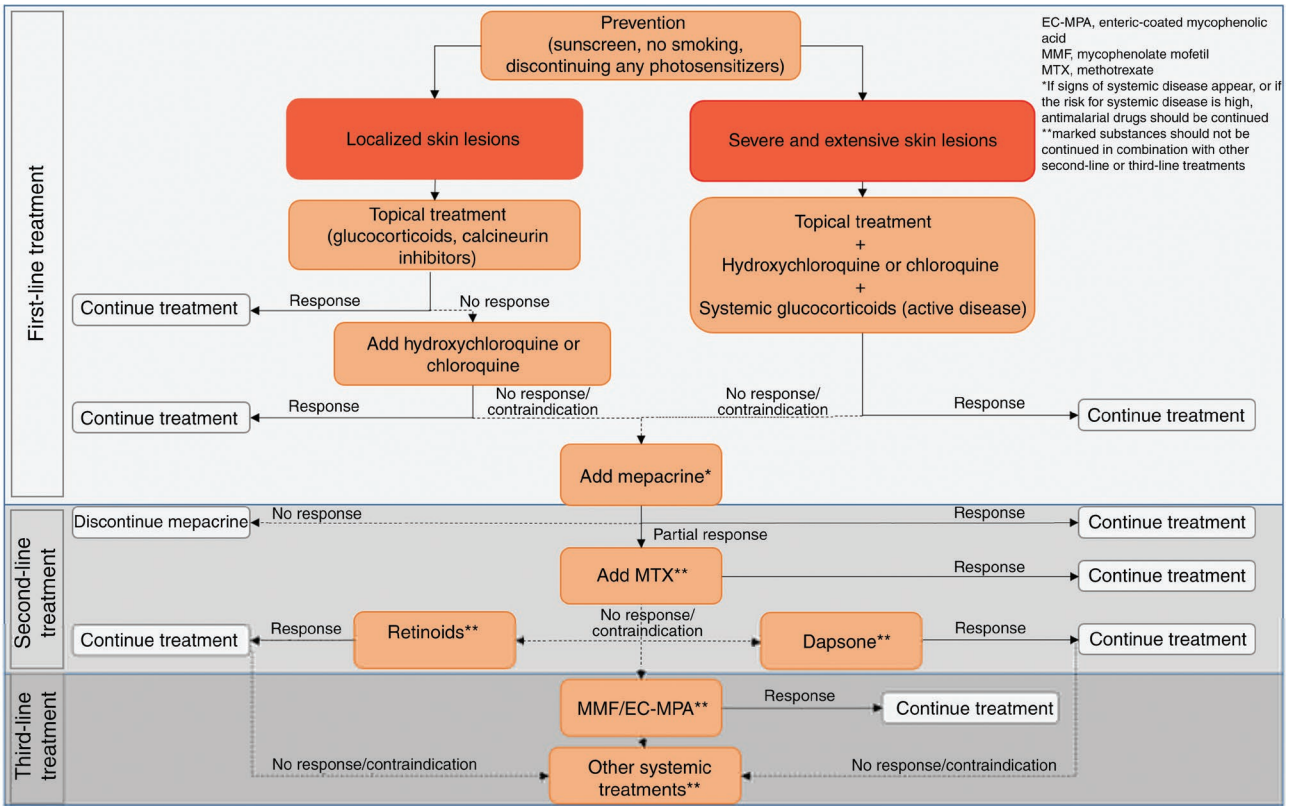

Figure 1 Treatment algorithm of cutaneous lupus erythematosus (adapted from [55, 123]).

oral dose of 5 mg folic acid should be given on the next day to reduce possible side effects. Methotrexate must be reduced in cases of impaired renal function, and from a GFR< 40 ml/min onwards it should be discontinued or at least administered only with tight nephrological monitoring. The risk of direct and/or irreversible hepatotoxicity is very low in patients with standard doses of MTX; increases of liver enzymes up to twice the normal values can be tolerated even over long periods of time if they are caused solely by MTX treatment. Additional risk factors must however be assessed before and during treatment, and monitored regularly. These include all hepatic and biliary autoimmune diseases, viral hepatitis, alcohol consumption exceeding the average, obesity, hemochromatosis and type-2 diabetes, as well as any concomitant use of hepatotoxic medications (including all types of painkillers even if only taken as needed). If transaminases exceed twice the normal value, use of MTX must be discontinued or at least paused until other causes have been evaluated and treated. If the values normalize quickly after pausing MTX treatment, medication may be resumed at a reduced dose (for example at half the previous dose) and with careful monitoring. Please refer to the Summary of Product Characteristics (SPC) for information on very rare side effects (such as pneumonitis, renal toxicity). Methotrexate is contraindicated before and during pregnancy and during lactation.

There are no controlled data on MTX for childhood CLE [63]. It is used predominantly for arthritis and SLE, but a small retrospective analysis did not find a long-term steroid-sparing effect [64]. This study also included patients with cutaneous lesions. A Mexican study with ten SLE patients did find a steroid-sparing effect [65]. Methotrexate has been used for a long time in pediatric rheumatology. It is safe and has proven effective in juvenile idiopathic arthritis (JIA) and dermatomyositis [66, 67]. Methotrexate is used both orally and subcutaneously at doses of 10–15 mg/m² body surface area (BSA); there are no clinical differences between the two forms of application. In cases of intolerance, it is possible to switch between the two types of MTX application.

Recommendation	Strength	Agreement
MTX is recommended as a systemic second-line treatment at doses of up to 25 mg per week, and if possible in combination with antimalarial drugs.	↑↑	100 %

Retinoids

The *American Academy of Dermatology* guidelines from 1996 suggested that retinoids be used as a second-line systemic treatment. A double-blind, randomized, multicenter study compared acitretin with HCQ over a period of eight weeks [33]. Response or remission were observed in 13 (46 %) of 28 patients using acitretin and in 15 (50 %) of 30 patients using HCQ. Acitretin was particularly effective in treating hyperkeratotic-verrucous forms of DLE on the hands, feet, and legs. Individual case reports describe a combination of acitretin with CQ and quinacrine with complete remission of DLE. Isotretinoin was reported to achieve remarkable improvement in SCLE within one month. Treatment of DLE and SCLE with isotretinoin was studied in about 50 patients in open studies and case reports, with a success rate of about 87 %. Etretinate 50 mg daily was used in an open, prospective study [68]. The study included 19 patients with localized or disseminated DLE and SCLE, and one patient with SLE and cutaneous lesions. Complete or nearly complete remission of the CLE lesions was observed in eleven patients while eight patients did not respond to etretinate.

The recommended dose for acitretin and isotretinoin in CLE is 0.2–1.0 mg/kg BW/day. Response usually occurs rapidly within the first 2–6 weeks after treatment initiation. Relapses are often just as rapid if treatment is discontinued. Another vitamin A derivative, alitretinoin, is approved for treating patients with chronic hand eczema who do not repond to topical glucocorticoids. A case report of three patients receiving oral alitretinoin [69] reported good efficacy in the treatment of skin lesions in two patients with CLE and one patient with SLE. Please refer to the chapter below for information on the use of retinoids before and during pregnancy and during lactation. The current EULAR recommendations consider retinoids a fallback treatment in SLE [8].

Systemic retinoids are neither studied nor approved for use in children and adolescents with CLE. Extensive communication is necessary for off label use. There are recommendations on systemic retinoids for childhood psoriasis [70].

Recommendation	Strength	Agreement
Retinoids are recommended as a second-line systemic treatment for hypertrophic CLE lesions, preferably in combination with antimalarial drugs.	↑↑	100 %
Retinoids are sugested as a second-line systemic treatment for all other forms of CLE.	↑	100 %

Dapsone

The efficacy of dapsone has only been shown in case series and individual case reports. Lindskov and Reymann [71] used dapsone in 33 DLE patients. Excellent results were reported in eight patients (24 %), moderate effects in eight patients (24 %), and no response in 17 patients (52 %). Ujiie and coworkers [72] reported another case of lupus erythematosus profundus (LEP) which was successfully treated with dapsone. They assessed ten more cases of Japanese patients with LEP. A retrospective analysis of 34 patients by Klebes and coworkers [73] reported an efficacy rate of more than 50 % for dapsone with or without additional antimalarial drugs. In summary, the published data suggest that dapsone may be effective in SCLE and LEP. Dapsone has also shown efficacy in bullous lupus erythematosus (BLE) after initial unsuccessful treatment with HCQ and systemic glucocorticoids. The current EULAR recommendations also include dapsone as a fallback medication for SLE [8]. With careful monitoring, the side effects of dapsone can be managed. However, neurological side effects such as sensory and motor neuropathy have been reported frequently after long-term treatment. Please refer to the chapter below for information on the use of dapsone before and during pregnancy and during lactation.

There are some individual case reports on the successful treatment of bullous LE in children with dapsone [74]. For safety reasons, methemoglobin levels in the blood should be monitored regularly during dapsone therapy.

Recommendation	Strength	Agreement
Dapsone is suggested as first-line therapy for bullous CLE.	↑	100 %
Dapsone is suggested as second-line therapy for refractory CLE, preferably in combination with antimalarial drugs.	↑	100 %
It is recommended to initiate dapsone treatment with low doses (50 mg/day), and increase the dose to a maximum of 1.5 mg/kg BW depending on clinical response and side effects. It is recommended to monitor G6PD activity before initiating treatment.	↑↑	100 %

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a standard medication in transplant medicine. Although there are only a small number of studies, this drug is clinically established for autoimmune

diseases of the skin, lupus nephritis, and various CLE subtypes. It is however approved only for transplant patients [75, 76]. Based on clinical data, the German G-BA (Gemeinsamer Bundesausschuss, Federal Joint Committee) has agreed to reimbursement of mycophenolate mofetil and mycophenolic acid for induction and/or maintenance treatment of class III–V lupus nephritis [77]. In cases of refractory CLE, MMF has also been proven effective in combination with HCQ and/or systemic glucocorticoids. Severe side effects (gastrointestinal, cytopenic, hepatotoxic, and allergic reactions) are rare and mainly dose-dependent. This also applies to the infection rate with long-term MMF treatment. Monitoring of hematological, hepatic, and renal laboratory parameters is recommended every 2–3 weeks initially, and every three months later if the course remains stable. Mycophenolic acid (MPA), the enteric-coated form of MMF, is effective as monotherapy for SCLE. The current EULAR recommendations also include MMF as second-line treatment for active SLE [8]. There are no controlled trials on treatment duration with MMF in CLE. After clinical remission has been achieved, tentative withdrawal of the medication should be considered, especially in patients without systemic organ involvement. Please refer to the chapter below for information on the use of mycophenolate before and during pregnancy and during lactation.

As for adults, MMF is only approved for transplant patients in pediatrics. It is, however, increasingly used for severe systemic forms of childhood SLE (grade IV nephritis), and is recommended on a European level [30, 78, 79].

Recommendation	Strength	Agreement
MMF is suggested as third-line therapy for refractory CLE lesions, preferably in combination with antimalarial drugs.	↑↑	100 %
2 x 500 mg MMF per day is recommended as an initial dose, with a subsequent dose increase to 2 g per day.	↑↑	100 %
MPA is suggested as an alternative treatment for MMF.	↑	100 %

Azathioprine, cyclophosphamide, and ciclosporin

Azathioprine, cyclophosphamide, and ciclosporin are frequently used for treating SLE [80, 81]. However, these drugs are not recommended for CLE patients without systemic organ involvement. Please refer to the chapter below for information on the use of azathioprine, cyclophosphamide, and ciclosporin before and during pregnancy and during lactation.

Azathioprine is recommended for moderate systemic lupus erythematosus in children, or as long-term treatment for severe SLE after achieving remission [30]. There are no data on cSLE in childhood. Due to its severe side effects, cyclophosphamide is not recommended for cSLE in children. Apart from its use in transplant medicine, ciclosporin is also used off label for severe atopic dermatitis in children, with doses lower than those used in transplant medicine. There are no data on cSLE and ciclosporin in children.

Recommendation	Strength	Agreement
Azathioprine may be considered for treating CLE.	0	100 %
Ciclosporin may be considered for treating CLE.	0	100 %
Cyclophosphamid is not recommended for treating CLE.	↓	100 %

Thalidomide and Lenalidomide

Thalidomide (α-Phthalimidoglutarimide) shows strong anti-inflammatory effects in erythema nodosum leprosum (leprosy) and CLE and has achieved excellent results in severe CLE. Its use however is limited by potentially severe and irreversible side effects. A meta-analysis (21 studies with a total of 548 patients) reported response rates of up to 90 % and similar efficacy in various CLE subtypes. In 24 % of patients (95 % confidence interval [CI] 14–35) thalidomide was discontinued due to side effects, including peripheral neuropathy in 16 % and thromboembolic events in 2 %. Thalidomide should be limited to patients with severely refractory CLE or with a high risk of severe scarring. For women of reproductive age, reliable contraception is essential (pregnancy program) [82]. Lenalidomide, a structural analog of thalidomide, poses a lower risk of polyneuropathy. In one case report and two open label studies [83, 84], the majority of patients (> 80 %) with treatment refractory SCLE, CCLE, and other subtypes showed a response after only two weeks of oral lenalidomide dosed at 5–10 mg/day. It should be noted however that lenalidomide can not only prevent systemic involvement but may also induce it. The reasons are currently unclear. Lenalidomide is absolutely contraindicated during pregnancy. In Germany, thalidomide and lenalidomide must be prescribed via a special procedure (T prescription).

An initial dosage of 100 mg per day is recommended, with subsequent reduction to the minimum effective dose after clinical response. It is recommended to observe the sedating and prothrombotic side effects. Due to the high incidence of polyneuropathies, electrophysiological examination of the peripheral nerves is recommended before and during treatment, depending on the clinical symptoms. Any signs of polyneuropathy necessitate discontinuation of this medication.

There are no data on thalidomide in pediatrics. If its use is considered in adolescent girls, reliable contraception must be ensured.

Recommendation	Strength	Agreement
Thalidomide may be considered in selected cases of refractory CLE lesions, preferably in combination with antimalarial drugs.	0	100 %

Fumaric acid esters

Fumaric acid esters have been used in Germany for psoriasis treatment for over twenty years, and have also been approved for multiple sclerosis. Their therapeutic mechanism remains largely unclear, but current findings suggest that suppression of both T and B lymphocytes may play a role. In 2016, an open-label Phase II pilot study investigated eleven CLE patients (DLE, SCLE) over a period of 24 weeks, and reported significant improvement in the RCLASI activity score (Revised Cutaneous lupus Erythematosus Disease Area and Severity Index) [85]. In this publication, fumaric acid derivatives were therefore recommended as an alternative and safe treatment for patients with treatment refractory CLE, even though there are currently no randomized controlled trials.

Side effects of fumaric acid derivatives include flush-like symptoms and sensations of heat, as well as gastrointestinal complaints such as nausea, diarrhea, and gastric cramps. These symptoms usually decrease over time, but still lead to treatment discontinuation in about 20 % of cases.

In rare cases, fumaric acid derivatives may also promote the development of PML (progressive multifocal leukencephalopathy), as stated in four case reports published in the *New England Journal of Medicine* [86]. However, a causal relationship with fumaric acid derivatives has not been established conclusively.

Antibiotics

The data in the medical literature are too scant to recommend antibiotics for the treatment of CLE.

Recommendation	Strength	Agreement
Antibiotics are not recommended for treating CLE.	↓	100 %

Intravenous immunglobulins

Intravenous immunglobulins (IVIG) are obtained from pooled plasma, usually from more than 10,000 donors. A dose-dependent effect on the immune response mediated by dendritic cells was reported recently. “High-dose” IVIG (2 g/kg BW/month) has been used successfully in autoimmune diseases. Several case reports and case series have shown positive effects in refractory CLE [87–89], but deterioration of skin lesions in SCLE and SLE has also been observed. One study treated 16 treatment-refractory patients with IVIG 500 mg/kg BW/day on four consecutive days up to a total of 2 g/kg BW/month over a period of three months. They were then followed up for another six months. The cumulative results indicated a general improvement of disease activity. The CLASI-A score initially fell by 100 % compared with the basic value and remained at about 70 % until the last day of the study. Three patients (19 %) showed transient CLE symptoms but recovered within one month [90]. The general side effects of IVIG include allergic reactions, headaches, and more rarely acute renal failure and aseptic meningitis [91].

Intravenous immunoglobulins are used successfully in some pediatric diseases (for example Kawasaki’s syndrome, immune deficiency syndromes, autoimmune thrombocytopenia) [92], and they are comparatively safe. There are no data on IVIG for cSLE in children.

Recommendation	Strength	Agreement
IVIG may be considered for treatment of CLE.	0	88.9 %

Belimumab

Belimumab received approval as a second-line treatment for active SLE in Germany in 2012. Data from two phase III studies show that belimumab improved SLE disease activity for mucocutaneous and musculoskeletal parameters. Cutaneous parameters were also investigated and showed a response in some patients. However, the studies were neither designed nor performed to prove the efficacy of belimumab in certain organs (including the skin). The drug was therefore approved as an add-on treatment in adult patients with antibody-positive systemic lupus erythematosus (SLE) whose disease is still highly active despite standard treatment [93, 94]. In the approved regimen, belimumab is administered at doses of 10 mg/kg BW every two weeks (for the first three doses), and then every four weeks. For subcutaneous application, a dose of 200 mg/week is used [95–97]. Please refer to the “Rote-Hand-Brief” (“Red Hand” letter, German equivalent to “Dear Doctor” letter) regarding neuropsychiatric side effects.

Belimumab has recently been approved for use in children aged 5 years or older at a dose of 10 mg/kg BW. There are no data on belimumab and CLE in children.

Recommendation	Strength	Agreement
Belimumab may be considered for CLE treatment.	0	100 %

Rituximab

Several case reports and open-label studies have shown that rituximab is effective in patients with treatment-refractory SLE [98–101]. The current EULAR recommendations mention rituximab as a fallback treatment for treatment-refractory active SLE [8]. Prospective registry data showed cutaneous improvement in 70 % of patients treated with rituximab, however, these results were not confirmed in two randomized, controlled, multicenter trials. Currently, rituximab has not been approved for treating SLE in any country. There has been only a small number of case reports and clinical studies [102] on the use of rituximab in CLE [99, 103], including one monocentric, retrospective cohort study. Adult patients with CLE and mucocutaneous involvement treated with rituximab were selected from a prospective database encompassing 709 SLE patients. Clinical response was assessed six and twelve months after treatment of the CLE and its subtypes acute CLE (ACLE), subacute CLE (SCLE), chronic CLE (CCLE) and non-specific LE (NSLE). Out of the 50 patients with predominant CLE, 38 patients (76 %) showed improvement of their mucocutaneous status after six months, including 20 (40 %) with remission. Fifteen patients (30 %) required repeat treatment with rituximab within twelve months because of mucocutaneous involvement [99, 103–105].

Rituximab is used for severe, treatment refractory systemic lupus in childhood, but there are no data on CLE and rituximab in children.

Recommendation	Strength	Agreement
Rituximab may be considered for CLE treatment.	0	83.3 %

Other immunomodulators

Use of other immunomodulators including tumor necrosis factor (TNF)-α antibodies, interferon (IFN) modulators, and leflunomide, showed divergent results. Although serum TNF-α levels are increased in SLE and correlate with disease activity, TNF-α blockers have actually shown stimulatory effects in CLE. Individual case reports on CLE patients treated with IFN-α2a reported exacerbation of skin lesions, induction of an SLE-like syndrome, but also improvement of skin lesions. Both open and placebo-controlled pilot studies have shown efficacy of leflunomide in treating SLE, yet the current EULAR guidelines do not offer a recommendation [8]. A number of side effects on the skin related to leflunomide were reported, including some rare cases of SCLE. A randomized, double-blind, controlled trial investigated the safety and pharmacokinetics of several intravenous infusions with sirukumab [106], an anti-interleukin (IL)-6 antibody, in 31 CLE patients and 15 SLE patients. The CLE patients showed a CLASI decrease from 6 to 3 points, the SLE patients from 4 to 1.5 points with sirukumab, yet this was not a statistically significant change from pre-treatment values. There have been individual case reports on the treatment of CLE and SLE with other biologicals such as ustekinumab, an interleukin-12 and interleukin-23 antibody. Inhibition of the IL12/23/17 pathway may however induce (cutaneous) LE as well [107–114]. Based on the results of a phase II study, apremilast also shows efficacy in CLE [115]. The current EULAR recommendations do not yet mention the Janus kinase inhibitors [8] although there are some promising results on chilblain CLE and SLE [116–120].

Vitamin D3

Vitamin D3 is thought to have immunomodulatory properties. Vitamin D3 deficiency has been described as a risk factor for, among other conditions, CLE or SLE. Treating vitamin D3 deficiency may have a positive effect on disease progression. Many CLE patients have low levels of vitamin D3 due to light sensitivity which necessitates avoidance of sunlight [121].

Current recommendations state that the level of 25(OH)D in serum should be at > 30 ng/ml Daily intake of 30–50 µg (1000–2000 IU) vitamin D3 is recommended. This is especially important when taking systemic glucocorticoids [122].

Recommendation	Strength	Agreement
Administration of vitamin D3 for CLE patients may be considered.	0	100 %

No recommendation for children.

Treatment algorithm

Figure 1 shows a summary treatment algorithm.

Neither topical nor systemic medications have yet been approved for treating CLE, and the current treatment is based on a small number of randomized controlled trials. There are, however, recommendations for treating CLE patients based on European consensus [124], which are reflected in an algorithm [55]. This algorithm covers first-line, second-line, and third-line treatment options. It was modified within the framework of this guideline. Mepacrine is frequently not reimbursed by health insurance companies, thus it is only listed as a potential and supplementary first-line treatment where applicable.

Risk factors

Ultraviolet (UV) rays

For many decades, UV radiation has been recognized as one of the most important trigger factors for LE [125]. Photoprovocation testing in more than 400 CLE patients induced LE-specific skin lesions with both UVA and UVB radiation [126]. In this retrospective study, LE-specific lesions were most frequently (in 53 %) provoked by combined UVA/UVB irradiation, followed by 42 % after UVB only and 34 % after UVA only. Other studies confirmed that different subtypes of CLE show varying sensitivity to photoprovocation. A history of sun sensitivity has been included in the ACR criteria for classification of SLE; it is, however, not clearly defined and thus a rather non-specific criterion [127].

Recommendation	Strength	Agreement
It is recommended to advise CLE patients that exposure to sunlight and artificial UV sources (such as tanning beds) may lead to exacerbation or induction of skin lesions and in rare cases even to systemic reactions such as lupus nephritis.	↑↑	100 %

Smoking

Smoking is a risk factor for CLE. Two case-control studies in DLE showed that skin lesions were more extensive in smokers than in non-smokers [128, 129].

Recommendation	Strength	Agreement
It is recommended that CLE patients be emphatically advised to avoid active and passive exposure to tobacco smoke.	↑↑	100 %

Köbner's phenomenon

Non-specific irritation (scratching) or trauma (such as wounds, tattoos, contact allergy, or burns) may provoke DLE (Köbner's phenomenon).

Recommendation	Strength	Agreement
It is recommended that CLE patients be informed about the possibility of Köbner's phenomenon.	↑↑	100 %

Medications

Classic drug-induced LE (DILE) resembles a mild form of idiopathic SLE with arthralgia, myalgia, serositis (mainly pleuritic), and fever. Affection of the skin or viscera is rare [130, 131]. Antinuclear antibodies (ANA) with a homogeneous pattern corresponding to anti-histone antibodies (up to 95 %) are characteristic for DILE, while antibodies against dsDNA and ENA are typically absent (< 5 %) [132]. Drug-induced CLE, however, always shows the skin lesions typical for the individual subtype. Evaluation of the literature on DILE and DI-CLE is limited by ill-defined clinical categorization of skin lesions and histopathological findings.

Drug-induced DLE, CHLE, and LET

DLE is not usually induced by medications. One exception is a collection of reports from Japan that state that a fluorouracil preparation (uracil tegafur, UFT) led to DLE-like skin lesions in areas exposed to light. These comprise 10 % of all drug reactions on the skin observed with fluorouracil treatment. Drug-induced CHLE or LET has only been reported in very rare cases, in connection with pantoprazole or in several cases with TNF-α inhibitors.

Drug-induced SCLE

As compared with other CLE subtypes, SCLE is most frequently induced by medications. Drug-induced SCLE is more probable in patients with predisposing diseases such as Sjögren's syndrome, or in patients with genetic predisposition (such as HLA-B8, -DR3) and/or anti-Ro/SSA antibodies. Drug-induced SCLE was first reported in five patients after treatment with hydrochlorothiazide [133]. These drugs should, if possible, be avoided in patients with established SCLE. Clinically, drug-induced SCLE corresponds to non-drug-induced annular or papulosquamous SCLE, with a similar distribution in areas exposed to light. The skin lesions however may also appear more generalized and affect the lower limbs as well [134]. Patients show the typical antibody profile with detection of ANA, anti-Ro/SSA and anti-La/SSB antibodies. Anti-histone antibodies, which are characteristic for classic DILE, have only been detected in a portion of patients with drug-induced SCLE; however this was not always examined. The skin lesions will typically disappear after the causative drug has been discontinued. Usually, ANA titers will also decrease, and anti-histone antibodies will no longer be detectable, while anti-Ro/SSA antibodies usually persist. Patients evaluated for HLA showed an association with HLA-B8, -DR3, and/or -DR2 [134]. Medications that may trigger drug-induced SCLE differ from those that trigger classic DILE (see review publications: [133, 135–137]). Hydrochlorothiazide and terbinafine

have been reported as the most common triggers. TNF-α antagonists can trigger classic DILE but there have also been case reports on the induction of various CLE subtypes (DLE, CHLE, LET). Induction of SCLE by etanercept has been reported [138], but on the other hand resolution of SCLE in a patient with rheumatoid arthritis treated with etanercept has also been reported [139]. Recently published reviews on DILE induced by TNF-α inhibitors also list skin lesions characteristic for DLE or SCLE [140, 141]. There have also been reports about SCLE induced by leflunomide, although this drug is actually used for CLE [142–150]. Antiandrogens such as flutamide may also trigger SCLE [151].

Table 1 offers a list of case reports on a possible association between drug intake and drug-induced SCLE (modified from [152]).

Table 1 Case reports that suggest a possible association between drug intake and drug-induced SCLE (modified in accordance to [152]).

Numerous reports	
Medication	*Drug group*
– Terbinafine	Antifungals
– Hydrochlorothiazide	Diuretics
– Diltiazem – Verapamil – Nifedipine – Nitrendipine	Calcium channel blockers
Individual case reports	
Medication	*Drug group*
– Griseofulvin	Antifungals
– Spironolactone	Diuretics
– Oxprenolol	Beta blockers
– Lansoprazol – Pantoprazol – Omeprazol	Proton pump inhibitors
– Simvastatin – Pravastatin	Statins
– Captopril – Enalapril – Lisinopril – Cilazapril	ACE inhibitors
– Cinnarizine – (Piperazine derivative) – Combination: Cinnarizine + Thiethylperazine (Phenothiazine)	Histamine H1 receptor antagonist and calcium channel blocker Neuroleptics
– Docetaxel (Taxotere)	Chemotherapeutics
– Interferon-beta 1a – Interferon-alpha	Interferons
– Carbamazepine – Tamoxifen – Penicillamine – Acebutolol – Anastrozol – Bupropione – Fluorouracil – Leuprorelin – Naproxen – Phenytoin – Piroxicam – Rifampicine – Ticlopidin-hydrochloride	Various
– Leflunomide	Immunosuppressants
– Etanercept – Efalizumab – Adalimumab – Infliximab (acute exacerbation of pre-existing SCLE)	Biologicals
– Flutamide	Antiandrogens

Recommendation	Strength	Agreement
In cases of dug-induced SCLE or deterioration of established SCLE, checking the patient's medication is recommended. If any of the medications is listed in Table 1, it is recommended to discontinue this drug.*	↑↑	100 %
*If, however, the SCLE patient has been taking one of the medications listed in Table 1 for many years, the SCLE has resolved with treatment such as antimalarial drugs, and has not relapsed after treatment was discontinued, the drug in question may be continued. It is therefore recommended to examine a patient's medications initially at diagnosis, and especially if the disease is treatment-refractory.		

Paraneoplasia

There have been a small number of case reports on CLE as a paraneoplastic dermatosis (associated with carcinomas of the lungs, stomach, liver, breast, prostate, and uterus as well as Hodgkin's lymphoma); this was almost always SCLE [153–164].

Recommendation	Strength	Agreement
In cases of treatment-refractory SCLE, late manifestation of SCLE (above 60 years of age), and symptoms that may indicate a carcinoma, searching for a tumor is recommended.	↑↑	100 %

Monitoring/therapy management

Any drug therapy should be regularly monitored as to its efficacy and side effects.

Antimalarial drugs are usually well tolerated, and discontinuation due to side effects is rare. Two types of side effects have been reported: *(1)* gastrointestinal or neurologic intolerance, pruritus and other skin reactions, which usually resolve after dose reduction and rarely require discontinuation, *(2)* retinal and in rare cases neuromuscular and cardiac damage.

There is no appropriate treatment for retinal damage in particular. Initially, it shows as depigmentation of the retinal epithelium near the central fovea. In the last stage, this type of damage is called "bull's eye maculopathy" because of its typical ring-shaped structure. It is very important to detect the development of retinopathy in an early, preclinical stage (please also refer to the ophthalmological guideline [165]).

Time intervals for desired effects can be determined individually in a "Treat-to-Target" concept. For undesired effects, however, the only way to determine monitoring intervals is by consensus. The German Society for Rheumatology (*Deutsche Gesellschaft für Rheumatologie, DGRh)* offers consensus-based treatment monitoring forms for most medications used in this disease (https://dgrh.de/Start/Versorgung/Therapieinformationen/Therapieinformationsbogen.html). Any necessary monitoring of laboratory values is also listed in these forms.

If a patient does not respond (sufficiently) to antimalarial drugs, one reason may be that the medication is not taken as prescribed. In these cases, adherence to treatment should be assessed.

Cardiotoxicity comprises both conduction disorders and congestive heart failure. These cardotoxic effects were reported for CQ and more rarely for HCQ as monotherapy.

Monitoring of laboratory values during treatment

Chloroquine/Hydroxychloroquine

Recommendation	Strength	Agreement
During CQ/HCQ treatment, routine evaluation of basic laboratory parameters used in normal patient care is recommended. Additional monitoring is unnecessary.	↑↑	100 %
Monitoring of all other treatments mentioned is recommended to be performed according to the guideline for bullous dermatitis/psoriasis.	↑↑	100 %

Discontinuation of treatment

There are no studies on tapering off/discontinuing an effective medical treatment in patients with CLE. Temporal limitations are based on the basic toxicities of the medications used: Due to the known side effects (such as atrophy, teleangiectasia, steroid-induced rosacea-like dermatitis), topical glucocorticoids should only be used for limited periods (please refer to the recommendation in the chapter on topical glucocorticoids), and if possible intermittently. Systemic glucocorticoids should only be prescribed for limited periods of time from the beginning, and the dose kept as low as possible; complete discontinuation is always the goal. For all other medications, a therapeutic goal with an expected time frame needs to be defined at initiation. For most medications, 3–6 months is a realistic goal.

Recommendation	Strength	Agreement
Monitoring		
In patients without any immunological disorders or systemic symptoms, it is recommended that systemic treatment be continued for up to one year after the skin lesions have resolved.	↑↑	100 %
For all other patients, an individual decision on treatment continuation is recommended.	↑↑	100 %

Special considerations

Vaccination

Patients with connective tissue disease have more viral and bacterial infections; in fact, these are one of the main reasons for morbidity and mortality in SLE. This is due to primary immunological dysregulation, and also to the frequently required medical immunosuppression. There is only limited data on the frequency of infections in CLE patients. Glucocorticoids (especially in doses > 10 mg/day or in children 0.2 mg/kg BW prednisolone equivalent) as well as immunosuppressants result in varying increases of infection risk. Patients should preferably be vaccinated during phases of stable disease and before planned immunosuppressive therapy.

Inactivated vaccines are safe even with immunosuppressive treatment, while live vaccines should be avoided during immunosuppressive treatment or may even be contraindicated (such as the BCG vaccine) [166, 167]. Influenza and pneumococcal vaccines are recommended in patients with immunosuppression. The German STIKO (Ständige Impfkommission, Standing Committee on Vaccination) recommends the inactivated herpes zoster vaccine for individuals with immunosuppression from age 50 onwards (medical indication).

While a small number of case reports indicated an association of vaccination with induction or exacerbation of SLE, neither large prospective studies nor careful case control studies have confirmed such an association. Provocation of CLE after hepatitis B vaccination has been reported in individual case reports [168–170].

There have as yet been no vaccination studies in CLE, so while there is some reservation on adopting the recommendations for patients with connective tissue disease (including SLE), we may assume that they are clinically equivalent. The current recommendations of EULAR and STIKO from 2019 apply [166, 167, 171, 172].

Inactivated vaccines may be used without restrictions in children with CLE, but their efficacy may be limited in cases of relevant immunosuppression (more than 0.2 mg/kg BW prednisolone equivalent in childhood). In cases of accompanying systemic immunosuppressive treatment, vaccination efficacy needs to be documented. Live vaccines (MMR, varicella) should be boostered before initiating systemic immunosuppressive treatment if protection is insufficient [172].

Recommendation	Strength	Agreement
It is recommended to evaluate, vaccinate, and monitor patients before and during immunosuppressive/immunomodulating treatment according to the current STIKO and EULAR guidelines.	↑↑	100 %
Annual influenza vaccination is recommended.	↑↑	100 %

Link to the STIKO vaccination calendar [173]:https://www.rki.de/DE/Content/Kommissionen/STIKO/Recommendationen/Aktuelles/Impfkalender.pdf

Link to the German Federal Health Bulletin (Bundesgesundheitsblatt) "Vaccination in cases of immunodeficiency":https://doi.org/10.1007/s00103-019-02905-1

Link to the EULAR vaccine recommendations:https://www.eular.org/recommendations_management.cfm

Pregnancy

Female CLE patients of reproductive age need clear and comprehensive information on the topic of family planning once the diagnosis has been confirmed. The risk of flare-ups during pregnancy appears to be lower in CLE patients than in SLE patients [174, 175]. Pregnant CLE patients without internal organ involvement and with negative antibodies such as antiphospholipid antibodies (aPI), anti-Ro/SS-A and/or anti-La/SS-B antibodies, no increased risk of obstetric complications was observed in comparison with women without CLE [176].

Miscarriages or thromboses in the medical history, false-reactive syphilis serology (VDRL), as well as a prolonged partial thromboplastin time (PTT) in CLE patients may indicate aPI [177].

Neonatal lupus erythematosus (NLE) may be caused by placental antibody transmission in women with antibodies to SS-A(Ro), or SS-B(La) [176, 178] (Table 2). There are two basic forms: cutaneous neonatal LE, and cardiac neonatal LE with the main symptom of congenital heart block (CHB).

Retrospective studies show that the risk of cutaneous NLE can be reduced, and the recurrence risk for CHB cut in half, if the mother is treated with HCQ [179–181].

The EULAR recommendations on family planning in patients with SLE and/or antiphospholipid syndrome [182] advise that women who previously had a child with CHB should be monitored via serial fetal echocardiograms from the 16th week of pregnancy onwards. Since the risk of congenital heart block is low in women who have not had an affected pregnancy before, such close monitoring is, however, not generally recommended for all anti-Ro/SS-A or anti-La/SS-B-positive women.

The benefits and risks of CLE treatment need to be assessed very carefully in women who desire to get pregnant as well as in pregnant and lactating women. EULAR has published recommendations on antirheumatic treatment during pregnancy and lactation [183, 184]. The safety and efficacy of antimalarial drugs in women with SLE, including reduction of disease activity and prevention of exacerbations during

Table 2 Neonatal lupus erythematosus (NLE) (modified in accordance to [152]).

Clinical appearance and special features of neonatal lupus erythematosus (NLE)
– Placental transfer of maternal anti-Ro/SSA and/or anti-La/SSB antibodies to the fetus – Mother may (frequently!) be asymptomatic or have SCLE, SLE, Sjögren's syndrome, or undifferentiated connective tissue disease
Cutaneous neonatal lupus (reversible): – Incidence in children of SS-A-AK/SS-B-AK-positive women: 5–16 % – Erythematous macules, papules, and annular plaques as in SCLE, especially in areas exposed to light (face, capillitium) as well as on the trunk and limbs – May be present at birth or appear within the first few weeks of life – Post-inflamatory hyperpigmentation, teleangiectasia, or scarring may occur in rare cases – Usually resolves within six months in parallel to the disappearance of the antibodies – hematological and hepatobiliary alterations may occur (usually reversible)
Congenital heart block (CHB) (usually irreversible): – Incidence in children of SS-A-AK/SS-B-AK-positive women with no previous history of CHB: 1–2 %, risk of recurrence: 15–20 % [178] – Diagnosis usually between 20th and 24th week of pregnancy (irreversible in most cases) – Overall mortality around 20 % (out of these: about 25 % intrauterine deaths and about 50 % within the first three months of life); about 75 % of all children with complete CHB require a pacemaker. The cumulative 10-year survival probability is about 85 % [176].
Recommendation: Affected women must be informed about the risk and the positive effects of HCQ. Serial fetal echocardiography from the 16th week of pregnancy onwards is only recommended for anti-Ro/SSA- and/or anti-La/SSB-antibody-positive women with a previous CHB pregnancy [182].

Table 3 Laboratory tests before a pregnancy for women with cutaneous lupus erythematosus.

Advised examinations before pregnancy in women with CLE
Medical history – Asking about symptoms and signs of active SLE (fever, arthralgia, rash, mucosal eruptions, alopecia, pleuritic chest pain)
Laboratory investigations – ANA, ENA (especially anti-Ro/SS-A, anti-La/SS-B), anti-ds-DNA – Complement (C_3, C_4) – Antiphospholipid antibodies (anticardiolipin antibodies, anti-beta2-glycoprotein-I-IgG/IgM; lupus anticoagulant (if positive: repeat within 12 weeks) – Blood count – Liver enzymes – Creatinine in serum/creatinine clearance – Urinalysis, if appropriate also protein clearance (protein/creatinine ratio)

pregnancy, have been proven in controlled trials [185–187]. Long-term monitoring of children exposed to intrauterine antimalarials has not observed any toxic ophthalmological effects [188]. Quinacrine should be avoided during pregnancy due to a lack of data. Breastfeeding is possible in women treated with HCQ. Use of dapsone is understood to be compatible with pregnancy and lactation, although available data are limited [189]. Fetal risks include hemolytic anemia and neonatal hyperbilirubinemia. G6PD activity must be determined before treatment.

A systematic review did not find any connections between topical glucocorticoid treatment during pregnancy and fetal malformations or premature births [190]. Animal studies had described a potentially somewhat increased risk of cleft palates after administration of glucocorticoids in the first trimester of pregnancy, though current epidemiological studies have not confirmed this [191]. Non-fluorinated glucocorticoids (prednisone and prednisolone) display limited placental transition (< 15 %). Pregnant women at all stages of pregnancy may be treated safely, though regular doses of 5–7.5 mg/day should not be exceeded if at all possible because higher doses increase the risk of side effects on both the woman and the fetus [192]. Vitamin D supplementation for prevention of osteoporosis should be considered.

Non-controlled trials indicate an acceptable benefit-risk ratio for azathioprine and calcineurin inhibitors during pregnancy and lactation [183]. The available data are insufficient for assessing the risk of belimumab and rituximab during pregnancy and lactation. Mycophenolic acid, methotrexate, retinoids, thalidomide, and leflunomide are all teratogenic, so reliable contraception is indispensible in women of reproductive age [184]. These medications are also not recommended during lactation. There is no evidence of teratogenicity for topical retinoids, yet their use during pregnancy is still not recommended [193].

In men with CLE who desire a child, a possible influence of immunosuppressants on fertility should be considered and initiate measures as appropriate [194].

Recommendation	Strength	Agreement
A pregnancy test is not recommended as part of the basic examination.	↓	100 %
It is recommended that female CLE patients of reproductive age should be informed and counseled about possible difficulties with pregnancy, as a precautionary measure.	↑↑	100 %
If a CLE patient gets pregnant or plans to do so, it is recommended to evaluate her treatment and adapt it as appropriate. It is also recommended to investigate laboratory values according to Table 2 and work in collaboration with her gynecologist/obstetrician.	↑↑	100 %
It is recommended to consider the influence of immunosuppressive treatment in men with CLE who desire to have a child, and initiate measures as appropriate [194].	↑↑	100 %

Recommendation	Strength	Agreement
Serial fetal echocardiographies starting in the 16th week of pregnancy are recommended in women positive for anti-Ro/SSA and/or anti-La/SSBantibodies with a previous CHB pregnancy.	↑↑	100 %

Recommendation	Strength	Agreement
In cases of active disease during pregnancy or lactation, HCQ is recommended as a first-line treatment for CLE.	↑↑	100 %
It is recommended to continue established HCQ treatment during pregnancy.	↑↑	100 %
In cases of active disease or flare-ups in HCQ-refractory CLE patients, dapsone is suggested as an alternative treatment during pregnancy or lactation.	↑	100 %
It is recommended to use systemic glucocorticoids at the lowest effective dose and if possible not at regular doses above 7.5 mg/day during pregnancy.	↑↑	100 %
In women of reproductive age without reliable contraception, treatment with methotrexate, mycophenolate mofetil or mycophenolic acid, retinoids, thalidomide, or leflunomide is not recommended.	↓	100 %

Hormone replacement therapy

Systemic forms of LE are seen more frequently in women, so treatment with female sex hormones has been discussed as a possible provocation factor. However, it appears that the main reason for the female preponderance lies more in sex-specific genetic variations and less in the natural release of female hormones [195]. Data on cutaneous LE are very limited [174].

Oral contraception

Two randomized, controlled clinical studies have shown that oral contraception with a combination pill (estrogen plus progestin) as well as with a progestin-only pill (POP) does not increase the risk of flare-ups in women with inactive or stable SLE [196–198]. However, women with high SLE activity and women with aPI were excluded from these studies. In these women, as in women with risk factors for thrombosis (such as smoking, obesity, or hypertension) estrogens should be avoided. [198]. Progestins alone probably do not increase the risk of thrombosis – however there are no studies on high-risk patients. In women with aPI, even the use of progestins should be carefully considered [199].

Intrauterine contraceptive devices are a good option for women without specific gynecological contraindications or severe thrombocytopenia. In women with menorrhagia due to oral anticoagulation, levonorgestrel-releasing intrauterine devices can have a positive effect on the duration and severity of menstruation [200].

Menopause and hormone replacement therapy

A number of randomized, controlled studies have investigated the efficacy and safety of hormone replacement therapy

(estrogen plus progestin) [198, 201, 202]. A slightly increased risk of mild flare-ups of LE was reported during twelve months of hormone replacement therapy [203]. Severe flare-ups or cardiovascular side effects were not observed [204]. The frequency of thromboses was slightly increased [205]. However, HRT was effective in LE patients, especially as regards vasomotor menopausal complaints [206]. EULAR only recommends hormone replacement therapy for severe vasomotor complaints women with stable LE without any additional risk of thrombosis (especially without phospholipid antibodies) [182]. A therapeutic decision should be taken early so bone protection may be achieved [182, 207]. Since there are no data on the optimum duration of HRT in LE patients, the shortest possible duration should be chosen (about 1–2 years) [182, 198]. There are no controlled data on hormone replacement therapy in purely cutaneous forms of LE.

Recommendation	Strength	Agreement
There is a very limited amount of data on the influence of contraceptives on CLE.	Statement	
In accordance with the recommendations for SLE, a preference for non-hormonal contraceptives or progestin-only contraceptives is suggested.	↑	100 %
In accordance with the recommendations for SLE, oral contraception with a combination pill (estrogen plus progestin) may be considered in women with inactive or stable lupus erythematosus without phospholipid antibodies.	0	100 %
In accordance with the recommendations for SLE, early initiation of short-term hormone replacement therapy may be considered in women with vasomotor complaints and stable LE who have no additional risk factors for thrombosis and no phospholipid antibodies.	0	100 %

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

Please refer to the long version of this guideline at www.awmf.org.

Correspondence to

Prof. Dr. med. Margitta Worm
Allergologie und Immunologie
Klinik für Dermatologie, Venerologie und Allergologie
Charité-Universitätsmedizin Berlin

Charitéplatz 1
10117 Berlin

E-mail: margitta.worm@charite.de

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