European Dermatology Forum

S2k - European Dermatology Forum Guideline on Diagnosis and Monitoring in Cutaneous Lupus Erythematosus

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S2k Guideline on Diagnosis and Monitoring in Cutaneous Lupus Erythematosus (CLE) -

guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV)

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Abstract

Cutaneous lupus erythematosus (CLE) is a complex autoimmune disease with a broad spectrum of clinical manifestations. To our knowledge, no standardized, consensus-based diagnostic and monitoring procedures have been developed up to date. Therefore, the aim of the present guideline was to achieve a broad consensus on diagnostic and monitoring approaches for the diagnosis of CLE by a European subcommittee, guided by the European Dermatology Forum (EDF) and supported by the European Academy of Dermatology and Venereology (EADV). In total, 15 European participants were included in this project and agreed on all recommendations. The diagnosis of CLE requires a specific approach based on patient´s history, clinical and laboratory findings, as well as histological analyses of skin biopsy specimens. In selected cases, direct immunofluorescence and photoprovocation using a standardized protocol may be applied to confirm the diagnosis or to exclude differential diagnoses. If the clinical picture and the laboratory signs are not in concordance, additional organ-specific diagnostics should be performed to evaluate systemic organ involvement. Monitoring of patients with CLE depends on the activity of the skin lesions and the applied therapeutic agents. In therapy-resistant patients, compliance and adherence needs to be confirmed. Moreover, female patients in childbearing age need to be informed on the necessity of planning pregnancy together with a gynecologist and/or lupus specialist, particularly with regard to the adaption of therapeutic agents. Although the influence of comorbidities on mortality and morbidity in CLE has not yet been evaluated, the presence of comorbidities should be recorded regularly.

Introduction

Lupus erythematosus is a heterogeneous autoimmune disease that includes a broad-spectrum of clinical manifestations, ranging from those with primary cutaneous involvement (cutaneous lupus erythematosus, CLE) to others that involve one or more vital internal organs, as occurs in systemic lupus erythematosus (SLE). Skin manifestations appear in 73-85% of patients with SLE and may occur at any stage of the disease [1]. In patients with CLE, the manifestations are primarily confined to the skin and may progress to systemic disease in up to approximately 18% of patients within 3 years (depending on the disease entity) with a high risk for further disease progression [2]. General practitioners are often the first physicians to be consulted by the patients with regard to their skin manifestations. However, the patient should be consulted by a dermatologist to confirm the diagnosis by clinical and histological analysis. The treatment should also be started by an expert (dermatologist), while monitoring may be conducted by general dermatologists, depending on their experience with autoimmune diseases. Therefore, the present guideline aims to provide general practitioners and dermatologists with recommendations for the diagnosis and the monitoring of CLE. Details regarding the options to care and treat CLE patients were recently published in the "S2k Guideline for Treatment of Cutaneous Lupus Erythematosus" by the same group of authors [3].

Methods

Due to the lack of standardized diagnostic procedures, the aim of the present project was the development of European Guidelines for the diagnosis and monitoring of CLE, in cooperation with the European Academy of Dermatology and Venerology (EADV) and the European Dermatology Forum (EDF). Prof. Annegret Kuhn as chairperson of the EDF guideline subcommittee and a small group of experts from

the European Society of Cutaneous Lupus Erythematosus (EUSCLE) nominated the members of the guideline subcommittee in 2013 and decided to invite a maximum of one expert from each center and/or country. To achieve a broad consensus on the planned objectives, a total of 16 participants from all over Europe were included. All participants of the guideline subcommittee agreed to develop a consensus-based (S2k) guideline ("k" for the German word "Konsensus"), which is based on a structured expert consensus process. Each of the invited members conducted an internet research of relevant medical databases and a literature survey, and developed a chapter. The following members of the guideline subcommittee were present at the Consensus Conference held on November 15-16, 2015, in Frankfurt Germany, to develop the guideline on diagnosis and monitoring in CLE: Prof. Elisabeth Aberer, Prof. Zsuzsanna Bata-Csörgö, Prof. Marzia Caproni, Prof. Camille Frances, Prof. Annegret Kuhn, Prof. Branka Marinovic, Prof. Rodica Olteanu, Prof. Jacek Szepietowski, and Prof. Beatrix Volc-Platzer. Andreas Dreher, who has long-term experience in the development of guidelines in the "Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften" (AWMF) participated as methodological advisor. Aysche Landmann, who has long-term experience in the coordination of clinical projects and trials with CLE, was responsible for the coordination of the project, the organization of the Consensus Conferences, and the drafting, the copy-editing, and the formatting of the manuscript. At the Consensus Conference, all diagnostic and monitoring options were evaluated, and a recommendation was developed and consented upon. All recommendations in the present guideline are based on a consensus of 100% of the included authors, unless otherwise indicated. Within the discussion about recommendations, internal and external evidence were taken into account. The guideline subcommittee agreed on using the following wording for grading the strength of the statement:

"Recommended"→ strong (positive) recommendation

"Suggested" → moderate (positive) recommendation

"Not recommended" → strong (negative) recommendation

"Not suggested" → moderate (negative) recommendation.

It needs to be stated that negative recommendations (i.e., "not recommended" and "not suggested") are due to the current status of research and the available clinical data.

Clinical Evaluation

The broad spectrum of skin lesions in LE have been subdivided by Gilliam et al into LE-specific and LE-non-specific skin manifestations [4]. The LE-specific skin manifestations encompass the subtypes of CLE: (i) acute cutaneous lupus erythematosus (ACLE), (ii) subacute cutaneous lupus erythematosus (SCLE), (iii) chronic cutaneous lupus erythematosus (CCLE), which consists of discoid LE (DLE), LE panniculitis/profundus (LEP) and chilblain LE (CHLE), and (iv) intermittent cutaneous LE (ICLE), synonymously LE tumidus (LET) (**Table 1**) [5, 6]. The possibility of developing several LE-non-specific manifestations and/or more than one CLE subtype during the course of the disease is high. This has recently been confirmed in an analysis by the European Society for Cutaneous Lupus Erythematosus (EUSCLE), in which 347 of the 1002 patients presented with two or more CLE subtypes [7]. The LE-non-specific cutaneous manifestations are most commonly associated with SLE or other autoimmune diseases, and include vascular skin changes, such as periungual telangiectasia, livedo racemosa, Raynaud's phenomenon, and acral occlusive vasculopathy (**Table 2)** [8-10]. Several scores have been developed to evaluate the clinical and serological manifestations of SLE, such as the ECLAM, the BILAG, or the SELENA-SLEDAI [11-13]. These scores assess the broad spectrum of

systemic organ involvement, including the skin, but are not specific enough to evaluate the broad spectrum of the cutaneous manifestations in CLE or SLE. In 2005, the first validated score with specific evaluation of skin lesions was published and named Cutaneous Lupus Erythematosus Disease Area and Severity Index" (CLASI) [14]. In 2010, the CLASI was revised and modified by including additional aspects of the mucocutaneous spectrum of the disease. Reliability analysis supported the validity and applicability of the "revised CLASI" (RCLASI) [15]. Due to its detailed and comprehensive structure, the RCLASI may not only be applied to evaluate and monitor the efficacy of treatment, but also to support the diagnosis of the various CLE subtypes.

Acute cutaneous lupus erythematosus (ACLE)

Symmetric erythema on the face, sparing the nasolabial folds, known as "butterfly" or "malar" rash, is the most characteristic skin lesion of localized ACLE [8]. Generalized ACLE is less common and is characterized by widespread, symmetrically distributed skin lesions, which may mimic a drug eruption or - on rare occasions - can simulate toxic epidermal necrolysis (TEN-like ACLE) [16, 17]. Usually, ACLE does not lead to depigmentation and is a non-scarring subtype, but diffuse thinning of the hair ("lupus hair") can occur along the hairline. In general, ACLE often coincides with exacerbation of systemic organ involvement and prolonged disease activity.

Subacute cutaneous lupus erythematosus (SCLE)

Skin lesions of SCLE characteristically appear in a symmetric distribution on sun-exposed areas (head, upper body). Two forms of SCLE can be distinguished: i) the annular variant, which occurs as ring-shaped erythema with peripheral collarette scaling at the inner border, central clearing, and polycyclic confluence and ii) the

papulosquamous variant, which shows more distinct scaling, thicker plaques and resembles psoriasis or chronic eczema [18]. Both forms may be found in the same patient. SCLE lesions heal without scarring, but often with pigmentation changes (leukoderma) [19]. In genetically susceptible individuals, SCLE can be triggered by exposure to UV-radiation/sunlight, infection (viral/bacterial) and different drugs (for further information on drugs inducing CLE, please see **Table 1** in the "S2k Guideline for Treatment of Cutaneous Lupus Erythematosus" [3]). SCLE is associated with SLE in 10-15% of SCLE patients [18].

Chronic cutaneous lupus erythematosus (CCLE)

CCLE includes three different forms of disease: discoid LE (DLE), LE profundus/panniculitis (LEP), and chilblain LE (CHLE).

Discoid lupus erythematosus (DLE)

DLE is the most common form of CCLE. The lesions of this subtype are sharply bordered and present as disc-shaped erythematous plaques. The localized form of DLE occurs in 80% of patients and has a predilection for the face and the scalp, especially cheeks, forehead, ears, nose, and upper lip. The disseminated/generalized form of DLE, which involves the upper part of the trunk and the extensor surfaces of the extremities, is rare [17]. Lesions of DLE heal with central scarring and pitted acneiform "vermicular" scars can develop in perioral localization. At the scalp, eyebrows and bearded regions of the face, DLE can progress to total, irreversible scarring alopecia. Exposure to UV light or irritating stimuli may provoke or exacerbate lesions of this subtype (Koebner phenomenon, isomorphic reaction) [20, 21]. Approximately 5% of patients will develop systemic disease [8, 17, 22].

Lupus erythematosus profundus/panniculitis (LEP)

LEP is considered a rare variant of CCLE and presents with indurated nodules or plaques resulting in deep lipatrophy, and is often associated with discoid skin lesions, but may also be present in the context of SLE [6, 8, 23]. Solitary or multiple well-defined, persistent asymptomatic or sometimes painful indurated subcutaneous nodules and plaques, which may later firmly adhere to the overlying skin, are characteristic for this subtype. The surface of the lesions may appear without clinical changes or can show signs of DLE. In the course of the disease, the nodules develop into deep, asymptomatic lipoatrophy or deep retracted scars; ulceration is rare. Skin lesions of LEP are typically located in areas of increased fat deposition, such as the gluteal region, the thighs or the upper and lower extremities, but face, scalp, and chest can also be involved. LEP can be induced by irritative stimuli, but usually not by UV exposure [17]. This subtype is associated with DLE in 70% of patients, but it is rarely present in the context of SLE [8, 17].

Chilblain lupus erythematosus (CHLE)

CHLE is a further subset of CCLE, which may be induced by environmental factors, such as cold, damp weather or a critical drop in temperature, and often clinically and histologically difficult to distinguish from frostbites ("chilblains"). This subtype is characterized by symmetrically distributed, circumscribed itchy or painful bluish plaques and nodules, as well as elevated ANA, anti-Ro/SSA antibodies and a positive rheumatoid factor [17, 24]. Edematous plaques and nodules may develop with central erosions or ulcerations, usually affecting fingers, toes, heels, nose, ears, elbows, knees, and calves [25]. Association of CHLE with other CLE subtypes, such as DLE, has been described in the literature; in up to 20% of patients, CHLE is associated with SLE [26-28].

Lupus erythematosus tumidus (LET)

Lupus erythematosus tumidus (LET) has been defined as a distinct entity of CLE and is therefore included in the "Duesseldorf classification" as "intermittent cutaneous LE" (ICLE) [29]. This subtype is characterized by sharply-bordered, "succulent", urticaria-like, single or multiple erythematous papules and plaques with a smooth surface without epidermal involvement [30]. Histologically, LET may present with similar features as reticular erythematosus mucinosis (REM), such as mucin deposition, and perivascular and perifollicular lymphocytic infiltrate [31]. In the course of the disease, the lesions may be semilunar or annular with swelling in the periphery and flattening in the center [32]. In contrast to annular SCLE, the lesions of LET show no scaling and resolve without scarring or pigmentation changes. As LET is the most photosensitive subtype of CLE, lesions appear typically on sun-exposed areas [33, 34]. Association with SLE is extremely rare [35].

Recommendations:

Diagnosis:

- We recommend assessing the patient´s history (general symptoms like fever, fatigue, arthralgia, photosensitivity, drug intake, smoking, family history with focus on autoimmune diseases).
- We recommend to assess the activity and damage of LE-specific skin lesions, scalp lesions and mucosal lesions (oral, nasal, genital, conjunctival) according to the morphological criteria in the RCLASI and to evaluate bullous lesions (72,7%).
- We recommend the clinical evaluation of LE-non-specific lesions according to

Table 2.

Monitoring:

- We recommend to reevaluate the diagnosis at each visit and to define the diagnosis of new LE-specific and LE-non-specific lesions by clinical evaluation, which might be confirmed by histology.
- We recommend to see all patients with high disease activity (e.g., treatment resistance, flare) by a lupus specialist in dermatology independently of the following recommendations on an individual basis.
- Patients without treatment: We recommend to see these patients on demand by a dermatologist/by the patient or any physician.
- Patients with topical treatment: We recommend to follow up these patients depending on the type of treatment and compliance (at least every 3-6 months).
- Patients with systemic treatment:
    - Patients at the start of treatment (1-3 months):
        - Antimalarials: We recommend to follow up these patients at least every 3-6 months (81,8%).
        - Others: We recommend to follow up these patients according to the required laboratory tests, drug toxicity and side effects, and according to any specific recommendation for each drug.
    - Patients on continuous treatment:
        - Antimalarials: We recommend to follow up these patients at least every 6 to 12 months (81,8%).
- Others: We recommend to follow up these patients according to the required laboratory tests, drug toxicity and side effects, and according to any specific

recommendation for each drug.

ACR Criteria/SLICC Criteria

The criteria of the American College of Rheumatology (ACR), which were first published in 1982 and revised in 1997, provide some degree of uniformity to the patient population of clinical studies [36] and may be applied to distinguish SLE from other autoimmune diseases [36, 37]. Four of the 11 criteria have to be fulfilled for a diagnosis of SLE (**Table 3**). However, as 4 of the 11 ACR criteria include mucocutaneous items (malar rash, discoid lesions, photosensitivity, and oral ulcers), it is obvious that especially the definition and understanding of "photosensitivity" can easily be misinterpreted and that the application of the ACR criteria may result in an overestimation of SLE [20, 38]. It has been shown that approximately 50% of SCLE patients, 10% of DLE patients and nearly all patients with ACLE meet criteria for SLE [39].

The ACR criteria for the classification of SLE have been revised by the Systemic Lupus Erythematosus Collaborating Clinics (SLICC) in 2012, an international group dedicated to SLE research [40] **(Table 4).** The SLICC criteria include 11 clinical (such as non-scarring alopecia or synovitis) and six immunological criteria (such as decreased complement and antiphospholipid antibodies), whereas "photosensitivity" is no longer listed. For a classification of SLE, >4 criteria (at least one clinical and one immunologic criterion) need to be fulfilled. In a retrospective study of 107 patients with SCLE patients, the comparison of the ACR and the SLICC criteria revealed that none sets of criteria distinguished patients with SCLE and major internal disease from patients with SCLE without major internal disease [41]. However, the applicability of the SLICC criteria in daily clinical practice still needs to be confirmed. The ACR and

the SLICC criteria are classification criteria and can be used to distinguish SLE from other autoimmune diseases.

Recommendations

Diagnosis:

- We recommend applying the ACR and/or the SLICC criteria to distinguish SLE from other autoimmune diseases

Monitoring:

- Patients with no/low skin disease activity: We do not suggest to apply the ACR and/or SLICC criteria for classification of SLE.
- Patients with high skin disease activity: We recommend to apply the ACR and/or the SLICC criteria in case of clinical or laboratory changes.

Histology and Direct immunofluorescence

Histology should be performed at the first visit from typical and atypical lesions. Exception is a malar rash, which is usually a sign or even one of the first signs of SLE and has only to be biopsied in unclear clinical conditions, as well as mucosal lesions that do not match with typical lesions. The diagnosis of all other subtypes requires histology. The different subtypes of CLE often show similar histological features with "interface-dermatitis", a lymphocytic infiltrate at the dermo-epidermal junction, a superficial and deep perivascular and periadnexial lymphocytic infiltrate [5, 8, 42]. A vacuolar degeneration of the dermo-epidermal junction with necrotic keratinocytes and thickening of basement zone (BMZ) is a characteristic finding of CLE lesions [42, 43]. Details of histological features of the CLE subtypes are given in **Table 5.** Since the first descriptions of immune deposits at the dermo-epidermal junction (DEJ) of

cutaneous lesions of LE in 1963 [44] and 1964 [45] direct immunofluorescence (DIF) using fluorescent anti-IgG, -IgM, -IgA, -C3 antibodies and anti-fibrinogen on frozen skin sections has become a well established diagnostic tool for CLE. IgG and IgM granular deposits have been described as predominant [46, 47]. Controversy exists with regard to the predominance of IgG and IgM and its possible significance. Moreover, several authors use the term „lupus-band-test" (LBT) not only for immunoglobulin and complement deposits in sun-protected non-lesional skin in SLE, but also in lesional skin in CLE. Therefore, the DIF can be useful in the differential diagnosis of CLE and other photosensitive skin diseases, when performed on the lesional skin. Instead on the non lesional, non-UV-exposed skin, the DIF is a further element, along with immunoserologic findings, to assess possible systemic involvement if the diagnosis could not be confirmed by histology.

Recommendations:

Diagnosis:

- To confirm the clinical diagnosis, we recommend taking a lesional biopsy (exception: malar rash and mucosal lesions).
- We recommend that the biopsy is read by an experienced dermatopathologist.
- We suggest special stainings, such as for mucin (as typical sign of CLE, in particular LET) (63,6%).
- We suggest direct immunofluorescence from older lesions in non-UV-exposed skin of patients in which diagnosis of CLE needs to be confirmed (consensus: 92%).
- We do not suggest direct immunofluorescence from UV-exposed non-lesional skin.

Photoprovocation

Photoprovocation according to a standardized protocol is an established tool to confirm the diagnosis of CLE [48]. In contrast to other UV-induced skin diseases, such as polymorphous light eruption (PLE), UV-induced lesions of CLE are characterized by a latency period of 8.0 ± 4.6 days (range: 1 day to 3 weeks), and persist for a longer period compared to PLE lesions [49]. The results of a retrospective analysis, which investigated the frequency and reproducibility of standardised photoprovocation in 431 patients with different subtypes of CLE [50] demonstrate that 61.7% of the patients exhibited a positive photoprovocation after UVA and/or UVB irradiation. Moreover, the analysis suggests that the response to UV light may alter during the course of the disease and that photosensitivity should not be defined solely on the basis of the patients' history.

Recommendations:

Diagnosis:

We suggest standardized photoprovocation in selected cases (e.g., exclusion of CLE, differentiation between CLE and PLE) in centers experienced in photoprovocation.

Monitoring:

We suggest to perform standardized photoprovocation on an individual basis in highly photosensitive and/or anxious patients to prove sunscreen protection and/or the efficacy of treatment in centers experienced in photoprovocation.

Laboratory Diagnostics

Especially in ACLE, which is most frequently associated with SLE, and in SCLE with its frequent association of arthritis and other mild systemic organ manifestations, laboratory diagnostics need to be performed to exclude or confirm systemic organ involvement. Blood analysis is necessary not only for the diagnosis but also for the monitoring of the patient to evaluate the progression of the disease and to assess any side effects of applied drugs. No data are available in the literature to suggest an optimal frequency of laboratory assessment in patients with CLE. The frequency depends on skin disease activity, drugs, comorbidities, and systemic involvement.

Blood count, differential blood count

Although hematological changes (anemia, leucocytopenia, lymphopenia, thrombocytopenia) are included in the ACR/SLICC criteria for SLE, these changes might also be observed in patients with CLE (anemia: 2% to 27%; leucocytopenia: 0%-30%; thrombocytopenia: 2% to 4% of patients) [51].

Erythrocyte sedimentation rate (ESR)

The erythrocyte sedimentation rate (ESR) is typically increased in patients with SLE, but can also be found elevated in 20% to 50% of patients with CLE [51]. Significantly elevated levels (more than 50mg/l) of C-reactive protein (CRP) is a marker for infection, but may also be elevated in serositis, arthritis, and sometimes in renal involvement in SLE [51, 52].

Creatinine

An elevated serum creatinine must be followed by creatinine clearance in 24-hours urine and glomerular filtration rate.

Urinary status, sediment and proteinuria

A complete microscopic urinalysis should be performed to provide information about renal involvement [53]. Urine protein/creatinine ratio can be used as a screening test for proteinuria. If abnormal results appear the findings may be confirmed by 24-hour urine collection sample [54, 55].

Liver Function

It is important to screen for hepatic involvement before starting any treatments. Liver function tests include transaminases (aspartate-aminotransaminase, ASAT, and alanine-aminotransaminase, ALAT) and gamma-GT. LDH and CK should also be determined as they can be elevated in a myositis associated with LE [56].

Electrophoresis

Electrophoresis can detect any abnormalities in serum proteins. A reduction in serum albumin may indicate renal involvement, while 2-4% of patients with SLE may present with a monoclonal gammopathy [57]. An immuno-electrophoresesis can be applied once to exclude other diseases that may clinically mimic CLE (IgA deficiency, hyper IgE syndrome). Levels of IgE may in some cases roughly correlate with disease activity [57].

Antinuclear antibodies (ANA) (HEp-2 cell test with fluorescence pattern)

Antinuclear antibodies (ANA) are used as a screening test (titer and fluorescence pattern) for connective tissue diseases and should be performed even in CLE patients. Usually, the ANA titer in CLE patients are low (≤ 1:320), varying in frequency and depending on the particular subtype (**Table 6**) [5, 39]. Anti-Ro/SS-A and – in less

cases – anti-La/SSB antibodies are characteristic for SCLE. Anti-histone antibodies are usually found in drug-induced LE, but they may also occur in conjunction with anti-dsDNA antibodies in idiopathic SLE (24–95%) [56]. Autoantibodies against ds-DNA and Sm are in the majority of cases associated with SLE and are not characteristic for the CLE subtypes [39, 56].

Antiphospholipid antibodies, lupus anticoagulant

Antiphospholipid antibodies (cardiolipin, beta-2-glycoprotein, lupus anticoagulant) are included in the ACR/SLICC criteria for the diagnosis of SLE and are considered as serologic marker for the antiphospholipid syndrome [41]. The presence of anti-phospholipid antibodies in patients with the various clinical subtypes of CLE has been investigated by few studies with variable prevalence ranging from 5.8% to 68% [51, 56]. Generally, the incidence of antiphospholipid antibodies is low in patients with CLE and more likely associated with systemic organ involvement [58-60]. Testing is especially indicated when partial thromboplastin time (PTT) is prolonged and syphilis serology (VDRL) is non-specifically reactive [51, 56, 58-63].

Complement C3, C4

The measuring of C3, C4, or total haemolytic complement activity (CH50) is included as ACR/SLICC criteria for SLE (34). Low C3 and/or C4 levels are common in patients with SLE, while they are usually normal in CLE [56]. A genetically determined deficiency of C3 and C4 can be associated with SLE, but also with CLE. Due to inflammation, complement factors may even be elevated in CLE [56]. CH50, C1q and anti-C1q antibodies should be measured only in cases of CLE with high suspicion of systemic disease or with associated hypocomplementemic urticarial vasculitis [56].

Thyroid-stimulating hormone (TSH)

Data regarding the association of autoimmune thyroid disease with CLE are not available. Several studies have shown a higher prevalence of thyroid diseases in patients with SLE than in the general population, and hypothyroidism is much more common compared to hyperthyroidism. Similarly, several studies have shown a higher prevalence of positive anti-thyroglobulin (ATG) and anti-thyroid peroxidase (TPO) antibodies in patients with lupus than in the general population, even in those who do not have clinical thyroid disease [56, 64, 65].

Recommendations for Diagnosis:

Diagnosis*:

As part of a core set of laboratory tests prior to treatment,

- We recommend to evaluate peripheral blood count and differential blood count (e.g., anemia, leucocytopenia, thrombocytopenia, lymphopenia).
- We recommend to evaluate ESR and/or CRP (54,5%).
- We recommend to evaluate serum creatinine for kidney involvement.
- We recommend evaluating urinary status, sediment and urine protein/creatinine ratio or 24h proteinuria.
- We recommend to perform ASAT, ALAT and gamma-t.
- We recommend to evaluate electrophoresis (9%).
- We recommend to evaluate ANA and ENA screen and anti-dsDNA antibodies, which should be performed in a certified laboratory.
- We recommend the large coagulation panel including lupus anticoagulant, antiphospholipid antibodies and anti-beta2.

- We recommend to evaluate C3 and C4.
- We recommend to perform functional tests (e.g., TSH).
- We suggest to evaluate TSH anti-thyroid antibodies and further laboratory investigations depending on clinical symptoms and planned treatment.

Monitoring:

1. Patients with no/low skin disease activity:
    a. We do not recommend any laboratory tests if there are no signs of systemic manifestation.
    b. We recommend to do laboratory tests according to the recommendation of each drug.
2. Patients with high skin disease activity:
    a. We suggest to perform urine analysis (urine cast, urine protein /creatinine ratio or 24h proteinuria) (81,8%).
    b. We recommend to perform complete blood cell count, erythrocyte sedimentation rate, albumin, serum creatinine or e-GFR, C3 and C4.
    c. We suggest to repeat ANA testing and ENA screen according to clinical signs and progress of the disease (63,6%).
    d. In addition, we recommend to do laboratory tests according to the recommendation of each drug.

*Not all tests may be necessary for all patients. Medical history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, and risks exposure (81,8%).

Vitamin D

Vitamin D mediates immunomodulatory functions, and its deficiency has been associated with an increased prevalence of immunological diseases including CLE [66]. CLE patients tend to have inadequate vitamin D levels since most of them are

photosensitive and have to avoid sunlight with a higher risk of osteoporosis [67]. Treating vitamin D insufficiency may be associated with improved disease severity [68, 69]. According to current recommendations, serum 25(OH)D levels of 20-30 ng/ml and <20 ng/ml were defined as vitamin D insufficiency and deficiency, respectively [66]. The desirable level of 25(OH)D should be more than 50 ng/ml [70]. In the literature, it daily intake of 1,200 to 2,000 IU of vitamin D (equivalent to 30- 50 micrograms) is recommended [66, 70, 71]. Moreover, it is proposed a regular exercise to stimulate bone to build strength. (http://www.lupusinternational.com).

Recommendations:

Diagnosis:

We do not suggest to evaluate Vitamin D levels before substitution, but we suggest to substitute **Vitamin D** in all CLE patients (please see the "**S2k Guideline for Treatment of Cutaneous Lupus Erythematosus**" [3]) (81,8%).

Monitoring:

We do not suggest to monitor Vitamin D level.

Organ-specific diagnostics and Interdisciplinary investigations

If the clinical picture and the laboratory signs are not in concordance, additional diagnostic procedures should be performed. Special emphasis should be given to the musculoskeletal, hematologic, renal, cardiopulmonary, and neurologic system [72, 73].

According to available studies, about 10-15% of patients with CLE develop systemic disease within 8 years [72]. If any abnormality in laboratory findings is observed, additional organ-specific diagnostics, such as X-ray and abdomen sonography (ultrasound), should be performed [72, 73].

Recommendations:

Diagnosis:

- Based on clinical or laboratory signs, we recommend to perform organ-specific diagnostics and/or to refer to lupus specialists for further diagnostic procedures and treatment.
- We suggest interdisciplinary investigations in cases of suspected SLE.

Monitoring:

Based on clinical or laboratory signs, we recommend to consider organ-specific diagnostics and to refer to lupus specialists for further diagnostic procedures and treatment.

Compliance

Patient compliance and adherence is an important issue in LE. Poor adherence to therapeutic regimens is associated with a higher risk of flares, morbidity, hospitalizations and poor renal outcome in SLE [74]. The rate of non-adherence can be 3%-76% [75]. Non-adherence is multifactorial, and may be unintentional or intentional. Indeed, all the following factors have been associated with poor adherence in various studies: problems with cognitive functioning, fears of drugs' side-effects, younger age [76], lower educational level, low socio-educational status, ethnicity,

rural residency, travel burden, higher depressive symptoms [77], limited confidence for caregivers, other financial priorities, pain and physical limitations [78], absence of a stable marital status, and three or more medications daily [79]. In a MEDLINE review, articles about adherence to oral or topical medications in CLE and SLE were analysed [75]. In 17 articles, treatment adherence was investigated in patients with SLE. Depression was consistently cited as detrimental to adherence [75]. In 3 studies, a clear connection between adherence and diseases activity could be noted [74, 75].

The accurate diagnosis of non-adherence may prevent from the incorrect interpretation of disease activity and thus can avoid unnecessary treatment escalation [74]. Measuring drugs´ blood levels helps the diagnosis of non-adherence; it is available for hydroxychloroquine in some countries; however, only very low blood levels suggest the non-adherence, while intermediate levels may be secondary to a poor absorption or to a high drug catabolism [80]. As smoking has been suggested to decrease the effect of antimalarials, patients should be advised to cease smoking completely [81].

Recommendations:

Monitoring:

- In therapy-resistant patients, we suggest to consider compliance.
- We recommend to educate patients on smoking cessation, to encourage the application of sunscreens and the avoidance of excessive sun exposure at each visit.

Pregnancy

Family planning is an important issue in all women with CLE in childbearing age and needs to be discussed as soon as the diagnosis has been confirmed. In the absence of systemic organ involvement, antiphospholipid antibodies, anti-Ro/SS-A and/or anti-

La/SS-B antibodies in women with CLE, there is no increased risk for children compared to those born by women without CLE. For patients with systemic organ involvement, please see the EULAR recommendations for women's health and the management of family planning [82]. In the presence of anti-Ro/SS-A, anti-La/SS-B or U1-RNP antibodies, the risk is high that the child will develop neonatal lupus erythematosus (NLE, please see chapter below).

In all pregnant women with CLE, a closer monitoring is important during the third trimester of pregnancy with detection by sonography of growth restriction and placental insufficiency. Doppler sonography of the umbilical arteries and uterine arteries is particularly performed at 20-28 weeks of gestation. This last examination has higher negative than positive predictive value for the diagnosis of pregnancy complications [83-85].

Recommendations:

Monitoring:

- We do not suggest pregnancy tests as part of the basic investigation panel.
- In women with CLE in childbearing age, we recommend to inform the patient on the necessity of planning pregnancy as soon as the diagnosis has been confirmed.
- In case of (planned) pregnancy in patients with CLE, we recommend to adapt treatment (please see the "**S2k Guideline for Treatment of Cutaneous Lupus Erythematosus**" [3]), to control laboratory investigations (**Table 7**) on a regular basis and to collaborate closely with a gynecologist.
- In women with systemic organ involvement, we recommend also to consult the "EULAR recommendations for women's health and the management of family

planning, assisted reproduction, pregnancy and menopause in patients with SLE and/or antiphospholipid syndrome"[82].

Neonatal lupus erythematosus (NLE)

The diagnosis of NLE may be suspected when a skin rash appears during the first weeks of life of a newborn from a mother with anti-Ro/SS-A, anti-La/SS-B antibodies or less frequently U1-RNP antibodies [86]. The mother may be a healthy carrier of antibodies or suffer from various autoimmune diseases, such as LE or Sjögren's syndrome [86].

The diagnosis of NLE is based on clinical examination of the newborn. Cutaneous lesions consist of transient non-scarring erythematosus annular plaques with a predilection for head and neck (photoexposed areas) [87]. However, skin lesions of NLE may appear anywhere on the body, but resolves within 4 to 6 months [87]. Telangiectasias or dyspigmentation, which occur secondly, are usually transient. Hematological abnormalities may be present, such as hemolytic anemia, neutropenia or thrombocytopenia. A skin biopsy is rarely needed to confirm the diagnosis. Two prospective studies of pregnancies involving mothers with maternal anti-SSA/Ro and/or anti-SSB/la autoantibodies provide the rates of cutaneous neonatal lupus between 7-16%, both higher than the 2% associated with cardiac neonatal lupus [88, 89]). Fetal echocardiography is the best examination to detect fetal cardiac abnormalities; its offers an accurate assessment of the fetal heart rate, rhythm and ventricular function. According to Brito-Zeron et al. [83], serial echocardiograms and obstetric sonograms are helpful and may be performed weekly from 16 weeks of gestation onwards, although the frequency might be reduced in the absence of a congenital heart block (CHB) after week 26 (<20% diagnosed after week 30). This

monitoring is justified in mothers with a previously affected child [82]; the generalization of this monitoring to all mothers with anti-Ro/SSA or anti-La/SSB antibodies is still discussed due to the absence of evaluation of its cost-effectiveness [82].

Recommendations:

Diagnosis:

- We recommend an interdisciplinary diagnostic and follow-up of children with NLE, in particular for cardiodiagnostic procedures.

Differential Diagnosis

Depending on the CLE subtype, several differential diagnoses, in particular PLE, may be considered and need to be evaluated by dermatologists (**Table 8**).

Recommendation:

Diagnosis:

We recommend excluding the differential diagnoses listed in **Table 8.**

Drug-induced CLE

Several agents (please see **Table 2** in the separately published "**S2k Guideline for Treatment of Cutaneous Lupus Erythematosus**" [3]) were reported to induce a lupus-like syndrome [90]. In contrast to drug-induced LE (DILE/DIL), drug-induced CLE (DI-CLE) may show all typical signs of the various disease subtypes [91, 92]. The clinical picture is accompanied by characteristic serological findings, such as anti-

histone and anti-Ro/SSA antibodies [91]. In drug-induced SCLE, the most common form of DI-CLE, skin lesions can be more widespread with extension to the lower extremities compared to idiopathic SCLE [7, 93]. The time between treatment initiation and the onset of DI-CLE lesions was reported to range from 4 to 20 weeks in DI-SCLE and up to 8 months in DI-DLE [91]. The skin manifestations of DI-CLE typically resolve after the discontinuation of the drug, and the titers of anti-histone antibodies decrease, while anti-Ro/SSA antibodies may persist [91].

Recommendations:

Diagnosis:

- We recommend asking for drug intake (see **Table 2** in the **"S2 Guideline on Treatment in CLE"**).
- In suspected drug-induced CLE, we recommend investigation for anti-histone and anti-Ro/SSA-antibodies.

Monitoring:

In case of new flares or treatment resistance, we recommend to consider drug-induced CLE.

Activity/Damage Score

While ACR [37] and SLICC [40] criteria have been developed and are used for the classification of SLE, there are two validated scoring systems for measuring the activity of CLE, the CLASI [14, 94] and the RCLASI [15]. There is currently more wide-spread experience of the CLASI as a tool, which is used by both rheumatologists and dermatologists and which has been validated for the use by rheumatologists,

against physician and patient reported outcomes, and in clinical trials [95]. The RCLASI, however, includes the morphological aspects of all CLE subtypes and provides a more detailed analysis of variables, i.e. edema/infiltration and subcutaneous nodules/plaques, and the improved evaluation of mucous membranes and alopecia [96] and is therefore more suitable for a dermatologist specialty setting with the aim of a detailed subtype analysis, also in clinical trials. The application of the RCLASI, however, needs to be further assessed in clinical practice. Nevertheless, it appears mandatory to implement these scores more widely and to achieve clear recommendations for the application of the RCLASI by rheumatologists as well.

Recommendations:

Diagnosis:

- We recommend the RCLASI for the evaluation of all CLE subtypes.
- We do not suggest the Visual Analogue Scale (VAS) for evaluation of the patient and patient´s self-evaluation for routine diagnosis, as long as it is not a validated tool for CLE patients.
- We do not suggest the physician global activity (PGA) score until a final adapted and validated version for CLE has been developed.

Monitoring:

- We recommend to apply the RCLASI.
- If a patient is diagnosed with SLE via ACR- or SLICC criteria, we recommend to assess and to record disease activity using a validated index at each visit.
- If a patient is diagnosed with SLE, we recommend to assess and to record disease damage using the SLICC/ACR damage index annually.

Quality of Life

CLE produces considerable morbidity resulting from its cutaneous lesions (i.e., disfiguring, painful scarring skin lesions, mucous membrane lesions, alopecia) and therefore has a strong negative impact on the quality of life. There is no disease-specific instrument for the assessment of the quality of life in CLE patients [97, 98]. However, there are general dermatologic indices, such as the DLQI or the skindex 29. Quality of life does not improve in parallel with decrease of disease activity. During monitoring, emphasis should be given if cosmetic outcomes can affect quality of life. If lesions are disseminated and scarring is present on the skin and on the scalp, quality of life can be very poor [98, 99].

Recommendations:

Diagnosis and Monitoring:

- We suggest to apply the DLQI or the skindex 29 (dermatology-specific instruments)
- In patients with systemic organ involvement, we suggest to apply other questionnaires, such as the SF 12 (72,7%).

Comorbidities

Mortality and morbidity in adult patients with SLE are significantly influenced by comorbidities related to both the disease itself and/or its treatment, including hypertension, hyperlipidemia, obesity, and atherosclerosis (which may be triggered by smoking) as well as osteoporosis and malignancy [100]. In addition, patients with SLE

have an increased prevalence of fibromyalgia and fatigue, which interferes with the quality of life [100, 101]. In CLE, possible comorbidities have not yet been investigated, but as many of these patients also fulfill criteria for SLE, the clinician might keep up-to date with recommendations for SLE patients [100]. It remains to be investigated whether the increased morbidity and mortality by other comorbidities than cancer in SLE also apply to patients with CLE.

An increased risk of malignancies has been observed for patients with SLE [101] and recently, patients with CLE were described to have a significantly increased risk for buccal cancer (HR 5.4), lymphomas (HR 4.4), respiratory cancer (HR 3.8), and non-melanoma skin cancer (NMSC) (HR 3.6), independently of a concomitant diagnosis of SLE [2].

Recommendations:

Diagnosis:

- We recommend assessing cardiovascular risk (incl. hypertension, diabetes and dyslipidemia) and osteoporosis.
- We suggest encouraging patients to follow routine screening for cancer as advised for the general population.

Monitoring:

We recommend recording the presence of comorbidities at least once per year.

Infection Risks / Vaccination

Bacterial and, less frequently, viral and fungal infections are another main cause of morbidity and mortality in SLE [53, 102-104]. However, little is known for patients

with CLE. Prednisone doses of >7.5 mg/day, immunosuppressants, B cell depleting therapy, and anti-TNF-alpha inhibitors variably increase the infection risk [53, 102-104]. Therefore, for CLE patients who need to be initiated on or are on immunosuppressants, the initial work up needs to exclude ongoing infections as well as to document the vaccination state or to recommend specific vaccinations [53, 102-104]. Vaccines are usually administered prior to the planned immunosuppression. Inactivated vaccines have been found to be safe, while life attenuated vaccines should be avoided in the immunosuppressed patient [53, 102-104].

Recommendations:

Diagnosis:

- We recommend to check for infection, if immunosuppression (including high-dose corticosteroids, equal to or more than 2mg/kg body weight) needs to be initiated (81,8%).
- We suggest that patients who are planned to be treated with immunosuppressants are vaccinated against seasonal influenza and pneumococcus according to local recommendations.

Monitoring:

We suggest to follow the SLE recommendations developed by Mosca et al [105] on screening for the presence of chronic infections and the documentation of vaccination.

Time Point to stop Treatment

A general consensus time point to stop treatment in a patient with CLE has not yet been determined and needs evidence-base studies. Due to the well-known side-effects (e.g., atrophy, telangiectasia, steroid-induced rosacea-like dermatitis), topical steroids

should be applied time-limited (2-4 weeks) and preferably intermittent. Systemic steroids should only be applied intermittently, in the lowest possible dosage with the aim to discontinue the application as soon as possible. After 3-6 months of treatment with other systemic agents it should be discussed to either continue or to change medication, depending on the efficacy of the treatment and possible side effects (please see Figure 1 in the "S2k Guideline for Treatment of Cutaneous Lupus Erythematosus") [3].

Recommendations:

Monitoring:

- We suggest to continue treatment in patients without any immunologic abnormalities and without any systemic organ manifestations for **up to** one year after the clearance of skin symptoms.
- In all other patients, we recommend to decide the stop of treatment on an individual basis.

Drug Toxicity/Ophthalmologic Evaluations

In general, antimalarials are well tolerated and rarely need to be discontinued because of an adverse reaction [106]. Two groups of side-effects may be encountered: The first group include gastrointestinal or neurological intolerance, pruritus and other cutaneous manifestations, which usually resolve with dose reduction and rarely require treatment withdrawal [106]. The second group is more severe, and includes retinal, and exceptionally, neuromuscular and cardiac impairment [106].

The manifestation of retinal toxicity is a ring of depigmentation near the foveal center termed "bull's eye retinopathy" [107]. This lesion produces a corresponding ring

scotoma. Nowadays, it is essential to detect retinopathy at an early preclinical stage. The most common screening test is the automated visual field, covering the central macula (called a 10-2 field because, it spans 10° on either side of the fovea) [108]. However, this test is subjective, and not always reproducible in the same patient. The spectral density optical coherence tomography can show early parafoveal thinning of the retina as well as early break-up of marker lines that define the outer segments of the photoreceptors [108]. Fundus autofluorescence is a photographic technique that identifies cellular breakdown products in the retinal pigment epithelium [109]. Multifocal electroretinogram can objectively document localized paracentral electroretinogram depression in early CQ and HCQ retinopathy [110].

Cardiotoxicity includes both heart conduction disturbances and congestive heart failure [111]. These cardiac toxic effects have been reported with CQ and less frequently with HCQ use alone [111]. Further issues, which need to be considered with regard to the application of antimalarials, are included in the "S2k Guideline for Treatment of Cutaneous Lupus Erythematosus" [3].

Recommendations:

Monitoring:

- Antimalarial treatment: According to the recommendations issued by the American Academy of Ophthalmology, ophthalmological consultation is recommended in CLE patients treated with HCQ or CQ at baseline annually after 5 years and earlier in the presence of risk factors [112] (63,6%).
- We recommend to consider the evaluation of toxicity based on the respective drug recommendation.

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Tables

Table 1. Subtypes of Cutaneous Lupus Erythematosus (CLE)*

Acute cutaneous lupus erythematosus (ACLE)
Localized form
Generalized form
Subacute cutaneous lupus erythematosus (SCLE)
Annular form
Papulosquamous form
Chronic cutaneous lupus erythematosus (CCLE)
Discoid lupus erythematosus (DLE)
Localized form
Disseminated form
Lupus erythematosus profundus (LEP; LE panniculitis)
Chilblain lupus erythematosus (CHLE)
Intermittent cutaneous lupus erythematosus (ICLE)
Lupus erythematosus tumidus (LET)

*Modified after [29]

Table 2: Non-lupus erythematosus (LE)-specific skin manifestations*

1. Cutaneous vascular disease

   Vasculitis:

   a) Leukocytoclastic (Urticarial vasculitis)
   b) Vasculitis of medium vessels
   a) Degos disease-like
   b) Atrophy blanche-like
   c) Periungual telangiectasia
   d) Livedo reticularis
   e) Thrombophlebitis
   f) Raynaud's phenomenon
   g) Erythromelalgia (erythemalgia)

2. Alopecia (non-scarring)
   a) 'Lupus hair'
   b) Telogen effluvium
   c) Alopecia areata
3. Sclerodactly
4. Rheumatoid nodules
5. Calcinosis cutis
6. LE-non-specific bullous
   a) Epidermolysis bullosa acquisita-like bullous LE
   b) Dermatitis herpetiformis-like bullous LE
   c) Pemphigus erythematosus Senear–Usher
   d) Bullous pemphigoid
   e) Porphyria cutanea tarda
7. Urticaria
8. Papulo-nodular mucinosis
9. Anetoderma/cutis laxa/mid-dermal elastolysis
10. Acanthosis nigricans (type B insulin resistance)
11. Erythema multiforme (Rowell's syndrome)
12. Lichen planus

*Modified after [113].

Table 3. Criteria of the American College of Rheumatology (ACR) for Classification of Systemic Lupus Erythematosus*

1. Malar rash
2. Discoid rash Erythematous
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
7. Renal disorder
8. Neurologic disorder
9. Hematologic disorder
10. Immunologic
11. Antinuclear antibody

*Modified after [36]

Table 4. The Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria*

Clinical Criteria
1. Acute cutaneous lupus erythematosus (including "butterfly rash")
2. Chronic cutaneous lupus erythematosus (e.g., localized or generalized discoid lupus erythematosus)
3. Oral ulcers (on palate and/or nose)
4. Non-scarring alopecia
5. Synovitis (≥ 2 joints) or tenderness on palpation (≥ 2 joints) and morning stiffness (≥ 30 min)
6. Serositis (pleurisy or pericardial pain for more than 1 day)
7. Renal involvement (single urine: protein/creatinine ratio or 24-hour urine protein, >0.5 g)
8. Neurological involvement (e.g., seizures, psychosis, myelitis)
9. Hemolytic anemia
10. Leukopenia (<4000/μL) or lymphopenia (<1000/μL)
11. Thrombocytopenia (<100 000/μL)
Immunologic Criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibodies
3. Anti-Sm antibodies
4. Antiphospholipid antibodies (anticardiolipin and a nti-β2-glycoprotein I [IgA-, IgG- or IgM-] antibodies; false-positive VDRL [Venereal Disease Research Laboratory] test)
5. Low complement (C3, C4, or CH50)
6. Direct Coombs test (in the absence of hemolytic anemia)

*Modified (short form) after [40].

Table 5. Prominent histological and immunohistological features of skin lesions in cutaneous lupus erythematosus (CLE)[*]

Subtypes	Histology/ Immunohistology
CLE	• Interface dermatitis • Hydropic degeneration of the basal epidermis • Lymphoid infiltration (most frequently plasmacytoid dendritic cells and T-cells) • Dermal mucin depositions • Strong expression of interferon-regulated chemokines (MxA, CXCL10)
ACLE	• Discrete infiltrate with modest interface dermatitis • Single neutrophils in infiltrate and nuclear debris
SCLE	• Cell-poor interface dermatitis with cutaneous-perivascular infiltrates • Moderate mucin deposits
CCLE	
DLE	• Follicular hyperkeratosis • Dense, patchy, perivascular and periadnexal lymphoid infiltrate • Cell-rich interface dermatitis • Marked mucin deposits • Thickened basement membrane zone
LEP	• Dense lymphoid lobular panniculitis • Subcutaneous mucin deposits • Necrosis and macrophages • In some cases interface dermatitis
CHLE	• Dense perivascular lymphocytic infiltrate • Interface dermatitis
ICLE	
LET	• Dense perivascular and periadnexal lymphoid infiltrate with pDC-clusters (CD123+) • Interface dermatitis missing or only discrete • Interstitial mucin

[*]Modified after [42].

Table 6. Autoantibodies in the subtypes of cutaneous lupus erythematosus (CLE)[*]

CLE Subtype	ACLE	SCLE	DLE	LET
ANA	+++	++	+	(+)
anti-ds-DNS	+++	0	0	0
anti-Sm	++	0	0	0
anti-Ro/SSA	+/++	+++	0	(+)
anti-La/SSB	(+)	++(+)	0	(+)

[*]Modified after [114]. In this table, the serology of the CLE subtypes was simplified.

Table 7. Laboratory tests prior to pregnancy in cutaneous lupus erythematosus (CLE)

Laboratory tests
• 24-hour proteinuria or protein/creatinine ratio in a single urine sample • Antinuclear antibodies (ANA) • Antibodies (anti-Ro/SS-A, anti-La/SS-B, anti Sm, and anti-RNP) • Anticardiolipin antibody IgG and IgM • Anti-dsDNA • Anti-β2 glycoprotein I IgG and IgM (which must be repeated in 12 weeks if positive) • Blood creatinine • C3,C4,CH50 • Complete blood count • Creatinine clearance • Lupus anticoagulant • Partial thromboplastin time • Platelet count • Prothrombin activation time • Transaminases • Uric acid • Urinary sediment

Table 8. Differential diagnoses of cutaneous lupus erythematosus*

Subtype	Differential Diagnosis
ACLE	Localized Form: Dermatomyositis, rosacea, seborrhoic eczema, tinea faciei, erysipelas, perioral dermatitis Generalized Form: Virus exanthema, drug-induced eruption, erythema exsudativum multiforme, toxic epidermal necrolysis (TEN)
SCLE	Tinea corporis, psoriasis vulgaris, mycosis fungoides, erythema exsudativum multiforme/ TEN, erythema annulare centrifugum, dermatomyositis, pityriasis rubra pilaris, drug-induced eruption, nummular eczema, seborrheic dermatitis, erythema gyratum repens
DLE	Tinea faciei, lupus vulgaris, sarcoidosis, psoriasis, actinic keratosis, contact dermatitis
LEP	Various forms of panniculitis, subcutaneous sarcoidosis, panarteriitis nodosa, subcutaneous panniculitis-like T-cell lymphoma, morphea profunda, subcutaneous granuloma annulare
CHLE	Perniones („chilblains), lupus pernio (chronic form of skin sarcoidosis of the acral regions), acral vasculitis/vasculopathy
LET	Jessner's lymphocytic infiltration/erythema arciforme et palpabile, polymorphous light eruption, pseudolymphoma, B-cell lymphoma, plaque-like cutaneous mucinosis, solar urticaria, reticular erythematous mucinosis (REM)

*modified after [115]

Conflicts of Interest

The Work Under Consideration for Publication					
		Elisabeth Aberer	**Szuszanna Bata-Csörgő**	**Luca Borradori**	**Marcia Caproni**
1	Grant	None	none	none	none
2	Consulting fee or honorarium	None	none	none	none
3	Support for travel to meetings for the study or other purposes	EADV	EADV	none	EADV
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	none	none	none
5	Payment for writing or reviewing the manuscript	None	none	none	none
6	Provision of writing assistance, medicines, equipment, or administrative support	None	none	none	none
7	Other	none	none	none	none

Relevant financial activities outside the submitted work					
1	Board membership	none	none	none	none
2	Consultancy	none	none	none	none
3	Employment	none	none	none	none
4	Expert testimony	none	none	none	none
5	Grants/grants pending	none	none	none	none
6	Payment for lectures including service on speakers bureaus	none	Berlin-Chemie, Janssen, Schering-Plough, MSD, Novartis	none	none
7	Payment for manuscript preparation	none	Novartis, MSD	none	none
8	Patents (planned, pending or issued)	none	none	none	none
9	Royalties	none	none	none	none
10	Payment for development of educational presentations	none	none	none	none
11	Stock/stock options	none	none	none	none
12	Travel/accommodations /meeting expenses unrelated to activities listed	Almirall	Janssen, Novartis, Ewopharma	none	none

13	Other (err on the side of full disclosure)	none	none	none	none

Other relationships					
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The Work Under Consideration for Publication					
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4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	none	none	none	none
5	Payment for writing or reviewing the manuscript	none	none	EADV	none
6	Provision of writing assistance, medicines, equipment, or administrative support	none	none	EADV	none
7	Other	none	none	none	none

Relevant financial activities outside the submitted work					
1	Board membership	none	none	none	none
2	Consultancy	none	none	Lilly, Forward, Grünenthal, GSK	none
3	Employment	University Paris VI and Hôpital Tenon	none	none	none
4	Expert testimony	none	none	none	none
5	Grants/grants pending	none	none	GSK, Biogen Idec	none
6	Payment for lectures including service on speakers bureaus	Sanofi, Actelion	none	GSK, La Roche Posay, Biogen Idec, Abbott, Basilea	none
7	Payment for manuscript preparation	none	none	Biogen Idec	none
8	Patents (planned, pending or issued)	none	none	none	none
9	Royalties	none	none	none	none
10	Payment for development of educational presentations	none	none	none	none
11	Stock/stock options	none	none	none	none

12	Travel/accommodate ons/meeting expenses unrelated to activities listed	none	none	Basilea, Biogen Idec, GSK, La Roche Posay, Lilly, Spirig	none
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The Work Under Consideration for Publication					
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3	Support for travel to meetings for the study or other purposes	none	EADV	none	EADV
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	none	none	none	none
5	Payment for writing or reviewing the manuscript	none	none	none	none
6	Provision of writing assistance, medicines, equipment, or administrative support	none	none	none	none
7	Other	none	none	none	none

Relevant financial activities outside the submitted work					
1	Board membership	none	none	none	Abbvie, Celgene, Pierre-Fabre, Novartis

2	Consultancy	Biogen	Pfizer, Abbvie, Alvogen	none	Dignity Sciences, Sandoz
3	Employment	none	none	none	none
4	Expert testimony	none	none	none	none
5	Grants/grants pending	none	Pfizer, Abbvie, Novartis, Alvogen	none	none
6	Payment for lectures including service on speakers bureaus	none	none	none	AbbVie, Astellas, Actavis, Janssen, Leo Pharma, Novartis, SunFarm, Sandoz, Eli Lilly
7	Payment for manuscript preparation	none	none	none	Bayer
8	Patents (planned, pending or issued)	none	none	none	none
9	Royalties	none	none	none	none
10	Payment for development of educational presentations	none	none	none	Bayer
11	Stock/stock options	none	none	none	none
12	Travel/accommodations /meeting expenses unrelated to activities listed**	none	none	none	Leo Pharma
13	Other (err on the side of full disclosure)	none	none	none	Abbvie, Actelion, Amgen, GSK, Merck, Novartis, Regeneron, Takeda, Trevi

Other relationships					
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The Work Under Consideration for Publication				
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1	Grant	none	EADV	none
2	Consulting fee or honorarium	none		none
3	Support for travel to meetings for the study or other	EADV	EADV	EADV
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	none	none	none
5	Payment for writing or reviewing the manuscript	none	EADV	none
6	Provision of writing assistance, medicines, equipment, or administrative support	none	EADV	none
7	Other	none	none	none

Relevant financial activities outside the submitted work				
1	Board membership	none	none	none
2	Consultancy	none	none	none
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6	Payment for lectures including service on speakers bureaus	none	none	none
7	Payment for manuscript preparation	none	none	none
8	Patents (planned, pending or issued)	none	none	none
9	Royalties	none	none	none
10	Payment for development of educational presentations	none	none	none
11	Stock/stock options	none	none	none
12	Travel/accommodations /meeting expenses unrelated to activities listed**	none	none	none
13	Other (err on the side of full disclosure)	none	none	none

Other relationships				
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