S2k - European Dermatology Forum Guideline for the Treatment of Cutaneous Lupus Erythematosus

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

Subcommittee Members:

Prof. Dr. Annegret Kuhn, Mainz (Germany)
Prof. Dr. Elisabeth Aberer, Graz (Austria)
Prof. Dr. Zsuzsanna Bata-Csörgö, Szeged (Hungary)
Prof. Dr. Marzia Caproni, Florence (Italy)
Mr. Andreas Dreher, Frankfurt (Germany)
Prof. Dr. Camille Frances, Paris (France)
Prof. Dr. Regine Gläser, Kiel (Germany)
Dr. Hans-Wilhelm Klötgen, Bern (Switzerland)
Mrs. Aysche Landmann, Heidelberg (Germany)
Prof. Dr. Branka Marinovic, Zagreb (Croatia)
Prof. Dr. Filippa Nyberg, Stockholm (Sweden)
Dr. Rodica Olteanu, Bucharest (Romania)
Prof. Dr. Annamari Ranki, Helsinki (Finland)
Prof. Dr. Jacek C. Szepietowski, Wroclaw (Poland)
Prof. Dr. Beatrix Volc-Platzer, Vienna (Austria)

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Prof. Dr. Christos Zouboulis, Dessau (Germany)
Prof. Dr. Dr. Torsten Zuberbier, Berlin (Germany)

Chairman of EDF Guideline Committee:

PD Dr. Alexander Nast, Berlin (Germany)

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EDF Guidelines Secretariat to PD Dr. Nast:
Bettina Schulze, Klinik für Dermatologie, Venerologie und Allergologie, Campus Charité Mitte,
Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
phone: ++49 30 450 518 062, fax: ++49 30 450 518 911, e-mail: bettina.schulze@charite.de

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Annegret Kuhn[1,2], Elisabeth Aberer[3*], Zsuzsanna Bata-Csörgő[4*], Marzia Caproni[5*], Andreas Dreher[6], Camille Frances[7*], Regine Gläser[8*], Hans-Wilhelm Klötgen[9*], Aysche Landmann[2], Branka Marinovic[10*], Filippa Nyberg[11*], Rodica Olteanu[12*], Annamari Ranki[13*], Jacek C. Szepietowski[14*], Beatrix Volc-Platzer[15*]

[1]Interdisciplinary Center for Clinical Trials (IZKS), University Medical Center Mainz, Germany

[2]Division of Immunogenetics, Tumor Immunology Program, German Cancer Research Center, Heidelberg, Germany

[3]Department of Dermatology, Medical University of Graz, Austria

[4]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

[5]Department of Medical and Surgical Critical Care Section of Dermatology, University of Florence, Italy

[6]Evidence-Based Medicine Frankfurt, Institute for General Practice, Goethe-University Frankfurt, Germany

[7]Department of Dermatology and Allergology, Hôpital Tenon, Paris, France

[8]Department of Dermatology, Venerology and Allergology, University Hospital of Schleswig-Holstein, Campus Kiel, Germany

[9]Department of Dermatology, Inselspital Bern - University Hospital, Bern, Switzerland

[10]Department of Dermatology and Venereology, University Hospital Center Zagreb and School of Medicine University of Zagreb, Zagreb, Croatia

[11]Department of Clinical Sciences, Karolinska Institutet, Department of Dermatology & Danderyd Hospital, Stockholm, Sweden

[12]Department of Dermatology, Colentina Clinical Hospital, Bucharest, Romania

[13]Department of Skin and allergic diseases, Inflammation Center, Helsinki University Central Hospital, Helsinki, Finland

[14]Department of Dermatology, Venereology and Allergology Wroclaw Medical University, Wroclaw, Poland

[15]Department of Dermatology, Donauspital, University affiliated Hospital, Vienna, Austria

*Authors contributed equally to the work.

Correspondence:
Prof. Annegret Kuhn, MD, MBA
Interdisciplinary Center for Clinical Trials (IZKS)
University Medical Center Mainz
Langenbeckstrasse 1
D-55131 Mainz, Germany
Phone: +49 (0) 6131 17-9912
Fax: +49 (0) 6131 17-9914
Email: research@izks-unimedizin-mainz.de

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Abstract

Cutaneous lupus erythematosus (CLE) is a rare inflammatory autoimmune disease with heterogeneous subtypes. To date, no therapeutic agents have been licensed specifically for patients with this disease entity and topical and systemic drugs are mostly used “off-label”. The aim of the present guideline was to achieve a broad consensus on treatment strategies for patients with 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, 16 European participants were included in this project and agreed on all recommendations. Topical corticosteroids remain the mainstay of treatment for localized CLE, and further topical agents, such as calcineurin inhibitors, are listed as alternative first-line or second-line topical therapeutic option. Antimalarials are recommended as first-line and long-term systemic treatment in all CLE patients with severe or widespread skin lesions, in particular in patients with a high risk of scarring or the development of systemic disease. In addition to antimalarials, systemic corticosteroids are recommended as first-line treatment in highly active and severe CLE. Second- and third-line systemic treatment include methotrexate, retinoids, dapsone, and mycophenolate mofetil or mycophenolate acid, respectively. Thalidomide should only be used in selected therapy-refractory CLE patients, preferably in addition to antimalarials. Several new therapeutic options, such as B-cell or interferon alpha targeted agents, need to be further evaluated in clinical trials to assess their efficacy and safety in the treatment of patients with CLE.

Introduction

Lupus erythematosus is an inflammatory autoimmune disease, which may encompass severe systemic organ involvement (systemic lupus erythematosus, SLE), but may also affect only the skin (cutaneous lupus erythematosus, CLE). Based on clinical features, histological changes, and serological abnormalities, four CLE subtypes can be defined: (i) acute CLE (ACLE), (ii) subacute CLE (SCLE), (iii) chronic CLE (CCLE), including discoid LE (DLE), chilblain LE (CHLE), and LE panniculitis (LEP), and (iv) intermittent CLE (ICLE), synonymously LE tumidus (LET). To date, no drugs have been licensed for the treatment of CLE, although several therapeutic agents are approved for SLE, including the novel monoclonal antibody belimumab [1]. Thus, topical and systemic agents in CLE are mostly applied "off-label" and are rarely supported by evidence from randomized controlled trials [2].

The present guidelines have been prepared with the aim to develop recommendations for the treatment of patients with CLE. Due to the heterogeneity of the skin manifestations, the therapeutic strategies need to be adapted to the individual patient and should be initialized by experts with long-term experience of the disease. Therefore, the target group of the present guidelines on treatment of CLE are disease specialists in dermatology or other experts treating patients with other disease entities, such as rheumatologists and nephrologists. Guidelines for diagnosis and monitoring of CLE targeting all dermatologists and also general practitioners are under development by the same group of authors and will be published separately.

Methods

Due to the lack of standardized therapeutic procedures, the aim of the present project was the development of European Guidelines for the treatment of patients with CLE, in cooperation with the European Dermatology Forum (EDF) and the European Academy of

Dermatology and Venerology (EADV). Prof. Annegret Kuhn as chairperson of the guideline subcommittee together with 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. Prior to a Consensus Conference each of the invited authors submitted a preliminary draft of a selected topic, based on an internet research of relevant medical databases and a literature survey. The following members of the guideline subcommittee were present at the 1st Consensus Conference held on July 20-21, 2014, in Frankfurt, Germany: Prof. Elisabeth Aberer, Prof. Szuszanna Bata-Csörgö, Prof. Marcia Caproni, Prof. Camille Frances, Prof. Regine Gläser, Prof. Annegret Kuhn, Dr. Hans-Wilhelm Klötgen, Prof. Branka Marinovic, Prof. Filippa Nyberg, Prof. Rodica Olteanu, Prof. Annamari Ranki, 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 clinical 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 1st Consensus Conference, each preliminary chapter including different treatment options for CLE patients was discussed, recommendations were developed and consented upon. All recommendations in the present guideline and the treatment algorithm (**Figure 1**) are based on a consensus of 100% of the participating authors. 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.

Preventive Measures and Risk Factors

Genetic variations together with immunological and environmental factors can result in an increased risk of developing autoimmune diseases such as CLE [3]. In rare cases, CLE (mainly SCLE) is reported as paraneoplastic disease [4]. Moreover, a Swedish study presented an increased risk for buccal cancer, lymphomas, respiratory cancer, and non-melanoma skin cancer among patients with CLE [5].

Ultraviolet (UV)-A and -B light is one of the most important risk factors of CLE, clearly documented by photoprovocation studies in large patient cohorts [2, 6-8]. In the past years, several trials have been performed to investigate the preventive effect of sunscreens in patients with UV-induced CLE. A randomized controlled trial demonstrated that the application of a broad-spectrum sunscreen with a high protection factor prevents UV-induced skin lesions under standardized conditions [9]. The clinical results have recently been confirmed by an open-label study with a liposomal sunscreen, supported by histology and immunohistochemistry [10, 11].

Smoking as a relevant risk factor for widespread CLE has been described in a cohort of 1,346 SLE patients from Canada [12]. A multicenter analysis of 1002 CLE patients in Europe confirmed that smoking influences disease severity and the efficacy of antimalarials [13]. However, other studies investigating the relationship between smoking and the efficacy of antimalarials in CLE patients indicate that cigarette smoking might not have any significant influence on the response to hydroxychloroquine (HCQ) and/or chloroquine (CQ) [14-16].

Drug-induced lupus erythematosus (DILE/DIL) in its classical form shows all features of idiopathic SLE with arthralgia, myalgia, serositis, and fever. The involvement of skin and systemic organs (e.g., lupus nephritis) is rare [17, 18]. In contrast, drug-induced CLE (DI-CLE) shows all typical signs of the various disease subtypes (**Table 1**) [19, 20]. DI-CLE was reported to have the highest prevalence in SCLE patients [5, 21].

The "Koebner phenomenon" in CLE is described following traumas, scratching effects, operation scars, contact dermatitis, pressure from sock tops, application of liquid nitrogen, infections, heat, and other stimuli [22-25].

Recommendations

- We recommend to avoid unprotected **UV-exposure** and to use daily preventive (chemical and physical) measures in all CLE patients.
- **Vitamin D supplementation** is suggested in all CLE patients.
- Cessation of **smoking** (active and passive) is recommended in all CLE patients.
- We recommend performing patient´s past and present drug history, particularly in SCLE patients (**Table 1**).
- We recommend the **avoidance of isomorphic trigger factors**, especially in DLE patients.

Pregnancy or Hormonal Therapy

Only one publication on the influence of pregnancy in 31 DLE and 2 SCLE patients exists, with a reported aggravation of the disease in 21% and first manifestation in 2 DLE patients [26]. In a cohort of 107 pregnant SLE patients with various organ manifestations (93% of patients in remission for 6 months minimum), the most frequently affected organs were the skin and joints [27]. One study with 41 SLE and 34 DLE patients undergoing hormone replacement therapy for more than 2 years showed a higher risk for development of disease in contrast to 295 controls with highest risk for estrogen monotherapy and a protective effect in combination with gestagen [28]. Patients with inactive or stable active SLE showed no higher risk for disease activation or thrombosis under hormonal contraception containing estrogens [29, 30].

Recommendations

- In patients with CLE and associated antiphospholipid syndrome, we do not recommend to take **hormonal contraception** containing estrogen.
- We do not suggest estrogen replacement therapy for patients with CLE.
- In active disease during **pregnancy or breastfeeding**, we recommend HCQ as first line treatment for CLE at usual dosage.
- We recommend continuing the maintenance of HCQ treatment during pregnancy, but we also recommend switching from CQ to HCQ in this period*.
- In active disease or during flares, we suggest dapsone for HCQ-refractory CLE patients as an alternative treatment in during **pregnancy or breastfeeding**.
- We recommend that systemic corticosteroids (prednisone and methylprednisolone) should be given in a dosage of not more than 10 - 15 mg per day during **pregnancy**

or breastfeeding.

- We do not recommend methotrexate (MTX), mycophenolate mofetil (MMF) or mycophenolate acid (MPA), retinoids, and thalidomide or lenalidomide in women of childbearing age without effective contraception.
- We recommend that a **pregnant or breastfeeding** patient with severe CLE and/or anti-Ro/SSA antibodies is treated by a multidisciplinary approach.

*****[31]

Topical Treatment

Topical Corticosteroids

Topical corticosteroids are the mainstay in the treatment of localized CLE being effective in all subtypes (**Figure 1**), but only few controlled studies have been published proving their efficacy. In 2009, the Cochrane Database of Systematic Review on the treatment of DLE [32] included only one randomized controlled trial, comparing efficacy of 0.05% fluocinonide (a potent corticosteroid cream) with 1% hydrocortisone (a low-potency corticosteroid cream). A 6-week-long treatment resulted in an excellent response in 10 (27.0%) of 37 patients on fluocinonide, compared to 4 (9.8%) of 41 patients using hydrocortisone cream, documenting that topical corticosteroids of higher potency are more effective than less potent ones in treating DLE lesions [33]. A study by Barikbin and co-workers [34] comparing the efficacy of 0.1% betametasone 17-valerate cream with 1% pimecrolimus cream in facial DLE demonstrated a 73% improvement of skin lesion severity in the 0.1% betametasone 17-valerate arm, which was similar to the improvement in the group applying 1% pimecrolimus cream (see below). In another study on 21 Thai patients with DLE, once-daily application of 0.05% clobetasol propionate (ultra-potent corticosteroid) for 6 weeks resulted in greater improvement of the disease activity when compared to twice-daily application of 0.1% tacrolimus ointment [35]. However, due to the well-known side effects, such as atrophy,

telangiectasia, and steroid-induced rosacea-like dermatitis, treatment with topical corticosteroids should be intermittent and not exceed an application of more than a few weeks.

Recommendations

- We recommend **topical** corticosteroids as first-line treatment for a time limited up to some weeks in all CLE lesions.
- In patients with widespread disease and/or the risk of scarring, we recommend concomitant treatment with **antimalarials**.

Calcineurin Inhibitors

Currently available topical calcineurin inhibitors (0.03% and 0.1% tacrolimus ointment, 1% pimecrolimus cream) have been licensed for the use in patients with atopic dermatitis. In addition, several studies documented the efficacy of topical calcineurin inhibitors in other inflammatory skin conditions including CLE [36, 37]. The major advantage of these agents is their better safety profile if compared with topical corticosteroids – these compounds do not cause any skin atrophy, purpura, or telangiectasia. A multicenter, randomized, double-blind, vehicle-controlled trial by Kuhn and co-workers [38] included 30 patients with various CLE subtypes. Significant improvement was observed for edema and erythema of CLE lesions using 0.1% tacrolimus ointment compared to the vehicle, while no effect was seen on desquamation and hypertrophy as well as on subjective symptoms, such as dysesthesia. The best response was noted in the group of LET followed by SCLE patients as well as within facial lesions compared to other locations and in lesions lasting less than 6 months. In another study on 21 Thai patients with DLE [35], the efficacy of 0.1% tacrolimus ointment was compared with 0.05% clobetasol propionate. Disease activity improved in both groups, albeit

0.05% clobetasol propionate showed better efficacy as evaluated by a modified Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). It has further been suggested that a specially formulated preparation (0.3% tacrolimus in 0.05% clobetasol propionate) might be superior to monotherapy with 0.1% tacrolimus or clobetasol propionate 0.05% ointment in terms of CLE improvement, being efficient even in therapy-recalcitrant disease [39].

The data on treatment of CLE with 1% pimecrolimus cream are less evident. In the study by Barikbin and co-workers [34], activity of DLE decreased by 84% after 8 weeks of treatment with 1% pimecrolimus comparing to 73% in patients treated with betamethamesone 17-valerate 0.1% cream ; however, the difference was not statistically significant. There are also other observational studies documenting the efficacy of treatment with 1% pimecrolimus cream in CLE patients [40, 41].

Recommendations

- In active, oedematous CLE lesions, particularly on the face, we recommend **calcineurin inhibitors** (0.1% tacrolimus ointment) as an alternative first-line or as a second-line topical treatment option.
- In patients with widespread disease and/or the risk of scarring, we recommend concomitant treatment with **antimalarials**.

Topical Retinoids and Other Topical Agents

Topical retinoids demonstrated their efficacy in the treatment of refractory CLE, especially in hypertrophic DLE lesions, 0.05% tazarotene gel (not available in all European countries), 0.025% tretinoin gel, and 0.05% tretinoin cream or tocoretinate ointment, a synthetic

esterified compound of tocopherol and retinoic acid, can be used as topical treatment [42-44]. Moreover, 0,5 % R-salbutamol, a β2-adrenergic receptor agonist, showed promising results in a double-blind, randomized controlled phase II trial, but has never been approved for CLE and is – to our knowledge - not commercially available as topical agent [45]. Imiquimod is a topical immune response modifying drug with controversial results in CLE lesions [46-51].

Recommendations

- In therapy-refractory hyperkeratotic lesions of CLE, we suggest **topical retinoids** as second-line treatment.
- We suggest **R-Salbutamol** as second-line topical treatment for therapy-refractory DLE.
- **Imiquimod** is not recommended as topical treatment in CLE.

UV Treatment, Cryotherapy, and Lasers

UVA1 light, cryotherapy, and lasers have been used in single cases and case series to treat CLE [51-57]; however, the induction of new lesions, due to photosensitivity and Koebner´s phenomenon, is a possible side effect.

Recommendations

- We do not recommend any **UV light** as treatment for CLE patients.
- We do not recommend **cryotherapy** on any CLE lesion.
- We do not recommend **laser treatment** on any active CLE lesion. Laser treatment performed by board-certified dermatologists might be an additive option in carefully selected lesions (e.g., telangiectasia).

Systemic Treatment

In general, systemic treatment, such as antimalarials, are not only applied for the treatment of existing skin lesions in CLE patients, but can also prevent the development of systemic disease. In particular, HCQ is associated with a higher rate of remission, fewer relapses, and reduced damage in the course of the disease, even in lupus nephritis [58, 59].

Antimalarials

Antimalarials include CQ, HCQ, and quinacrine (synonym: atabrine, atebrine, mepacrine); quinacrine is not available in all European countries and therefore not reimbursed by any insurance. Since a long time, antimalarials are considered the first-line systemic treatment in all subtypes of CLE; however, only two randomized, double-blind studies in CLE or SLE with skin lesions were - to our knowledge - performed until now. The study by Ruzicka and co-workers [60] compared HCQ to acitretin in different CLE subtypes; approximately 50% of the patients treated with HCQ improved, whereas 46% of the patients showed improvement after being treated with acitretin. In 33 patients with SLE and active skin lesions, Bezerra and co-workers [61] compared clofazimine with CQ. A complete response was seen in 18.8% of patients treated with clofazimine and in 41.2% of patients treated with CQ, but the difference was not significant. A good response was observed in 12 of 16 patients (75%) from the clofazimine group and in 14 of 17 patients (82.4%) from the CQ group. In an analysis by EUSCLE, HCQ and CQ were applied by 56.7% and 30.8% of the included 1002 patients, respectively, with an efficacy of 81.5% and 86.9%, respectively [62]. In their review of clinical efficacy and side effects of antimalarials in SLE using the GRADE system, Ruiz-Irastorza and co-workers [63] found high evidence supporting the global safety of HCQ and CQ, and moderate grade of evidence that HCQ suggests a safer profile than CQ. Therefore, HCQ is usually the first prescribed treatment in all CLE patients with severe or widespread

skin lesions, in particular in patients with the risk of scarring and development of systemic disease. Moreover, antimalarials are recommended as standard therapy in all SLE patients [64]. The main side effect of HCQ and CQ is retinal toxicity. Early retinal changes (so-called premaculopathy) do not give visual complaints and must be detected by regular screening. Intervals for screening of retinal changes should follow the guidelines of the "American Academy of Ophthalmology" [65-67].

The calculation of the daily dose of HCQ or CQ is discussed in the literature. Until recently, the ideal body weight of a patient was used to determine the maximum daily dose of HCQ and CQ [68]. Only if the real body weight was less than the ideal body weight, the real body weight was used for calculation of the maximum daily dose [68]. Recently, the "American Academy of Ophthalmology" [69] retrospectively evaluated data of 2,361 patients who had applied HCQ continuously for at least five years. The results of this study suggest that daily consumption of ≤ 5.0 mg HCQ/kg real body weight is associated with a low risk for HCQ retinal toxicity for up to 10 years. Based on these data, the "American Academy of Ophthalmology" recommend to apply a maximum daily dosage of 5.0 mg HCQ/kg real body weight and suggest to apply a maximum dosage of 2.3 mg CQ/kg real body weight [67].

In any case of refractory to HCQ or CQ, it is necessary to ensure that the CLE patient is adherent to treatment before considering therapeutic changes [70]. Moreover, smoking, disseminated DLE, and concomitant SLE were found to be significantly associated with the lack of response to antimalarials [13, 14]. If monotherapy with HCQ or CQ is not successful, quinacrine (100 mg/day) may be added, resulting in synergistic efficacy, without increasing the risk of retinopathy [71]. The most frequent side effect of quinacrine is yellow discoloration of the skin and mucous membranes, and the most serious, but extremely rare side effect is aplastic anemia depending on dose and duration of therapy. Antimalarials and antibiotics containing sulphonamides are the most common precipitating factors for

haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Therefore, determination of G6PD activity before antimalarial treatment is performed in several countries, such as Asia, Africa, and Mediterranean countries, but also in middle and north of Europe due to G6PD deficiency or mutations [72].

Recommendations

- We recommend **antimalarials** as first-line and long-term systemic treatment in all CLE patients with severe or widespread skin lesions, in particular in patients with the risk of scarring and development of systemic disease.
- We recommend to apply **HCQ** in a maximum daily dosage of 5 mg/kg real body weight or **CQ** in a maximum daily dosage of 2.3 mg/kg real body weight. A combination of HCQ with CQ must be avoided due to the risk of irreversible retinopathy.
- In **refractory cases**, we recommend to add quinacrine to either HCQ or CQ.
- In cases of **contraindication** for HCQ or CQ (e.g., retinopathy), monotherapy with quinacrine is recommended.
- **Ophthalmological consultation** is recommended in all CLE patients treated with HCQ or CQ at baseline, annually after 5 years of starting treatment or earlier in the presence of risk factors.
- We suggest to measure **HCQ or CQ blood levels** in therapy-refractory patients.
- Determination of **G6PD activity** is suggested before antimalarial treatment.

Systemic Corticosteroids

In a prospective, cross-sectional, multicenter study performed by EUSCLE, systemic corticosteroids showed the highest efficacy in comparison to all other systemic drugs used for

CLE therapy, providing to be effective in 94.3% of the 413 treated patients [62]. Moreover, systemic corticosteroids were most frequently (in 58.1%) and most successfully (in 96.8%) applied in cases of ACLE, probably due to the frequent association with SLE. The usual oral dosage of systemic corticosteroids is 0.5 to 1 mg/kg body weight per day for about 2 to 4 weeks followed by tapering of the dose to a minimum (≤7.5mg/day) with the aim to discontinue the application due to the well-know side effects, such as osteoporosis [31, 51, 73, 74]. Alternatively, a 3-day intravenous (i.v.) pulse therapy with 1g methylprednisolone has been successfully used in patients with persistent CLE not responsive to conventional therapy [75].

Recommendations

- In severe or widespread active CLE lesions, **systemic corticosteroids** are recommended as first-line treatment in addition to antimalarials.
- We recommend **to taper the dose** of systemic corticosteroids to a minimum with the aim to discontinue the administration, as soon as the disease being treated is under control.
- **Long-term therapy** with corticosteroids in CLE without systemic involvement is not recommended due to the well-known serious **side effects**.

Methotrexate (MTX)

Methotrexate (MTX) has been successfully applied as second-line treatment in therapy-refractory SCLE and DLE [76] and is broadly used as treatment option in SLE [77]. A retrospective study examined 43 patients with various subtypes of CLE, treated with i.v. MTX (15 to 25 mg once weekly) [78]; 98% demonstrated significant improvement in disease activity. The best clinical improvement was observed in patients with DLE and SCLE;

however, seven patients discontinued treatment due to side effects. In a subsequent follow-up study, 15 of these 43 CLE patients, who had received i.v. MTX, changed the treatment to a subcutaneous (s.c.) application obtaining similar efficacy [79]. To date, there is no evidence-based study directly addressing the question of how long MTX can be administered to CLE patients. Previous experiences in other dermatologic diseases, such as psoriasis, suggest that MTX may be given to patients for as long as it remains effective and well tolerated. During therapy with MTX, folate replacement is necessary to reduce side effects [80]. In most cases, the risk of liver toxicity with MTX therapy is low [81]; however, the impact of additional risk factors, such as baseline liver disease (including HBV or HCV), alcohol intake, obesity, and type 2 diabetes, as well as the use of concomitant medications should be considered. Therefore, according to the existing guidelines of other dermatologic diseases, in which MTX is administered, screening and monitoring of patients are required [82].

Recommendation

We recommend **MTX** up to 20 mg per week as a second-line treatment, primarily in SCLE patients, preferably subcutaneously and in addition to antimalarials.

Retinoids

Retinoids were suggested as second-line systemic therapy by the "American Academy of Dermatology" guidelines in 1996 [83]. In a double-blind, randomized, multicenter trial, acitretin was compared with HCQ for 8 weeks duration with marked improvement or clearing in 13 of 28 patients (46%) using acitretin and in 15 of 30 (50%) patients treated with HCQ [60]. Acitretin was especially useful in treating hyperkeratotic verrucous forms of DLE on hands, feet, and legs [84]. Single case reports describe a combination of acitretin with CQ and quinacrine with complete resolution in hypertrophic DLE [85] or isotretinoin in SCLE with a

remarkable improvement within 1 month [86]. Treatment of DLE and SCLE with isotretinoin has been reported in approximately 50 patients in open studies and in case reports with a success rate of approximately up to 87% [51, 87-91]. Etretinate 50 mg daily was used in an open prospective trial by Ruzicka and co-workers [92] including 19 patients with localized and disseminated DLE, SCLE, and one patient with cutaneous manifestations of SLE. A complete or almost complete clearing of CLE lesions was seen in 11 patients, treatment failure was observed in 8 patients.

In CLE, the recommended dose for acitretin and isotretinoin is 0.2 to 1.0 mg/kg body weight/day. The response to retinoid therapy usually is rapid, occurring within the first 2 to 6 weeks of treatment [93]. Relapses often occur quickly once the drug is stopped [90]. Both retinoids are teratogenic; therefore, effective contraception is essential during and after treatment (isotretinoin: 1 month; acitretin: 2 years) [94]. In 2008, another vitamin-A derivate, alitretinoin, was approved for the treatment of severe chronic hand eczema in patients refractory to potent topical corticosteroids A recent case report on three patients who received oral alitretinoin described high efficacy in the treatment of skin manifestations in 2 CLE and 1 SLE patient [96].

Recommendation

We recommend **retinoids** as second-line systemic treatment in selected CLE patients unresponsive to other treatments, preferably in addition to antimalarials.

Dapsone

The efficacy of dapsone has been proven only in case series and single reports. Lindskov and Reymann [97] treated 33 DLE patients with dapsone showing excellent results in 8 (24%) patients, some effect in 8 (24%) patients, and no response in 17 (52%) patients. Ujiie and co-

workers [98] reported a further case of LEP successfully treated with dapsone and reviewed 10 further Japanese cases with LEP. A retrospective analysis of 34 patients by Klebes and co-workers reported that dapsone with or without antimalarials was effective in more than 50% of patients with CLE [99]. In summary, dapsone has been reported to be effective in SCLE, LEP, urticarial vasculitis, and oral ulcerations [94, 100-104]. Dapsone was also effective in bullous lupus erythematosus (BLE), also after initial unsuccessful treatment with HCQ and systemic corticosteroids [105-108]. When carefully monitored, the side effects of dapsone can be controlled [109, 110]; neurological side effects with sensory and motor neuropathies are reported after prolonged therapy [111].

Recommendations

- We suggest dapsone as first-line treatment in **BLE**.
- We recommend **dapsone as second-line treatment in refractory CLE**, preferably in addition to antimalarials.
- We recommend to start dapsone with a **low dose treatment** (50 mg/day) and to increase it to a maximum of 1.5 mg/kg according to clinical response and side-effects. Determination of G6PD activity must be performed prior to therapy.

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF) is a standard-of-care medication in transplantation medicine [112] and, albeit the lack of randomized controlled studies, has been shown to be effective in autoimmune disorders of the skin [113, 114], lupus nephritis [115, 116], and various subtypes of CLE [51, 76, 80, 117-119]. In refractory CLE, MMF has also be shown to be effective in combination with HCQ and/or systemic corticosteroids [51, 76, 80, 120-123]. Side effects (gastrointestinal, cytopenic, hepatotoxic and hypersensitivity reactions) are minor and mainly

dose-dependent. Monthly laboratory monitoring is mandatory for hematological, hepatic and renal toxicities [76, 80]. Mycophenolate acid (MPA), the enteric-coated form of MMF, is effective as monotherapy of SCLE [124]. First pharmacogenetic data have been published for MPA and childhood-onset SLE [125], but further relevance for CLE is still unclear.

Recommendations

- We recommend **MMF** as **third-line treatment** in refractory CLE patients, preferably in addition to antimalarials.
- We recommend 2 x 500 mg MMF per day as **starting dose** that can be increased up to 3 g per day depending on the clinical response.
- We suggest **MPA** as an alternative treatment to MMF.

Azathioprine, Cyclophosphamide, and Cyclosporine

Azathioprine, cyclophosphamide, and cyclosporine have been widely used for the management of SLE since the early 1960s [126-128]. Moreover, azathioprine has been applied as a maintenance drug following intravenous pulses (IVP) of cyclophosphamide for severe, refractory SCLE [129]. However, these agents are not recommended for CLE patients without systemic organ involvement.

Recommendations

- We do not suggest **azathioprine** for treatment of CLE without systemic involvement.
- We do not suggest **cyclophosphamide** for CLE without systemic involvement.
- We do not suggest **cyclosporine** for CLE without systemic involvement.

Thalidomide and Lenalidomide

Thalidomide (alpha-N-phtalimido-glutarimide) has potent anti-inflammatory effects in erythema nodosum leprosum and CLE [130]. Marked to complete remissions of recalcitrant lesions of SCLE or DLE were reported in several case reports and case series [131, 132]. However, peripheral neuropathy occurs in 17-27% of patients [133-135], is only partly reversible [136], and thus significantly limits the use of thalidomide for therapy-refractory cases. With lenalidomide**,** a structural analogue of thalidomide, the risk of polyneuropathy is less frequent [137, 138]. In one case report and two open-label studies [139-141], the majority of patients (>80%) with recalcitrant SCLE, CCLE, and other subtypes responded to 5-10 mg/day lenalidomide orally, as early as after two weeks. However, lenalidomide may not only prevent but also induce systemic disease [141].

Recommendations

- We recommend **thalidomide** for selected refractory CLE patients, preferably in addition to antimalarials.
- We suggest a starting dose of 100 mg per day and, after clinical effectiveness, to taper to a minimum dose. The sedative and prothrombotic effect should be taken into consideration. Due to high incidence of polyneuropathy electrophysiological examination of the peripheral nerves must be performed prior to use and during treatment according to clinical symptoms. Any sign of **polyneuropathy** should indicate the stop of the drug.
- We do not suggest **lenalidomide** for treatment of CLE.

Antibiotics

In the literature, only very few data on antibiotics are available to recommend the application of these agents in CLE [76].

Recommendation

We do not recommend **antibiotics** / **antimicrobials** (clofazimine / sulfasalazine / cefuroxime axetil) for treatment of CLE.

Intravenous Immunoglobulins (IVIG)

Intravenous immunoglobulins (IVIG) are extracted from pooled plasma from >10,000 donors. Recently, a dose-related effect on the dendritic-cell mediated immune response has been reported [142]. "High-dose" IVIG (2 g/kg body weight/month) has been used successfully in autoimmune diseases [143-145]. Several case reports and case series showed beneficial effects in refractory CLE [146-152], but worsening of skin lesions in SCLE and SLE has also been reported [153]. Common side effects include headache; cutaneous lesions, acute renal failure, and aseptic meningitis occur less frequently [144].

Recommendation

We do not suggest the use of **IVIG** for treatment of CLE.

Belimumab

Belimumab is licensed for SLE in Europe and North America since 2012 [154, 155]. In data pooled from two phase-III trials [156, 157], belimumab demonstrated improved SLE disease activity on mucocutaneous and musculoskeletal parameters [1]. However, the trials were not designed or powered to determine the efficacy of belimumab in any specific organ domain

[1]. In the approved regimen, belimumab is administered at 10 mg/kg at 2 weeks intervals for the first three doses, and then it is given every 4 weeks.

Recommendation

We do not suggest **belimumab** for treatment of CLE without systemic involvement.

Rituximab

Several open-label studies have demonstrated the efficacy of rituximab in the treatment of patients with SLE who were resistant to standard treatment [158]. Prospective registry data showed cutaneous improvement in 70% of rituximab-treated patients [159]. However, these results were not confirmed by two multicentre randomized controlled trials [160, 161]. Currently, rituximab is not approved for the treatment of SLE in any country. Phase III trials in lupus nephritis are ongoing, and only a few case reports have been published on its use in CLE [162-164].

Recommendation

We do not suggest **rituximab** for treatment of CLE.

Anti-CD4 Antibodies

A recombinant chimeric CD4 monoclonal antibody has been used for the treatment of refractory CLE in one study [165], but no controlled comparative studies have been performed.

Recommendation

We do not recommend **anti-CD4-antibodies** for treatment of CLE.

Further Biological Drugs

The use of other biological drugs, such as anti-tumor necrosis factor (TNF)-alpha, interferon (IFN)-alpha agents, and leflunomide may turn a double-edged sword in the treatment of CLE, since they may even exacerbate underlying CLE and SLE. Although serum TNF-alpha levels are increased in SLE and correlate with disease activity [123], TNF-alpha blockers have proven to be exacerbators rather than remedies for CLE. In single CLE patients treated with IFN alpha 2a, the exacerbation of skin lesions [166, 167], the induction of a SLE-like syndrome [168], and stable improvement of skin lesions have been reported [169]. Leflunomide has shown efficacy in the treatment of SLE in open-label and placebo-controlled pilot studies [170, 171]. However, a number of leflunomide-related cutaneous adverse effects, including a few cases of SCLE has been reported [141, 172-178]. A randomized, double-blind, placebo-controlled, open-labeled, dose-ascending phase I study evaluated the safety and pharmacokinetics of multiple intravenous infusions of sirukumab in 31 patients with CLE and 15 patients with SLE [179]. As evaluated by the CLASI, no significant changes compared to baseline were observed in patients with CLE (decrease from 6 points to 3 points) and in patients with SLE (decrease from 4 points to 1.5 points), who received sirukumab. Therefore, further trials are warranted to define conclusions on the efficacy of sirukumab. Only a few case reports have been published on the application of further biologicals, such as ustekinumab, for the treatment of CLE [180, 181]. Several new treatment modalities, mostly targeting the proinflammatory cytokine pathways, are currently in clinical trials for the treatment of CLE. In particular, monoclonal antibodies targeting IFN-alpha are a promising new treatment for patients with different disease subtypes (**Table 2**).

Recommendations

- We do not recommend **TNF-alpha antibodies** for treatment of CLE.
- We do not recommend **IFN-alpha** for treatment of CLE.
- We do not recommend **leflunomide** for treatment of CLE.
- We do not suggest **danazol** for treatment of CLE.
- We do not recommend **extracorporeal photopheresis** for treatment of CLE.

Summary

Many treatment options exist for CLE, but only single agents are supported by evidence from randomized controlled trials [2]. Topical corticosteroids are the mainstay of treatment for all different subtypes of the disease, but they are of limited value because of their well-known side effects, such as atrophy and telangiectasia. A safe and effective alternative topical treatment for CLE are the topical calcineurin inhibitors tacrolimus and pimecrolimus. Irrespective of the subtype of the disease, antimalarials, such as HCQ or CQ, are the first-line systemic treatment for disfiguring and widespread skin manifestations and for the prevention of systemic disease. Systemic corticosteroids can be used additionally in patients with highly acute and severe skin lesions, but should be time-limited due to the well-known side-effects. Further second-line treatment options include MTX, retinoids and dapsone, as well as MMF or MPA are third-line treatment options. Biologicals, such as belimumab or sirukumab, are promising new therapeutic options, but their efficacy and safety in the treatment of patients with CLE still needs to be evaluated in clinical trials.

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Tables

Table 1*: Drugs inducing CLE

Drug Class	**Low Risk (< 5%)**	**High Risk (> 5%)**
Antifungal agents		Griseofulvin, terbinafine
Antihypertensives	Angiotensin converting enzyme inhibitors: cilazapril, captopril	Calcium channel blockers: diltiazem, verapamil, nifedipine, nitrendipine β-blockers: oxprenolol, acebutolol Diuretics: hydrochlorothiazide, spironolactone
Chemotherapeutic agents	5-Fluorouracil, capecitabine	Docetaxel
Antacids	Omeprazole lansoprazole, ranitidine	
Antiepileptics	Phenytoin, oxcarbazepine	
Immunomodulators	Etanercept, infliximab, efalizumab, IFN-α, leflunomide	
Lipid lowering agents	Pravastatin, simvastatin	
Anti-inflammatory drugs	Naproxen, piroxicam	
Antidepressants	Bupropion	
Antidiabetic drugs	Sulfonylurea (glyburide)	
Antiarrhythmia agents	Procainamide	
Benzodiazepines	Tetrazepam, lormetazepam	
Platelet aggregation inhibitors	Ticlopidine	
Estrogen receptor antagonists	Tamoxifen	
Miscellaneous	D-penicillamine, insecticides	

*modified after [5, 19]

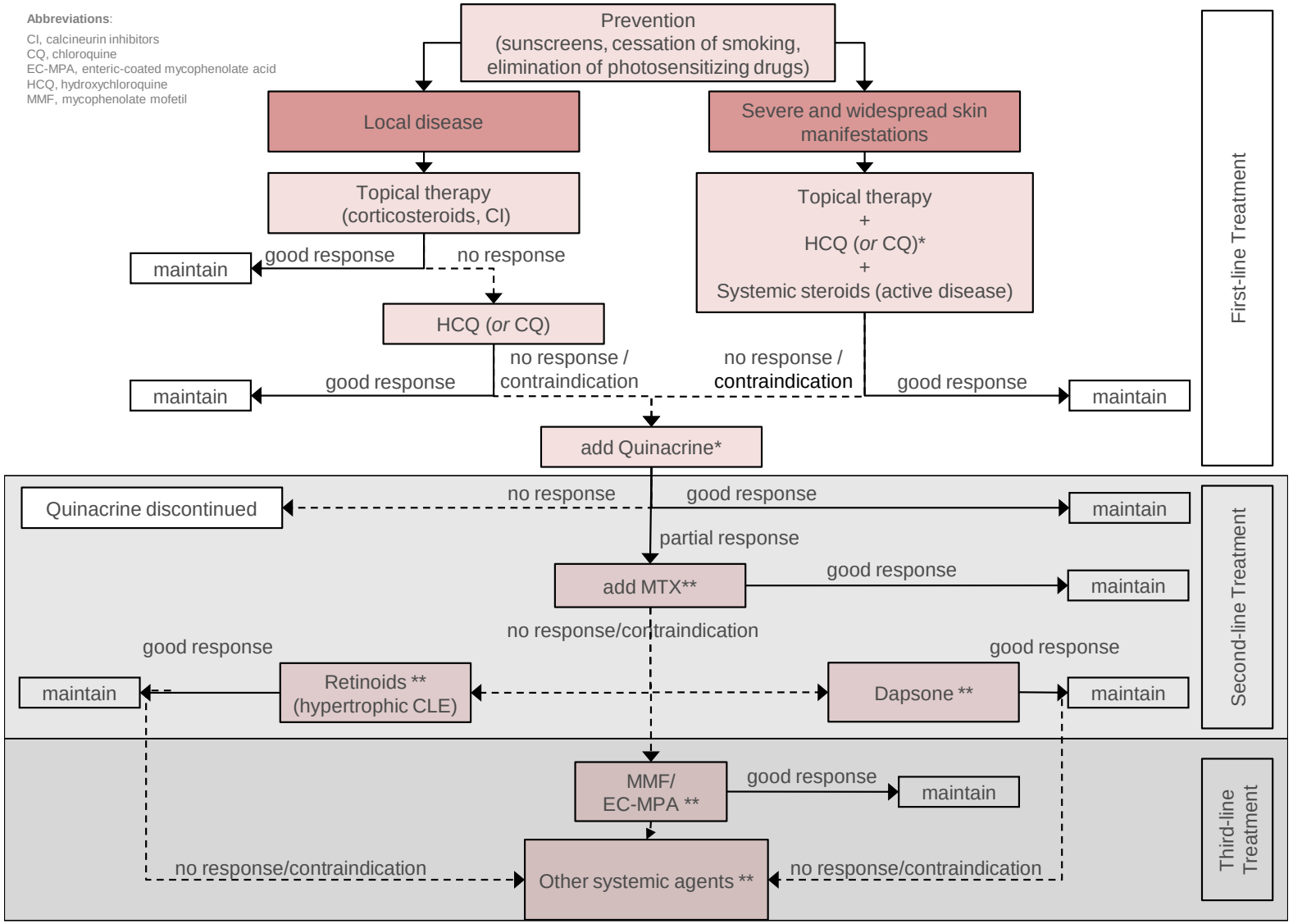
Table 2. Trials applying new treatment modalities in patients with SLE/CLE*

Name of Drug/ Intervention	Type	Study Design	Condition	Enrollment	ClinicalTrials.gov Identifier	Status
Etanercept (intradermal)	anti-TNF alpha antibody	Phase II, open label study	DLE	25 patients	NCT02656082	ongoing
Ex vivo expanded human autologous polyclonal regulatory T cells	-	Phase I, open-label, dose escalation study	SLE (ACLE, SCLE, DLE, LET)	18 patients	NCT02428309	ongoing
RSLV-132	mono-specific nuclease Fc-fusion protein	Phase IIa, randomized, placebo-controlled, double blind study	SLE (CLE)	50 patients	NCT02660944	ongoing
ALX-0061	anti-IL-6 receptor nanobody	Phase II, randomized, placebo-controlled, double blind study	SLE	300 patients	NCT02437890	ongoing
BMS-931699 (lulizumab pegol)	anti-CD28 antibody	Phase II, randomized, placebo-controlled, double blind study	SLE	350 patients	NCT02265744	ongoing
CC-220	small molecule	Phase II, randomized, placebo-controlled, double blind study	SLE	140 patients	NCT02185040	ongoing
Abatacept	fusion protein	Phase II, randomized, placebo-controlled, double blind study	SLE	60 patients	NCT02270957	ongoing
Anifrolumab	type I IFN receptor antagonist	Phase III, randomized, placebo-controlled, double	SLE	450 patients	NCT02446912	ongoing

		blind study				
TAB08	CD28 superagonist	Phase II, randomized, placebo-controlled, double blind study	SLE	60 patients	NCT02711813	not yet ongoing
CC-11050	small molecule	Phase II, randomized, placebo-controlled, double blind study	DLE, SCLE	48 patients	NCT01300208	completed, not yet published
KRP203	S1P1/4/5 agonist	Phase II, randomized, placebo-controlled, double blind study	SCLE	10 patients	NCT01294774	completed, not yet published
Apremilast (CC10004)	phosphodiesterase 4 (PDE-4) inhibitor	Phase I/II, open-label study	DLE	10 patients	NCT00708916	published [182]
Fumaderm	Fumaric Acid Esters	Phase II, open-label pilot study	CLE (DLE, SCLE)	11 patients	NCT01352988	published [183]
Paquinimod (ABR-215757)	small molecule	Phase II, open-label study	SLE	13 patients	NCT00997100	published [184]
AMG 811	anti-IFN-gamma IgG1 antibody	Phase I, randomized, placebo-controlled, double blind study	DLE	16 patients	NCT01164917	published [185]
PD-0360324	IgG1 antibody	Phase I, randomized, placebo-controlled, double blind study	DLE, SCLE	28 patients	NCT01470313	published [186]

*Only studies are listed, in which a skin score is applied to evaluate skin manifestations, modified after [187].
ACLE, acute cutaneous lupus erythematosus; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; LET, lupus erythematosus tumidus; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

Figure 1. Treatment Algorithm.



modified after *Kuhn A et al. J Am Acad Dermatol (2011): Part I: 65: e179–193, Part II: 65: e195–213; *if patient shows any sign of systemic disease or the risk for the development of systemic disease is high, antimalarials should be continued. **marked agents should not be continued in addition to further second or third line treatment options.*

Figure Legend

Figure 1: Algorithm of treatment for cutaneous lupus erythematosus (CLE). 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 considered to either continue or to change medication, depending on the efficacy of the treatment and possible side effects.

Conflicts of Interest

The Work Under Consideration for Publication					
		Elisabeth Aberer	**Szuszanna Bata-Csörgő**	**Marcia Caproni**	**Camille Frances**
1	Grant	none	none	none	none
2	Consulting fee or honorarium	Bayer, GSK	Novartis, Ewopharma, Janssen	none	none
3	Support for travel to meetings for the study or other purposes	EADV	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	none
5	Payment for writing or reviewing the manuscript	none	none	none	none
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6	Payment for lectures including service on speakers bureaus	Bayer, GSK, Ratiopharm	Glaxo, Schering-Plough, MSD, Novartis, Berlin-Chemie	none	Sanofi, Actelion
7	Payment for manuscript preparation	none	Novartis, MSD	none	none
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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
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7	Payment for manuscript preparation	none	none	Biogen Idec	none
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9	Royalties	none	none	none	none
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		Filippa Nyberg	**Rodica Olteanu**	**Annamari Ranki**	**Jacek C. Szepietowski**
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	EADV	none
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
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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	none	none	AbbVie, Astellas, Actavis, Adamed, Berlin-Chemie Mennarini, Fresenius, Janssen-Cilag, Leo Pharma, Takeda, Vichy

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9	Royalties	none	none	none	none
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		Beatrix Volc-Platzer	**Aysche Landmann**	**Andreas Dreher**	
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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	
5	Payment for writing or reviewing the manuscript	none	EADV	none	
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6	Payment for lectures including service on speakers bureaus	Biotest, Meda, Galderma	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	
11	Stock/stock options	none	none	none	
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