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)

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S2 Guideline for Treatment of Cutaneous Lupus Erythematosus -
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Abstract

Lupus erythematosus is an inflammatory autoimmune disease, which may affect only the skin (cutaneous Lupus erythematosus, CLE), but may also encompass severe systemic organ involvement (systemic Lupus erythematosus, SLE). Although several agents are approved for the treatment of SLE, no drugs have been licensed specifically for the treatment of skin manifestations of the disease. Thus, topical and systemic agents in CLE are mostly used "off-label". Topical corticosteroids remain the mainstay in the treatment of localized CLE being effective in all subtypes. 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 the risk of scarring and development of systemic disease. In severe or widespread active CLE lesions, systemic CS are recommended as first-line treatment in addition to antimalarials. Second- and third-line treatment options are metothrexate and retinoids, respectively. Several new therapeutic options, such as belimumab, interferon alpha and TNF-alpha antagonists, need to be 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 affect only the skin (cutaneous Lupus erythematosus, CLE), but may also encompass severe systemic organ involvement (systemic Lupus erythematosus, SLE). Based on clinical features, histological changes, serological abnormalities, and average duration of skin lesions, four CLE subtypes can be defined: acute cutaneous LE (ACLE), subacute CLE (SCLE), and chronic cutaneous LE (CCLE), including discoid LE (DLE), Chilblain LE (CHLE), and LE panniculitis (LEP). Although several agents are approved for the treatment of SLE, including the novel monoclonal antibody belimumab [1], no drugs have been licensed specifically for the treatment of skin manifestations of the disease. Thus, topical and systemic agents in CLE are mostly applied "off-label". Many treatment options exist for the disease, but only single agents are supported by evidence from randomized controlled trials [2].

The present guidelines have been prepared with the aim to develop treatment recommendations for CLE, but also cutaneous lesions in the setting of SLE. Due to the complexity of the disease, the treatment strategies need to be adapted to the individual patient and his/her lesions and should be initialized by an expert with long-term experience of the disease. Therefore, the target group of the present guidelines on the treatment of CLE are lupus specialists in dermatology and/or rheumatology. Guidelines for diagnosis and monitoring of CLE targeting resident practitioners are under development, and will be published separately.

Methods

Due to the lack of standardized therapeutic procedures, the aim of the present project was the development of S2k European Guidelines for the treatment of patients with CLE, in cooperation with the European Academy of Dermatology and Venerology (EADV) and the European Dermatology Forum (EDF). In 2013, a small group of experts nominated the

members of the guideline subcommittee and decided to invite a maximum of one experts from each center and/or county. To achieve a broad consensus on the planned objectives, a total of 16 participants from all over Europe were included. Each of the invited members conducted an internet research of relevant medical databases and a literature survey, and developed a chapter. The members of the guideline subcommittee agreed to develop a consensus-based (S2k) guideline (k for German "Konsensus"), which is based on a structured expert consensus process. The following members of the guideline subcommittee met at the 1st Consensus Conference held on July 20-21, 2014, in Frankfurt Germany: Prof. Elisabeth Aberer, Prof. Szuszanna Bata-Csörgö, Prof. Marcia Caproni, Andreas Dreher, Prof. Camille Frances, Prof. Regine Gläser, Prof. Annegret Kuhn, Aysche Landmann, Dr. Hans-Wilhelm Klötgen, Prof. Branka Marinovic, Prof. Filippa Nyberg, Prof. Rodica Olteanu, Prof. Annamari Ranki, Prof. Beatrix Volc-Platzer. Each treatment option was discussed, and a recommendation was 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 included 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 subacute cutaneous lupus erythematosus, SCLE) was reported as paraneoplastic disease [4]. Moreover, a Swedish study reported 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 liposomal sunscreen prevents UV-induced skin lesions under standardized conditions [9].

Smoking as a relevant risk factor for widespread CLE was recently described in a cohort of 1346 SLE patients in Canada [10]. A multicentre analysis of 1002 CLE patients in Europe confirmed that smoking influences CLE disease severity and the efficacy of antimalarial treatment [11]. However, other studies investigating the relationship between smoking and the efficacy of antimalarials in CLE patients indicate that cigarette smoking does not have any significant influence on response to HCQ and/or CQ [12-14].

Drug-induced lupus erythematosus (DILE/DIL) in its classical form shows all features of idiopathic SLE with arthralgia, myalgia, serositis, and fever. Involvement of skin and organs is rare [15, 16]. In contrast, drug-induced CLE (DI-CLE) shows all typical signs of the various disease subtypes (**Table 1**) [17, 18]. DI-CLE was reported to have the highest prevalence in SCLE patients [5, 19].

The “Koebner phenomenon“ in CLE was described following traumas, scratching effects, operation scars, contact dermatitis, pressure from sock tops, application of liquid nitrogen, infections, heat, and other stimuli [20-23].

Recommendation:

- 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 presenting drug history, particularly in SCLE patients (**Table 1**).
- We recommend the **avoidance of isomorphic trigger factors**, especially in DLE patients.
- We suggest **immunization** against pneumococcal pneumonia and influenza in CLE patients with stable disease, irrespective of systemic treatment.

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 [24]. In a cohort of 107 pregnant SLE patients with systemic organ manifestations (93% of patients in remission for 6 month minimum), the most frequently affected organs were the skin and joints [25]. 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 [26]. Patients with only inactive or stable active SLE had no higher risk for disease activation or thrombosis under hormonal contraception containing estrogen [27, 28].

Recommendation:

- In patients with antiphospholipid syndrome, we do not recommend to take **hormonal contraception** containing estrogen.
- We do not suggest oestrogene 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-HCQ-therapy during pregnancy, but we also recommend switching from CQ to HCQ in pregnancy*.
- We suggest dapsone for HCQ-refractory CLE patients as an alternative treatment in active disease or during flares during pregnancy **or breastfeeding**.
- We recommend that systemic CS (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), retinoids, thalidomide or lenalidomide in women of childbearing age without effective contraception
- We recommend that a pregnant **or breastfeeding** patient with a severe CLE and/or anti-Ro/SSA antibodies is treated by a multidisciplinary approach.

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Topical Treatment

Topical Corticosteroids

Topical corticosteroids remain 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. The Cochrane Database of Systematic Review on the treatment of discoid lupus erythematosus (DLE) [30] 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 [31]. A study by Barikbin et al. [32] comparing 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 six weeks resulted in greater improvement of the disease activity when compared to twice-daily application of 0.1% tacrolimus ointment [33].

Recommendation:

- We recommend **topical steroids** 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 (CI)

Currently available topical CI (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 CI in other inflammatory skin conditions including CLE [34, 35]. The major advantage of CI 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 et al. [36] included 30 patients with various CLE subtypes. Significant improvement was observed for erythema and edema 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 lupus erythematous tumidus (LET) followed by SCLE 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 [33], 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 CLASI. It has further been suggested that a specially formulated preparation (0.3% tacrolimus in 0.05% clobetasol propionate) might be superior to other topical treatments in terms of CLE improvement, working even in therapy-recalcitrant disease [37].

Regarding 1% pimecrolimus cream, the data are less evident. In the study by Barikbin et al. [32], activity of DLE markedly decreased by 84% after 8 weeks of treatment comparing to 73% in the betamethamesone 17-valerate 0.1% cream group; however, the difference was not statistically significant. There are also other observational studies documenting efficacy of treatment with 1% pimecrolimus cream in CLE subjects [38, 39].

Recommendation:

- 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, a synthetic esterified compound of tocopherol and retinoic acid, can be used as topical treatment [40-42]. Imiquimod is a topical immune response modifying drug with controversial results in CLE lesions [43-48]. Even though 0,5 % R-salbutamol cream, a β2-adrenergic receptor agonist, showed promising results in a double-blind, randomized controlled phase II trial, it has never been approved for CLE [49].

Recommendation:

- In refractory hyperkeratotic lesions of CLE patients, we suggest **topical retinoids** as second-line single treatment.
- **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 [48, 50-55]; however, the induction of new lesions, due to Koebner´s phenomenon, is a possible side effect.

Recommendation:

- We do not recommend any **UV treatment** in 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, but also to prevent (further) 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 [56, 57].

Antimalarials

Antimalarials include chloroquinesulfate (CQ), hydroxychloroquine diphosphate (HCQ), and quinacrine (synonym: atabrine, atebrine, mepacrine); quinacrine is not available in all European countries and therefore difficult to be reimbursed. 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 in SLE with skin lesions were performed until

now. The study by Ruzicka et al. [58] 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 et al. [59] 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 the literature series, a good response to HCQ or CQ within 1 to 3 months was observed in 50% to 90% of patients with different CLE subtypes [11]. In their review of clinical efficacy and side effects of antimalarials in SLE using the GRADE system, Ruiz-Irastorza et al. [60] 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 [61]. 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 [62-64].

The calculation of the daily dose of HCQ or CQ is discussed in the literature; if the real body weight was less than the ideal body weight, the real body weight was used for calculation of maximum daily dose [65]. Melles et al. [66] retrospectively evaluated data of 2361 patients who had applied HCQ continuously for at least five years. The results of this study suggest that daily consumption of ≤ 5.0mg 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 5mg HCQ /kg real body weight and suggest to apply a maximum dosage of 2.3 mg CQ/kg real body weight [64].

In the presence of CLE refractory to treatment with HCQ or CQ, it is necessary to ensure that the patient is adherent to treatment before considering therapeutic change [67]. 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 [68]. The most frequent side effect of quinacrine is yellow discoloration of the skin and mucous membranes, and the most serious 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. Smoking, disseminated DLE and concomitant SLE were found significantly associated with the lack of response of CLE to antimalarials [11, 12].

Recommendation:

- 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 5mg/kg real body weight or CQ in a maximum daily dosage of 2.3mg/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 CLE patients treated with HCQ or CQ at baseline, annually after 5 years and earlier in the presence of risk factors.
- Determination of **G6PD activity** is suggested before antimalarial treatment.

- We suggest to measure **HCQ or CQ blood levels** in therapy refractory patients.

Systemic Corticosteroids (CS)

In a prospective, cross-sectional, multicentre study performed by EUSCLE, systemic CS showed the highest efficacy in comparison to all other systemic drugs used for CLE treatment, providing to be effective in 94.3% of the 413 treated patients [69]. Moreover, systemic CS were most frequently (in 58.1%) and most successfully (in 96.8%) applied in cases of acute cutaneous lupus erythematosus (ACLE), probably due to the frequent association with SLE. The usual oral dosage of systemic CS 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 [29, 48, 70, 71]. Alternatively, a 3-day intravenous (i.v.) pulse therapy (1g methylprednisolone) has been successfully used in patients with persistent CLE not responsive to conventional therapy [72].

Recommendation:

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

Methotrexate (MTX)

MTX has been successfully applied as second-line treatment in therapy-refractory SCLE and DLE [73] and is broadly used as a treatment option in SLE [74]. A retrospective study examined 43 patients with various subtypes of CLE, treated with i.v. MTX (15 to 25 mg once weekly) [75]; 98% demonstrated significant improvement in disease activity. The best clinical improvement was observed in patients with DLE and SCLE. Due to side effects, seven patients discontinued treatment. In a subsequent follow-up study, in 15 of these 43 CLE patients, who had received i.v. MTX, the treatment was changed to a subcutaneous (s.c.) application obtaining similar efficacy [76]. However, there is no evidence-based study directly addressing the question of how long MTX can be administered to 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 [77]. In most cases, the risk of liver toxicity with MTX therapy is low [78]; 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 [79].

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 [80]. 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 [58]. Acitretin was especially useful in treating hyperkeratotic verrucous forms of DLE on hands, feet, and legs [81]. Single case reports describe a combination of acitretin with CQ and quinacrine with complete resolution in hypertrophic DLE [82] or isotretinoin in SCLE with a remarkable improvement within 1 month [83]. Treatment of DLE and SCLE with isotretinoin has been reported in approximately 50 patients in open studies and case reports with a success rate of approximately up to 87% [48, 84-88]. Etretinate 50 mg daily was used in an open prospective trial by Ruzicka et al. [89] in 19 patients with localized and disseminated DLE, SCLE, and one patient with cutaneous manifestations of SLE. A complete or almost complete clearing of CLE skin 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 [90]. Relapses often occur quickly once the drug is stopped [87]. Both retinoids are teratogenic; therefore, effective contraception is essential during and after treatment (isotretinoin: 1 month; acitretin: 2 years) [91]. In 2008, another vitamin-A derivate, alitretinoin, was approved for the treatment of severe chronic hand eczema in patients refractory to potent topical CS A recent case report on three patients who received oral alitretinoin describes high efficacy in the treatment of skin manifestations in 2 CLE and 1 SLE patient [93].

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 [94] 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 et al. [95] reported a further case of lupus erythematosus profundus (LEP) successfully treated with dapsone and published 10 Japanese cases with LEP. A retrospective analysis of 34 patients by Klebes et al. reported that dapsone with or without antimalarials was effective in more than 50% of patients with CLE [96]. In summary, dapsone has been reported to be effective in SCLE, LEP, urticarial vasculitis, and oral ulcerations [91, 97-101]. Dapsone was also effective in bullous SLE, also after initial unsuccessful treatment with HCQ and corticosteroids [102-105]. When carefully monitored, the side effects of dapsone can be controlled [106, 107]; neurological side effects with sensory and motor neuropathies are reported after prolonged therapy [108].

Recommendation:

- 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 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 glucose-6-phosphate dehydrogenase activity must be performed prior to therapy.

Mycophenolate Mofetil (MMF)

MMF is a standard-of-care medication in transplantation medicine [109] and, albeit the lack of randomized controlled studies, has been shown to be effective in autoimmune disorders of the skin [110, 111], lupus nephritis [112, 113] and various subtypes of CLE [48, 73, 77, 114-116]. In refractory CLE, MMF has also be shown to be effective in combination with HCQ and/or CS [48, 73, 77, 117-120]. 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 [73, 77]. Mycophenolate acid (MPA), the enteric-coated form of MMF, is effective as monotherapy of SCLE [121]. First pharmacogenetic data have been published for MPA and childhood-onset SLE [122], but further relevance for CLE is still unclear.

Recommendation:

- We recommend **MMF** as **third-line treatment** in refractory CLE patients, preferably in addition to antimalarials.
- We recommend 2 x 500 mg 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 [123-125]. Moreover, azathioprine has been applied as a maintenance drug following intravenous pulses (IVP) of cyclophosphamide for severe, refractory SCLE [126]. However, these agents are not recommended for CLE patients without systemic organ involvement.

Recommendation:

- We do not suggest **azathioprine** for 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 [127]. Marked to complete remissions of recalcitrant lesions of SCLE or DLE were reported in several case reports and case series [128, 129]. However, peripheral neuropathy occurs in 17-27% of patients [130-132], is only partly reversible [133], 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 [134, 135]. In one case report and two open-label studies [136-138], the majority of patients (>80%) with recalcitrant SCLE, chronic cutaneous lupus erythematosus (CCLE) and other forms responded to 5-10 mg/day lenalidomide orally, as early as after two weeks. However, lenalidomide may not only prevent but may also induce systemic disease [138].

Recommendation:

- We recommend **thalidomide** for selected refractory CLE patients, preferably in addition to antimalarials.
- We suggest a starting dose of 100 mg per day, 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 stop of the drug.
- We do not suggest **lenalidomide** for CLE.

Antibiotics

In the literature, only very few data on antibiotics are available to recommend the application of these agents in CLE [73].

Recommendation:

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

Intravenous Immunoglobulins (IVIG)

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 [139]. “High-dose” IVIG (2 g/kg bodyweight/month) has been used successfully in autoimmune diseases [140-142]. Several case reports and case series showed beneficial effects in refractory CLE [143-149],

but worsening of skin lesions in SLE and SCLE has also been reported [150]. Common side effects include headaches; cutaneous lesions, acute renal failure, and aseptic meningitis occurr less frequently [141].

Recommendation:

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

Belimumab

Belimumab is licensed for SLE in Europe and in North America since 2012 [151, 152]. In data pooled from two phase-III trials [153, 154], belimumab demonstrated an 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 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 [155]. Prospective, registry data showed cutaneous improvement in 70% of rituximab-treated patients [156]. However, these results were not confirmed by two multicentre randomized controlled trials [157, 158].

Currently, rituximab is not approved for the treatment of SLE. Phase III trials in lupus nephritis are ongoing, and only a few case reports have been published on its use in CLE [159-161].

Recommendation:

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

Anti-CD4 Antibodies

A recombinant chimeric CD4 monoclonal antibody has been used for the treatment of refractory CLE in one study [162], but no controlled comparative studies have been performed.

Recommendation:

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

Further Biological Drugs

The use of other biological drugs, such as interferon (IFN)-alpha and TNF-alpha antagonists or leflunomide, may turn a double-edged sword in the treatment of CLE, since they may even exacerbate underlying CLE and SLE. In single CLE patients treated with IFN alpha 2a, the exacerbation of skin lesions [163, 164], the induction of a SLE-like syndrome [165] as well as stable improvement of skin lesions have been reported [166]. Although serum TNF-alpha levels are increased in SLE and correlate with disease activity [120], TNF-alpha blockers have proven to be exacerbators rather than remedies for CLE. Leflunomide has shown

efficacy in the treatment of SLE in open-label and placebo-controlled pilot studies [167, 168]. However, a number of leflunomide-related cutaneous adverse effects, including a few cases of SCLE has been reported [138, 169-175]. However, monoclonal antibodies targeting IFN-alpha are a promising new treatment for SLE and for the cutaneous manifestations of the disease (**Table 2**). Only a few case reports have been published on the application of further biologicals, such as ustekinumab, in patients with CLE [176, 177].

Recommendation:

- We do not recommend **anti-TNF-α antibodies** for CLE patients.
- We do not recommend **leflunomide** for CLE patients.
- We do not suggest **danazol** for CLE patients.
- We do not recommend **extracorporeal photopheresis** for CLE patients.

New Treatment Modalities

Several new treatment modalities, mostly targeting the proinflammatory cytokine pathways, are currently in clinical trials for the treatment of CLE. These drugs are presented in **Table 2**.

Summary

Many treatment options exist for the disease, 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 hydroxychloroquine or

chloroquine, are the first-line systemic treatment for disfiguring and widespread skin manifestations. Systemic steroids 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 metothrexate and dapsone.

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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, 17]

Table 2: Biologicals: Overview on new treatment modalities in research

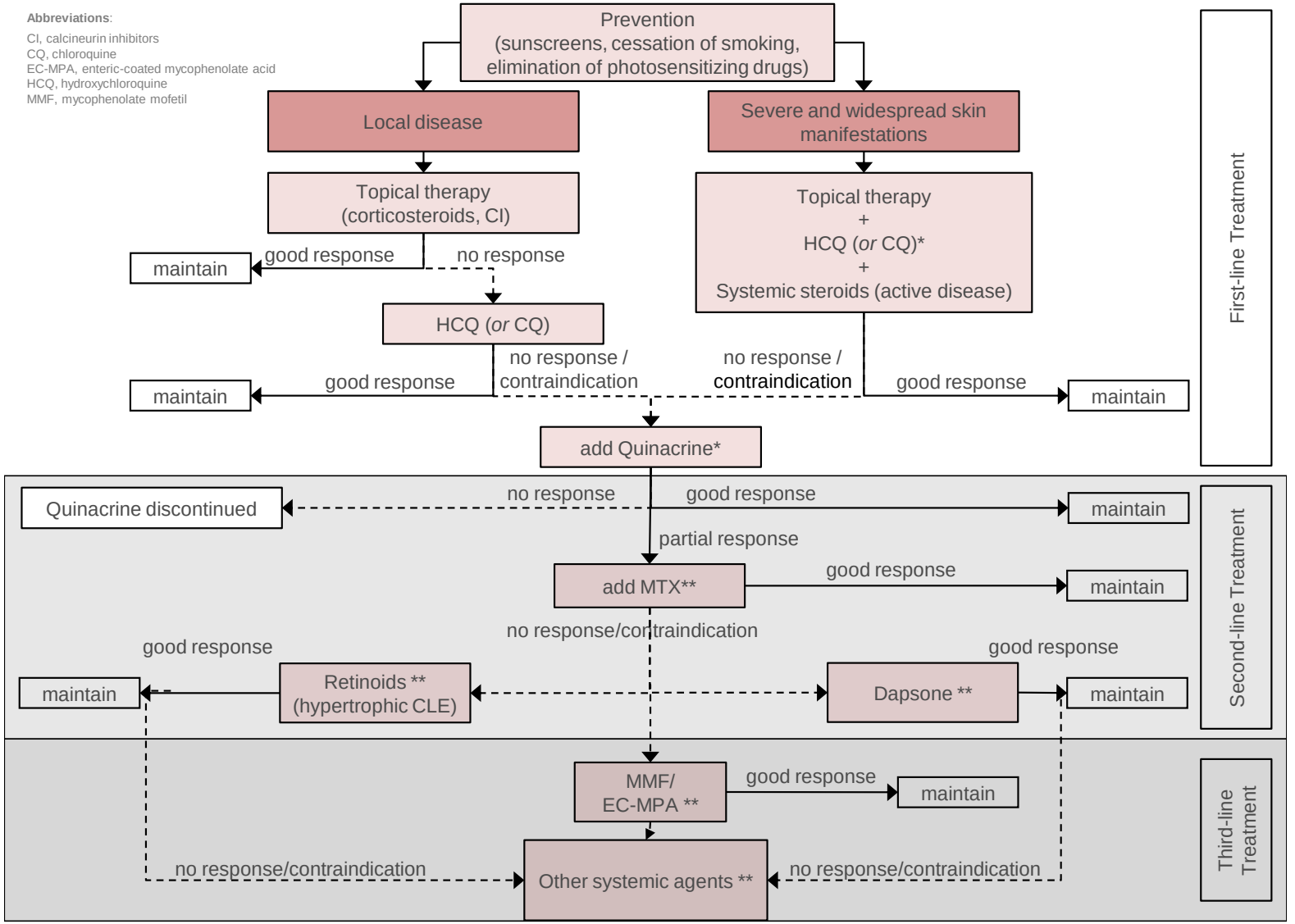
Drug	**Patient group treated / phase of drug development**	**Clinical Trials.gov Identifier**	**Dosing**	**Outcome**
Anti-CD4 mAb: recombinant chimeric	Five patients with severe cutaneous manifestations of DLE, SCLE, and SLE	-	Total doses of 275, 400, or 475 mg in single administrations of 20 to 50 mg during a period of 5 to 8 weeks	All patients showed a nearly complete improvement in cutaneous inflammation, and the responsiveness to conventional therapies was restored as a long-term effect.
Anti-IL6 mAb: sirukumab	Phase I, double-blind, placebo-controlled study for CLE patients with mild, stable, active disease	NCT01702740	i.v. dosing, 1, 4, or 10 mg/kg every 2 weeks	CLE did not seem to respond to therapy, as measured by the CLASI.
Anti-IL6R mAb: tocilizumab	Clinical trials in progress, a phase I, open-labeled, dose-ascending clinical trial has been completed in CLE	-	-	-
Anti-IFN-alpha mAb: rontalizumab (humanized) and sifalimumab (human)	Clinical trials in progress	NCT00962832 and 00541749, NCT01283139	i.v. or s.c.	In the phase IIb study on SLE patients, sifalimumab significantly improved skin lesions, measured by CLASI.
Anti-IFN-gamma: fontolizumab	A randomized, double-blind, placebo-	NCT01164917	-	No results are yet published.

(humanized)	controlled, single dose, crossover study for DLE			
TNF-alpha inhibitor (CC-11050) (oral small molecule)	Phase II, pilot sequential, ascending dose study for patients with DLE and SCLE	NCT01300208	-	No results are yet published.
Fumaric acid esters (FAE)	A prospective open pilot study on 11 patients with various subtypes of CLE in 2011	NCT01352988	FAE administered for 24 weeks (six tablets /day), observation period of an additional four weeks, evaluation with the RCLASI.	Final results not yet published.
Phosphodiesterase type 4 inhibitor: apremilast (CC-10004)	Phase I and II clinical studies and with potential efficacy in cutaneous lupus	NCT00708916	In an ongoing open label, pilot study on 10 CLE patients, the drug is administered for 12 weeks	No results are yet published.
anti-M-CSF mAb (human, PD-0360324)	Phase II study evaluating the safety and tolerability in patients with CLE	NCT01470313	i.v. administration	No results are yet published.
Anti-B7RP-1 mAb (human), ICOS ligand (AMG 557)	A randomized, double-blind, placebo-controlled, multiple dose study, in subjects with SCLE	NCT01389895	-	No results are yet published.
Immunomodulatory compound (KRP-203)	A double-blind, placebo-controlled, proof-of-	NCT01294774	-	No final results available yet.

	concept study in patients with active SCLE			

CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; i.v., intravenously; mAb, monoclonale antibodies; RCLASI, Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index; s.c. subcutaneously.

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 (eg, 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
6	Provision of writing assistance, medicines, equipment, or administrative support	none	none	none	none
7	Other	none	none	none	none

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	none	none	PIP Psoriasis	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	Bayer, GSK, Ratiopharm	Glaxo, Schering-Plough, MSD, Novartis, Berlin-Chemie	none	Sanofi, Actelion
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	none	none	none

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

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	none	none	none	none

The Work Under Consideration for Publication					
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1	Grant	none	none	EADV	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	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	EADV	none
6	Provision of writing assistance, medicines, equipment, or administrative support	none	none	EADV	none
7	Other	none	none	none	none

* This means money that your institution received for your efforts on this study.

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	none	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	GSK, Abbvie	none	GSK, La Roche Posay, MSD, 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/accommodations/meeting expenses unrelated to activities listed**	none	none	Basilea, Biogen Idec, GSK, La Roche Posay, Lilly, Spirig	none

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

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	none	none	none	none

The Work Under Consideration for Publication					
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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
7	Other	none	none	none	none

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	none	none	none	Novartis, Leo Pharma, Pierre-Fabre, Samdoz, Merck-Serono
2	Consultancy	none	none	none	AbbVie, Biogenetica International Laboratories, Toray Corporation
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

7	Payment for manuscript preparation	none	none	none	Sunpharm, Nordic Pharma
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**	none	none	none	Astellas
13	Other (err on the side of full disclosure)	none	none	none	none

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	none	none	Advisory Board Member of ImmunoQure Ltd, Germany	none

The Work Under Consideration for Publication					
		Beatrix Volc-Platzer	**Aysche Landmann**	**Andreas Dreher**	
1	Grant	none	EADV	none	
2	Consulting fee or honorarium	none		none	
3	Support for travel to meetings for the study or other purposes	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	
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	

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	none	none	none	
2	Consultancy	Novartis	none	none	
3	Employment	none	none	none	
4	Expert testimony	none	none	none	
5	Grants/grants pending	none	none	Research grant for MD by Horst-Görtz-Stiftung (clinic for urology/Goethe University Frankfurt)	
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	
12	Travel/accommodations/meeting expenses unrelated to activities listed**	CLB Behring	none	none	
13	Other (err on the side of full disclosure)	none	none	none	

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	none	none	none	