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Current concepts and future approaches in the treatment of cutaneous lupus erythematosus: a comprehensive review

Running heading: Treatment of cutaneous lupus erythematosus

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Abstract: Standard treatment of cutaneous lupus erythematosus (CLE) includes preventive measures such as smoking cessation and photoprotection associated with topical therapies and antimalarial agents, which are recommended as first-line systemic treatment. In more severe disease, alternative therapeutic options include immunosuppressive and immunomodulatory drugs. Recently, the development of specific tools to assess CLE activity and the publication of European CLE guidelines have improved the management of CLE. Moreover, several biologic agents are currently studied specifically in CLE or in systemic lupus erythematosus with assessment of skin involvement and may be promising therapies. However, improvement of the management of CLE remains a major unmet need. In this review, we summarize current concepts in the management of CLE as well as future approaches for more targeted treatments.

Key points:

- Some targeted agents that have shown some promise in skin manifestations with systemic lupus erythematosus.
- Future studies are needed specifically for cutaneous lupus erythematosus (CLE), with responses for each of the CLE subtypes reported separately.

1. Introduction

1.1 Cutaneous lupus erythematosus (CLE) subtype classification

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of auto-antibodies to nuclear antigens and a broad spectrum of clinical manifestations, including specific cutaneous findings in 75% to 80% of patients[1]. Cutaneous lupus erythematosus (CLE) may be associated with SLE or present as a separate entity with isolated cutaneous manifestations. Currently, we have no uniform definition of cutaneous CLE, and different grouping schemes have been discussed on the basis of clinical findings, duration of lesions, pathological findings, direct immunofluorescence results and immunological laboratory abnormalities[2,3]. CLE is generally subdivided into different subtypes including acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE)[4]. CCLE includes discoid CLE (DLE), chilblain lupus, lupus panniculitis and lupus tumidus (LET). Some groups suggest classifying LET as a separate entity of CLE, namely intermittent CLE subtype (ICLE), because of its better course and prognosis [3,5].

1.2 Epidemiology

The incidence of CLE ranges from 2.59 to 4.3 cases per 100,000 persons per year[6–8] and is globally similar to that of SLE ranging from 3.32 to 9.11 cases per 100,000 persons per year[9]. Considering the epidemiology of CLE subtypes, a large population-based cohort of 1088 patients in Sweden found that the most common subset was DLE (80%), followed by SCLE (15.7%) and other subtypes[8]. However, a study of 1002 CLE patients of the European Society of Cutaneous Lupus Erythematosus (EUSCLE) cohort reported a prevalence of CCLE of 47%, followed by SCLE (24%), ACLE (22%) and ICLE (7%). In this study, 347 (34.6%) patients presented two or more different CLE subtypes[10]. Recent advances in the pathogenesis of CLE emphasize a multifactorial disease involving genetic susceptibility[11]; environmental factors such as UV exposure, drugs, smoking, radiotherapy[12]; and induction of deregulated innate and adaptive immune responses[13].

1.3 CLE treatment generalities

Standard treatment of CLE includes preventive measures such as smoking cessation and photoprotection associated with topical therapy especially for mild disease. Antimalarials (AMs), including hydroxychloroquine (HCQ), chloroquine (CQ) and quinacrine/mepacrine (QC), are recommended as first-line systemic treatment of CLE. In more severe disease, alternative therapeutic options include immunosuppressive and immunomodulatory drugs.

More recently, several biologic agents have been developed for SLE and may be promising for CLE [14]. Recently, the management of CLE has been improved with the development of European guidelines for CLE treatment[15]. However, improvement in the management of CLE remains a major unmet need. Indeed, most published studies of CLE are of poor-quality randomized studies are difficult to perform in rare diseases. In this review, we summarize current concepts in the management of CLE as well as future approaches for more targeted treatments in CLE.

1.4 Literature search

This review summarizes several systematic reviews and meta-analyses performed by our group using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[16] focusing on AMs[17,18] and thalidomide[19] use in CLE. For other immunosuppressive/immunomodulatory drugs and biological therapies, we searched MEDLINE/PubMed until March 2019 by using the MeSH terms “Lupus Erythematosus, Cutaneous” and “Lupus Erythematosus, Systemic” and reviewed studies assessing cutaneous response in lupus patients with a focus on CLE subtypes when available. For biological therapies, we also searched studies specifically designed for CLE identified in ClinicalTrials.gov.

2. Assessment of CLE activity and damage

The Safety of Estrogens in Lupus Erythematosus National Assessment– Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)[20] and British Isles Lupus Assessment Group (BILAG) scale[21] are currently used to assess activity and response to treatment in SLE patients. These scores include cutaneous components; however, they do not accurately reflect disease severity or cutaneous improvement of CLE. Recently, a quantitative scoring tool, the CLE Disease Area and Severity Index (CLASI), was specifically developed to assess CLE activity and damage[22]. A 4-point or 20% decrease in activity score has been associated with an objective clinical improvement[23]. However, a 50% decrease in activity score is considered an appropriate definition for cutaneous improvement and has been used in several recent phase II trials[24,25]. Moreover, CLASI activity allows for classifying CLE severity: mild (CLASI activity score 0 to 9), moderate (score 10 to 20) and severe (score 21 to 70)[23].

- **The CLE Disease Area and Severity Index (CLASI) is an appropriate tool to assess CLE severity or cutaneous improvement in clinical trials. SELENA-SLEDAI and BILAG skin components should not be used to assess skin improvement.**

3. Preventive non-pharmaceutical measures

3.1 Smoking cessation

A meta-analysis showed an increased risk of developing SLE among smoking patients as compared with non-smokers (pooled odds ratio [OR] 1.56 [95% confidence interval (CI) 1.26-1.95])[26]. Moreover, several studies showed increased CLE activity, cutaneous damage index, and scarring scores in CLE among smokers as compared with non-smokers[27,28]. In a retrospective study of 218 patients, current smokers had higher median CLASI scores than never smokers (9.5 vs 7, $p=0.02$) [29] and were more likely to receive a combination of HCQ and QC, thereby suggesting refractory disease[29]. Also, an interaction between smoking and efficacy of AMs has been suggested. Indeed, a meta-analysis from our group showed that smoking is associated with a 2-fold decrease in the proportion of patients with CLE achieving cutaneous improvement with AMs[17]. Moreover, smoking has been found associated with decreased efficacy among SLE patients receiving belimumab[30].

- **The smoking status of patients with CLE should be assessed systematically and appropriate intervention offered to those who smoke, especially those with refractory CLE.**

3.2 Photoprotection: In a study of 431 CLE patients, 61.7% exhibited positive photoprovocation with ultraviolet (UV) B (or UVA). The frequency of positive photoprovocation varied by CLE subtype, with ICLE and SCLE the most photosensitive (74.8% and 67.5%) [31]. UVB exposure plays a central role in CLE pathogenesis. In mice and human CLE lesions, UVB irradiation has been shown to induce a recruitment of inflammatory cells and production of pro-inflammatory cytokines including interleukin (IL) IL-1 β , IL-6 and tumor necrosis factor alpha (TNF- α) and type I interferon (IFN) [32,33]. UVB irradiation is responsible for apoptosis of keratinocytes[34]. Keratinocytic apoptosis results in the release of endogenous nucleic acids that can induce a type I IFN response in keratinocytes via pathogen recognition receptors[35]. The LE-prone MRL/lpr mouse showed a recruitment of

plasmacytoid dendritic cells (pDCs) and an increase in the type I IFN response after UVB irradiation[36]. pDCs are the main IFN- α producer and are thought to play a central role in SLE pathogenesis[37]. Previous studies showed that pDCs accumulate in CLE lesions and their density correlated well with the number of cells expressing the IFN α/β -inducible protein MxA, which suggests that they produce IFN α locally[38]. However, recent studies suggested that pDCs could not be the only producer of type I IFN in CLE lesions. Indeed, keratinocyte-produced IFN- κ has been found the source of basal type I IFN activity in healthy skin[39]. Moreover, IFN- κ secretion can activate DCs/pDCs and may participate in recruiting pDCs in skin and IFN- α and initiate a deregulated immune response in CLE lesions[39].

All these data support the crucial role of UV exposure in the pathogenesis of CLE lesions and the need for photoprotection in the management of CLE. Photoprotection should include protective clothing and chemical methods. Indeed, a randomized controlled trial (RCT) demonstrated that the application of a broad-spectrum sunscreen (UVB and UVA) with a high protection factor (SPF 60) could prevent UV-induced skin lesions in CLE patients[40]. Moreover, a study showed that applying a broad-spectrum liposomal sunscreen 20 min before combined standardized UVA/UVB irradiation could reduce lesional tissue damage and inhibit the typical IFN-driven inflammatory response in CLE lesions[41]. Also, vitamin D supplementation may be included in photoprotective methods. Indeed, data suggested that patients with CLE show vitamin D deficiency throughout the year [42]. Moreover, an RCT of healthy adults found vitamin D supplementation associated with reduced expression of proinflammatory mediators such as TNF- α and increased skin expression of the anti-inflammatory mediator arginase-1 as well as genes related to skin barrier repair[43]. Finally, a retrospective study showed that treating vitamin D deficiency improved CLASI activity in CLE patients[44].

- **RCTs support the use of photoprotection to prevent UV-induced skin lesions in CLE patients.**
- **Photoprotection should include protective clothing and broad-spectrum sunscreen (UVB and UVA) as well as vitamin D supplementation.**

3.2 Drug-induced cutaneous lupus and drug withdrawal

Drug-induced CLE (DILE) should be suspected with SCLE. Indeed, among a cohort of 90 SCLE patients, 11 (12%) had DILE[45]. Subacute DILE more frequently exhibited widespread cutaneous involvement with malar rash and was more frequently bullous or

erythema multiforme-like as compared with idiopathic SCLE[45]. However, in a recent multicentric study of 232 patients, including 67 (29%) with subacute DILE, the presentation pattern or serology did not differ, except that people with subacute DILE were older than those with idiopathic SCLE[46]. A case-control study of 234 SCLE patients found subacute DILE frequently associated with use of the drugs terbinafine (OR 52.9, 95% CI 6.6-∞), TNF- α inhibitors (OR 8.0, 95% CI 1.6-37.2), antiepileptics (OR 3.4, 95% CI 1.9-5.8) and proton pump inhibitors (OR 2.9, 95% CI 2.0-4.0) [47]. This study showed that subacute DILE is reversible once the drug is discontinued, which indicates the importance of screening patients with SCLE for potentially triggering drugs[47].

- **Drug-induced CLE (DILE) should be suspected particularly with SCLE.**
- **Treatment discontinuation leads to resolution of DILE lesions in most cases.**

4. Topical treatments

Recent European guidelines for CLE treatments recommended topical therapy as first-line treatment for localized CLE and/or mild disease[15]. Topical treatments mostly include topical corticosteroids and calcineurin inhibitors.

4.1 Topical corticosteroids

Potent topical corticosteroids are more effective than less potent ones in treating DLE lesions. Indeed, in an RCT enrolling 37 DLE patients, 0.05% fluocinonide (a potent corticosteroid cream) conferred a better cutaneous improvement at 6 weeks as compared with 1% hydrocortisone (a low-potency corticosteroid cream)[48]. Because of cutaneous side effects, including atrophy, telangiectasia, and steroid-induced rosacea-like dermatitis, it is recommended that treatment with topical corticosteroids be intermittent and not exceed a treatment duration of a few weeks[15]. However, for scarring alopecia of DLE, prolonged use may be necessary to achieve satisfactory results.

4.2 Intralesional corticosteroids

Intralesional corticosteroids have been used only in retrospective case series. Intralesional therapy showed interesting results particularly for hyperkeratotic DLE lesions, which are often unresponsive to topical treatments[49]. Injections of triamcinolone acetonide suspension 2.5 to 10 mg/ml (depending on the site) may be repeated at 4- to 6-week intervals, and some

authors suggested that this may be useful in preventing further hair loss in DLE lesions of the scalp[50].

4.3 Topical calcineurin inhibitors

Topical calcineurin inhibitors represent a good alternative to topical corticosteroids. Indeed, an RCT found similar efficacy between pimecrolimus 1% cream and betamethasone valerate 0.1% cream in treating facial DLE lesions[51]. Moreover, in an RCT, both twice-daily 0.1% topical tacrolimus and once-daily 0.05% clobetasol propionate conferred significant improvement in DLE lesions. Better improvement was observed with 0.05% clobetasol propionate in this study but with a higher rate of cutaneous adverse events[52]. In another RCT, CLE patients receiving tacrolimus 0.1% ointment showed significant improvement of skin lesions after 28 and 56 days but not after 84 days as compared with skin lesions treated with vehicle, which suggests transient efficacy or short-term adherence. In this trial, patients with LET had the most improvement[53]. Furthermore, in a case series of 3 patients, topical tacrolimus lotion, 0.3%, in an alcohol base demonstrated improvement in lesion severity and hair regrowth after 3 months for treating AM-refractory scarring alopecia in DLE patients[54].

4.4 Other topical treatments

Among other topical agents that may be used in CLE, 0.5% R-salbutamol, a β_2 -adrenergic receptor agonist, showed promising results in a double-blind, phase II RCT of 37 DLE patients[55]. However, topical R-salbutamol is not currently commercially available. Topical retinoids have been found effective in CLE lesions in a few case reports [56,57]. Recently, a case report suggested that topical clindamycin may be a potential treatment for refractory CLE lesions[58].

- **RCTs support the use of topical corticosteroids and topical calcineurin inhibitors for treating CLE lesions.**
- **Because of cutaneous side effects, the use of topical corticosteroids should not exceed a treatment duration of few weeks except for use in scalp DLE lesions.**

5. Systemic treatments

5.1 Antimalarials

5.1.1 Antimalarial efficacy in CLE

AMs including HCQ, CQ and QC are recommended as first-line systemic treatment for CLE[15]. In 1965, a randomized placebo-controlled trial suggested the efficacy of HCQ in chronic CLE[59]. More recently, in a randomized placebo-controlled trial of 103 Japanese CLE patients, the mean CLASI activity score at week 16 did not significantly differ between HCQ and placebo treatment. However, the investigator's global assessment demonstrated a greater proportion of "improved" and "remarkably improved" patients in the HCQ group (51.4% vs 8.7% in the placebo group, $p = 0.0002$)[60]. In a systematic review and meta-analysis, among 1990 courses of treatment with AMs from 31 included studies, the overall response to AMs was 63% (95% CI 55-70). The response to AMs differed between CLE subtypes, ranging from 31% (95% CI 20-44) for chilblain lupus to 91% (95% CI 87-93) for acute CLE[18]. In this study, HCQ had higher overall efficacy than CQ but not significantly (OR 1.48, 95% CI 0.98-2.23).

HCQ is usually prescribed as a first-line AM agent because of its better safety profile as compared with chloroquine. Indeed, in a meta-analysis, the prevalence of retinopathy was 2.5% with CQ versus 0.1% with HCQ[61]. Moreover, in a recent study of 534 patients, the risk of retinopathy was higher with CQ than HCQ (hazard ratio 30.35 [95% CI 1.50-613.30])[62].

5.1.2 HCQ blood concentration measurement

Measuring HCQ blood concentration is recommended with persistent CLE activity. Indeed, a very low blood concentration of HCQ < 200 ng/ml is a good marker of poor adherence and may be useful to discriminate between failure of HCQ and non-adherence [63]. Moreover, a threshold of 750 ng/ml is associated with cutaneous response in CLE patients receiving HCQ[64]. In a prospective study, 26/32 (81%) CLE patients showed a significant decrease in CLASI activity after increasing HCQ doses to reach blood concentrations > 750 ng/ml. In all, 50% of responders achieved a decrease in HCQ doses without further CLE flare (median follow-up 15.8 months [range 3.06-77.4]) [65].

5.1.3 Switch of AM agent or addition of QC

In a retrospective study of 63 patients, in case of inefficacy of a first AM agent, 56% of responders had a switch to another agent (CQ > HCQ or HCQ > CQ) at 3 months. However, the median duration before failure of the second AM agent was 9 months (95% CI 6-24). For patients with a switch because of adverse events, the second AM agent was well tolerated in 69% of cases[66]. In case of failure of HCQ or CQ, the addition of QC is useful in about two thirds of patients[18] and is recommended in European CLE guidelines[15]. QC has recently been shown to inhibit both IFN- α and TNF- α , whereas HCQ inhibited only IFN- α , which may explain the synergic association of both molecules[67]. However, QC is not available in most European countries because of reports of aplastic anemia. Of note, in the study of Mittal et al., no severe anemia or retinopathy was observed with QC[62].

5.1.4 Dosage of HCQ and CQ and risk of retinopathy

The dosage of HCQ and CQ is an important parameter in reducing the risk of retinopathy. Initially, daily doses of HCQ \leq 6.5 mg/kg and CQ \leq 4mg/kg ideal body weight were the highest advocated by the American Academy of Ophthalmology in 2002. Later, the risk of toxicity was found to increase sharply after 5 to 7 years, or a cumulative dose of 1000 g and a dose of 400 mg/day HCQ and 250 mg/day CQ were considered acceptable by the 2011 revised recommendations of the American Academy of Ophthalmology [68]. Finally, in a large series of 2361 patients, real body weight predicted risk of retinopathy better than ideal body weight. In this study, daily doses delivered by pharmacists (not prescribed dose) \geq 5 mg/kg real body weight for HCQ were associated with increased risk of retinopathy[69] and were used in the latest revisions of the recommendations on screening for CQ and HCQ retinopathy[70].

- **RCTs support the use of AMs (mostly HCQ) as a first-line systemic agent for CLE.**
- **HCQ blood concentration measurement is useful to discriminate between failure of HCQ and non-adherence and a threshold of 750 ng/ml is associated with cutaneous response.**
- **With failure of a first AM agent, a switch to another agent or the addition of QC may be useful.**

5.2 Systemic corticosteroids

Systemic corticosteroids remain the mainstay of SLE treatment and have led to improved survival among high-risk patients[71]. Systemic corticosteroids 0.5 to 1 mg/kg are recommended as first-line treatment in addition to AMs in severe or widespread active CLE lesions by European CLE guidelines. Systemic corticosteroids should be used for 2 to 4 weeks followed by a tapering of the dose to a minimum (≤ 7.5 mg/day) with the aim of discontinuing the treatment[15]. These recommendations are based on the results of the EUSCLE study showing 94.3% of 413 CLE patients with cutaneous improvement[72]. However, in this study, response was obtained by a questionnaire and therefore results should be interpreted with caution[72]. Moreover, the use of systemic corticosteroids is associated with significant side effects, including infections, hypertension, hyperglycemia, osteoporosis, avascular necrosis, myopathy, cataracts, and glaucoma in lupus patients[73,74].

- **In the absence of associated SLE, the benefit–risk balance of the use of systemic corticosteroids in CLE remains uncertain and long-term use should be strictly avoided.**

5.3 Methotrexate

5.3.1 Methotrexate efficacy in CLE

Methotrexate is an antimetabolite agent, inhibiting the enzyme dihydrofolate reductase. Dihydrofolate reduces folic acid to tetrahydrofolic acid, which plays an important role in the synthesis of purine nucleotides and thymidylate. Mechanisms of action are thought to relate to antagonism of folate-dependent processes, stimulation of adenosine signalling, inhibition of methyl-donor production, generation of reactive oxygen species, downregulation of adhesion-molecule expression, and modification of cytokine profiles[75]. Indeed, methotrexate induces apoptosis of inflammatory cells[76]. It also reduces levels of inflammatory cytokines, particularly IL-1, IL-6 and TNF- α . It increases IL-10 and IL-4 levels, which promotes T-helper 2 (Th2) cytokine effects that may be protective against autoimmune manifestations[77]. Methotrexate is recommended as the preferred second-line agent by the European CLE guidelines[15]. In a small RCT, results were similar for 10 mg methotrexate weekly and 150 mg/day CQ for skin manifestations in SLE [78]. Moreover, in a retrospective study of 12 CLE patients who were refractory to AMs and/or low-dose oral glucocorticosteroids, 10 showed cutaneous improvement, including 6 with complete response with methotrexate 10 to 25 mg weekly[79]. In a retrospective study of 43 CLE

patients receiving methotrexate 15 to 25 mg per week, 98%, particularly DLE and SCLE patients, showed improvement of cutaneous lesions [80]. In the large retrospective EUSCLE study, the response rate to methotrexate was 50% for ICLE, 57.1% for DLE, 68.8% for SCLE and 72.7% for ACLE[72]. However, again, in this study, cutaneous response was obtained by a questionnaire and thus results should be interpreted with caution[72].

5.3.2 Methotrexate safety profile

The safety profile of methotrexate is favorable. Methotrexate is teratogenic, and adequate contraception should be used. The most common adverse events include nausea/vomiting, elevated transaminase levels, mucosal ulcerations, leucopenia, thrombocytopenia and infectious events. In a recent meta-analysis including 68 trials and 6938 participants receiving methotrexate ≤ 30 mg/week for any condition, the risk of serious adverse events or death was not increased with low-dose methotrexate as compared with placebo[81]. The concomitant prescription of folic/folinic acid is recommended to reduce adverse events, particularly nausea and vomiting. Moreover, methotrexate prescribed subcutaneously or by intramuscular injection has been found associated with reduced risk of abdominal pain as compared with oral prescription[81].

- **A small RCT of SLE with a focus on skin involvement and observational studies support the use of methotrexate as a second-line agent in CLE.**
- **The safety profile of methotrexate is favorable and the concomitant prescription of folic/folinic acid is recommended to reduce adverse events.**

5.4 Retinoids

Retinoids, vitamin-A derivatives, have been used in CLE or refractory cutaneous manifestation in SLE. European CLE guidelines recommended retinoids as second-line systemic treatment associated with AMs, particularly for hypertrophic CLE lesions[15]. In a double-blind RCT, acitretin 50 mg/day showed similar efficacy as HCQ 400 mg/day at 8 weeks, with marked improvement or clearing of CLE lesions in 50% of patients receiving HCQ and 46% using acitretin. However, tolerance was better for patients receiving HCQ[82]. Other retinoids, isotretinoin and alitretinoin, have shown efficacy in CLE in small case series[83]. All retinoids are teratogenic; therefore, effective contraception is essential during and after treatment (isotretinoin: 1 month; acitretin: 3 years). Thus, acitretin should not be used in females of childbearing potential because of the longer half-life. The most common side

effects of retinoids include skin and mucous membrane dryness, gastrointestinal disturbance, muscle pain and arthralgia. Psychiatric disorders such as depression and suicidal ideation have been reported in patients during and after isotretinoin therapy. However, data for patients receiving isotretinoin for acne are reassuring[84].

- **An RCT supported the use of acitretin as a second-line systemic agent in CLE.**
- **Small case series suggested that isotretinoin or alitretinoin may be potential alternatives.**

5.5 Dapsone

Dapsone has both antimicrobial/antiprotozoal properties and anti-inflammatory effects. Particularly, it has been shown to block neutrophil chemotaxis and suppress neutrophil-mediated auto-oxidative tissue injury[85]. Dapsone is recommended as a second-line agent for CLE by European CLE guidelines. Of note, dapsone is the only second-line agent recommended during pregnancy or breastfeeding[15]. From the results of retrospective studies, dapsone may be more efficacious in SCLE than DLE. Indeed, in a retrospective study of 34 CLE patients, response (improvement) was 75% for SCLE and 60% for DLE patients[86]. Moreover, in a retrospective study of 33 DLE patients, excellent results were observed in only 8 (24%) [87]. Furthermore, dapsone may be discussed as a first-line agent in neutrophilic bullous lupus. Indeed, a recent literature review of 128 published cases found a response of 90%[88]. A low starting dose of 50 mg/day is recommended, then the dose could be increased to usually about 100 to 150 mg/day (maximum 400 mg/day or 2 mg/day/kg in children)[89]. Before starting dapsone, laboratory tests should include G6PD activity, complete blood count including reticulocyte count, methemoglobin level, liver and renal function. During follow-up, some authors recommended only complete blood count with reticulocytes[89], but others suggest assessing liver and renal function as well as haptoglobin every 2 weeks for 3 months and then every 3 months[15,85]. Methemoglobin level should be monitored between 8 to 14 days after treatment initiation and may be useful later to determine adherence[85,89]. Then, checking methemoglobin levels is unnecessary in the absence of symptoms. The main adverse effects are hemolysis and methemoglobinemia. Others include a mononucleosis-like hypersensitivity syndrome, occurring usually during the first month of treatment; neuropathy; and agranulocytosis[86].

- **Dapsone may be considered a first-line systemic agent in neutrophilic bullous lupus.**
- **Several observational studies suggest the use of dapsone as second-line systemic treatment for CLE.**

5.6 Thalidomide

Thalidomide (alpha-N-phthalimido-glutarimide) was originally introduced as a non-barbiturate hypnotic but was withdrawn from the market in 1961 because of teratogenic effects. Thalidomide has immunosuppressive and anti-angiogenic activity. It inhibits the release of TNF- α from monocytes and modulates the action of other cytokines. Moreover, thalidomide has photoprotective properties and can inhibit UVB-induced keratinocyte apoptosis[90]. In 1983, Knop et al. reported a series of 60 DLE patients receiving high-dose thalidomide 400 mg/day; complete response or marked improvement was noted in 90% of patients[91]. Thereafter, other case series found similar results with a lower dose of 100 or 50 mg/day thalidomide[92]. In a recent systematic review from our group, among 548 patients from 21 included studies, the overall response to thalidomide was 90% (95% CI 85-94), with similar response rates between CLE subtypes[19]. Moreover, the clinical benefits need to be balanced against potential adverse events such as high teratogenicity, peripheral neuropathy[93,94] (which is sometimes only partially reversible after treatment cessation[95]) and thromboembolic events. Indeed, in our meta-analysis, the pooled rate of thalidomide withdrawal related to adverse events was 24% (95% CI 14-35), including confirmed peripheral neuropathy in 16% (95% CI 9-25) and thromboembolic events in 2% (95% CI 1-3). The efficacy of thalidomide is only suppressive with a rate of relapse of 71% (95% CI 65-77) after thalidomide withdrawal. Therefore, a minimal maintenance dose should be used to avoid relapse. Of note, a prospective study showed no peripheral neuropathy with daily doses ≤ 25 mg per day, which supports the use of a minimal maintenance dose[96]. Considering the occurrence of thromboembolic events, in a retrospective study of 139 CLE patients receiving thalidomide, the risk of overall thrombosis was 2.74 for 100 patient-years, whereas the risk of arterial thrombosis was 1.72 and that of venous thrombosis was 1.03 for 100 patient-years[97]. The risk of all thromboembolic events was higher for patients with a history of previous arterial thrombosis and those with hypercholesterolemia. Conversely, the risk was lower with a starting dose of thalidomide of 50 mg/day as compared with 100 mg/day and with HCQ associated with thalidomide. The risk of thromboembolic events did not

significantly differ according to antiphospholipid syndrome or significant antiphospholipid antibody (aPL) titers[97]. Therefore, the benefit–risk balance should be carefully examined before prescribing thalidomide in patients with high cardiovascular risk. Overall, thalidomide is recommended as a third-line agent in European CLE guidelines[15]. Since 2015, thalidomide has received a temporary recommendation for use in France for CLE patients. In our opinion, thalidomide should be used as a second-line agent for severe, refractory CLE with high scarring risk. We suggest a starting dose of 50 mg/day thalidomide associated with HCQ because it has similar efficacy and reduced adverse events rate as compared with \geq 100 mg/day [19,97]. In France, given the high teratogenicity rate, adequate contraception for at least 4 weeks before and until 4 weeks after completion is mandatory, and plasma beta human chorionic gonadotropin level should be measured monthly under treatment[98]. In the United States, sexually active females of childbearing potential must use two methods of birth control before, during and after treatment[99]. The usefulness of a systematic prescription of low-dose aspirin to reduce thromboembolic events in CLE treated with thalidomide has not been proven but should be advised, at least in patients with substantial aPL titers[100,101].

- **A recent systematic review and meta-analysis of 548 patients found that the response to thalidomide was 90% (95% CI 85-94), with similar response rates between CLE subtypes.**
- **However, the rate of thalidomide withdrawal related to adverse events was 24% (95% CI 14-35), which limits thalidomide prescription to refractory CLE with high scarring risk.**
- **The efficacy of thalidomide is only suppressive, and a minimal maintenance dose should be used to avoid relapse.**
- **The benefit–risk balance should be carefully examined before prescribing thalidomide in patients with high cardiovascular risk because of increased risk of thromboembolic events.**

5.7 Lenalidomide

Lenalidomide is a 4-amino-glutamyl analogue of thalidomide. The drug has immunomodulatory, antiangiogenic and anti-inflammatory properties by inhibiting the secretion of the pro-inflammatory cytokines such as TNF- α , IL-1, IL-6, and IL-12 by monocytes. Lenalidomide immunomodulatory effects have been found 100 to 2,000 times more potent than those of thalidomide, in particular for inhibiting TNF- α [102]. In a

prospective, open-label study of 5 patients, 4/5 patients showed significant improvement in CLASI activity score [103]. Of note, clinical response was also associated with increased circulating T regulatory cells (Tregs) and decreased circulating pDCs[103]. However, one patient with isolated CLE had new-onset proteinuria after 20 weeks of treatment and therefore the authors suggested that lenalidomide may trigger systemic disease in CLE patients[103]. However, in a prospective phase II study of 15 patients, lenalidomide did not affect double-stranded DNA (dsDNA) antibody titers and complement levels of SLE patients receiving lenalidomide, and no SLE flare was observed[104]. In this study, 12 patients showed complete response defined by CLASI activity score = 0 after 6 weeks, but a relapse rate of 75% was observed after lenalidomide withdrawal. In a retrospective study of 16 CLE patients receiving lenalidomide, including 14 who previously received thalidomide, 88% of patients were responders with a starting dose of 5 mg/day with no cases of new or worsening peripheral neuropathy [105]. No relapse was observed after the dose was tapered to reach a minimum effective dose. In this study, two patients with previous SLE experienced SLE flare according to SLEDAI criteria, after 36 and 26 months of lenalidomide treatment. No patient without initial SLE showed SLE flare. Overall, in our opinion, lenalidomide is currently one of the best therapeutic options for severe refractory CLE. However, it is approved for only haematological diseases and should be prescribed only for very severe diseases because of its high cost. No peripheral neuropathy has been reported with low-dose lenalidomide in CLE patients. Lenalidomide should be started at a dose of 5 mg/day. The co-prescription of low-dose aspirin and the continuation of HCQ should be discussed regarding the risk of thromboembolic events[105]. As for thalidomide, the efficacy of lenalidomide is only suppressive and the dose should be tapered to reach a minimum effective dose. Also, as for thalidomide, adequate contraception is required for at least 4 weeks before and until 4 weeks after completion of treatment.

- **Some observational studies suggested that lenalidomide may be a promising alternative treatment for severe refractory CLE.**
- **The high cost and the tolerance profile limit the prescription of lenalidomide in CLE.**

5.8 Iberdomide

Recently, thalidomide and its analogues were found to induce the degradation of the zinc finger transcription factors Ikaros (*IKZF1*) and Aiolos (*IKZF3*). *IKZF1* and *IKZF3* are

susceptibility loci for SLE and play a role in B-cell, T-cell and monocyte regulation[106,107]. *IKZF1* and *IKZF3* mRNA levels were increased in SLE patients as compared with healthy volunteers. Recently, CC-220 (iberdomide), a cereblon modulator targeting Ikaros and Aiolos, has been developed and may be a promising therapeutic option in CLE and SLE[108].

- **Targeting Ikaros (IKZF1) and Aiolos (IKZF3) may be a promising therapeutic strategy in CLE.**

5.9 Mycophenolate mofetil (MMF) and mycophenolic acid (MPA)

MPA was first discovered in 1913 and first used clinically in the 1970s as an immunosuppressant to prevent organ transplantation rejection. Several RCTs have established the efficacy of MMF for induction treatment[109,110] and maintenance regimen[111] for lupus nephritis. MMF and MPA are recommended as third-line treatment in refractory CLE patients by European CLE guidelines. Indeed, in a retrospective study of 24 CLE patients refractory to AMs, every patient experienced at least partial response to MMF, including 9 (37%) with complete response[112]. Moreover, in the EUSCLE study, 47/52 (90%) CLE patients receiving MMF showed clinical improvement[72]. Adverse events including gastrointestinal, cytopenic, hepatotoxic and hypersensitivity reactions are usually mild and mainly dose-dependent. Monthly laboratory monitoring is mandatory for hematological, hepatic and renal toxicities[15]. MMF and MPA are teratogenic, and adequate contraception should be used. Considering MPA, in a prospective, open-label study of 10 SCLE patients refractory to AMs, MPA 1440 mg daily was given for a total of 3 months and resulted in cutaneous improvement in 9/10 patients[113].

- **Some observational studies suggest the use of MMF and MPA for severe refractory CLE.**

5.10 Azathioprine

Azathioprine is a derivative of 6-mercaptopurine that acts as an antimetabolite agent by affecting purine nucleotide synthesis and metabolism. Data on CLE are scarce. In a retrospective study of 6 CLE patients, 3 showed an excellent response to azathioprine[114]. Moreover, in the EUSCLE study, the response to azathioprine was 29/40 (72%) for ACLE, 10/12 (83%) for SCLE and 8/15 (53%) for DLE[72]. The use of azathioprine is not

recommended by European CLE guidelines[15] in the absence of associated SLE¹⁵. Of note, azathioprine is considered to have an acceptable benefit–risk profile in controlling SLE activity during pregnancy[115].

- **Data regarding the use of azathioprine in CLE are scarce.**
- **Azathioprine has an acceptable benefit–risk profile in controlling SLE activity during pregnancy and could therefore be used to treat active CLE lesions associated with SLE during pregnancy.**

5.11 Intravenous immunoglobulin (IVIg)

IVIg is a therapeutic preparation of human polyspecific IgG derived from the plasma of healthy donors. IVIg was initially used, in the early 1980s, as replacement therapy in patients with primary or secondary immunodeficiencies. To date, three case series assessing the efficacy of IVIg involving ≥ 5 CLE patients have been reported. In a case series of 5 DLE patients, 3 showed significant improvement with IVIg 1g/kg/day for 2 days monthly[116]. Moreover, in a retrospective study of 12 patients, 5 showed complete response and 3 partial response with IVIg 1g/kg/day for 2 days followed by 400 mg/kg/day for a maximum of 6 months[117]. Finally, in a case series of 16 CLE patients, 5 (31%) showed significantly improved CLASI activity with IVIg 500 mg/kg/day for 4 days monthly for 3 months[118].

- **Data on the efficacy of IVIg are limited. Given its high cost, we do not suggest the use of IVIg in CLE.**

5.12 Pulsed dye laser (PDL)

PDL has a wavelength of 585 nm or 595 nm, which corresponds to one of the oxyhaemoglobin absorption peaks. This causes selective thermal damage to dermal microvessels, which play an important role in the pathogenesis of CLE. PDL was used in a prospective study of 10 patients with lupus tumidus, with an overall response of 90% without flare of CLE lesions after treatment[119]. Moreover, in a prospective study of 12 DLE patients with mild disease (baseline CLASI activity score 3-5), baseline CLASI activity significantly decreased after PDL, from a mean (SEM) of 4.4 ± 0.2 to 1.3 ± 0.3 after follow-up ($p < 0.001$)[120]. However, in a recent RCT involving 48 lesions in 9 DLE patients, no difference was seen in CLASI improvement with PDL as compared with the control[121].

- **Some observational studies suggested the use of PDL in CLE, but a recent RCT failed to demonstrate clinical efficacy.**

5.13 Extracorporeal photopheresis (ECP)

ECP is a leukapheresis-based therapy that uses 8-methoxypsoralen and UVA irradiation. ECP is frequently used for mycosis fungoides/Sézary syndrome[122] and graft-versus host disease[123]. Some case reports or small case series suggested that ECP may be a therapeutic alternative for refractory CLE [124,125], but data are limited.

- **Data regarding the use of ECP in CLE are limited and further studies are needed to determine its potential interest.**

6. Targeted therapies

Improvement in the comprehension of the pathogenesis of SLE and CLE has led to the development of several targeted treatments. Most targeted therapies have been developed for SLE, but recently CLASI has been used in SLE studies to assess cutaneous improvement as secondary outcomes, which has allowed for insights into the potential effect on CLE. Recently, a recent systematic review of targeted therapies under clinical development in SLE [126] in 17 main online registries of clinical trials identified 74 targeted therapies for SLE among 1140 trials. Treatment strategies under current clinical development for SLE target B cells or plasma cells (n=17), inflammatory cytokines or chemokines and their receptors (n=17), intracellular signalling pathways (n=10), T/B-cell co-stimulation molecules (n=8), IFNs (n=7), pDCs (n=3), and other targets (n=12). Some targeted therapies are being developed specifically for CLE (**Table 2**). Among available targeted therapies or those currently under development, we detail below the drugs with available data for CLE.

6.1 Targeting B cells

6.1.1 Rituximab

Rituximab is a chimeric monoclonal antibody (mAb) against the protein CD20. CD20 is expressed from early pre-B cells to those later in differentiation, but it is absent on terminally differentiated plasma cells. The Fc portion of rituximab mediates antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, inducing apoptosis of CD20⁺ cells. Rituximab has been investigated in two phase III RCTs of SLE, LUNAR¹¹³ and EXPLORER, that did not meet their primary endpoint [128]. However, the off-label use of rituximab is

recommended by international consensus for severe kidney disease, central nervous system involvement or severe autoimmune thrombocytopenia[129]. Considering CLE, some data suggested that rituximab might benefit mostly ACLE patients. Indeed, in a retrospective study of 26 SLE patients with CLE lesions treated with rituximab, only 9 were responders, including those with ACLE (6/14) and SCLE (1/2) but not CCLE (0/8)[130]. Moreover, in a recent retrospective study of 50 SLE patients with CLE, 76% showed cutaneous improvement after 6 months of rituximab, but complete response was observed in only 2/6 (33%) with SCLE and 5/12 (42%) with CCLE [131].

- **Data regarding the use of rituximab in CLE are limited.**
- **Observational studies suggested that rituximab may benefit mostly ACLE patients versus SCLE and CCLE patients.**

6.1.2 Belimumab

Belimumab is a fully humanized mAb against B lymphocyte stimulator (BLyS) also called B-cell-activation factor (BAFF) that belongs to the TNF family. Administration of belimumab leads to depletion of naive, activated and plasmacytoid CD20⁺ B cells, and a reduction in anti-dsDNA titers. Belimumab demonstrated efficacy versus placebo in reducing SLE disease activity and the time to lupus flares in addition to standard care in two phase III RCTs (BLISS-52 and BLISS-76 [132,133]). It is currently the only biological therapy approved by the US Food and Drug Administration and European Medicines Agency for SLE. Recently, Wenzel et al. showed high expression of BAFF, BAFF receptor and B-cell maturation antigen (BCMA) on immunohistochemistry of CLE lesions, which suggested a potential interest of belimumab in CLE[134]. Data regarding the efficacy of belimumab of CLE are scarce. Indeed, most SLE patients included in the phase III clinical trials[132,133] had skin involvement; however improvement was assessed by the BILAG or SLEDAI and therefore no conclusion can be drawn. In a retrospective study of 67 patients including 19 with CLE involvement, median CLASI activity score was decreased from 5 (range 1-14) to 0.5 (0-6) at 24 months[135].

- **Belimumab is currently the only biological therapy approved by the US Food and Drug Administration and European Medicines Agency for SLE.**

- **Although most SLE patients included in phase III trials had skin involvement, specific assessment of CLE improvement using the CLASI is limited and no conclusions can be drawn.**

6.2 Targeting IFN and pDCs

6.2.1 Sifalimumab

Sifalimumab is a fully human IgG1 mAb that neutralizes IFN- α . In a randomised, double blind, placebo-controlled study, the proportion of patients achieving the SRI-4 response index at week 52 was significantly higher in the three treatment groups as compared with placebo. Moreover, among patients with CLASI activity score ≥ 10 at baseline, sifalimumab conferred a significantly greater 4-point decrease as with compared with placebo: 73.1% for 1200 mg versus 48.6% for placebo, $p=0.049$ [136]. However, development of sifalimumab has been stopped by Astra-Zeneca[©].

6.2.2 Anifrolumab

Anifrolumab is a fully human mAb that binds to subunit 1 of the type I IFN receptor, blocking the activity of all type I IFNs. In a phase II, randomized, placebo-controlled study comparing intravenous anifrolumab (300 mg or 1,000 mg) or placebo in addition to standard therapy, anifrolumab showed promising results in several clinical endpoints including SLE Responder Index [4] response at week 24 with sustained reduction of oral corticosteroids[24].

Considering cutaneous involvement, among patients with CLASI activity score ≥ 10 at baseline, a 50% decrease at week 52 was significantly greater in patients receiving anifrolumab (63% for 300 mg and 58.3% for 1000 mg) as compared with placebo (30.8%) ($p=0.013$ and 0.077 , respectively). Of note, in a post-hoc analysis, patients receiving anifrolumab showed significantly improved cutaneous involvement as compared with placebo in the high IFN gene signature subgroup only, which suggests that IFN signature may be a biomarker of response to anifrolumab[137]. Although no results have been published yet, results of TULIP1, the first phase III trial of anifrolumab, failed to demonstrate superiority as compared with placebo[138].

6.2.3 Janus kinase (JAK) inhibitors

Baricitinib is an orally administered selective and reversible inhibitor of JAK1 and JAK2, which inhibit type I IFN but also IL-21 and IL-6[139] playing a central role in the

pathogenesis of SLE. In a recent double-blind, placebo-controlled phase II trial, baricitinib at 4 mg but not 2 mg (in addition to standard treatment) significantly improved the symptoms of active SLE[140]. However, baricitinib and placebo did not differ in CLASI activity score decrease at week 24: mean decrease -1.7 for baricitinib 2 mg, -2.3 for baricitinib 4 mg and -2.8 for placebo[140]. However, familial chilblain lupus associated with three prime repair exonuclease 1 (TREX1) mutation and Aicardi-Goutières syndrome was significantly improved with baricitinib 4 and 2 mg/day, respectively[141,142]. Filgotinib is an oral selective JAK1 inhibitor that has shown promising results in two-phase II studies of active ankylosing spondylitis and psoriatic arthritis with acceptable safety profile[143,144]. A randomized placebo-controlled study is ongoing in CLE patients. Ruxolitinib is an oral JAK1/2 inhibitor originally developed for treating JAK2-mutated primary myelofibrosis[145]. Ruxolitinib 20 mg/day twice daily conferred rapid improvement of chilblain lupus associated with primary myelofibrosis[146]. Moreover, in vitro studies demonstrated that ruxolitinib significantly decreased the production of CLE associated with cytokine (C-X-C motif) ligand 10 (CXCL10), CXCL9, and MxA[147]. Finally, in an RCT, the topical R333 inhibitor of γ c/JAK1/3- dependent cytokines did not significantly improve lesion activity after 4 weeks[148].

6.2.4 Anti-BDCA2

BIIB059 is a humanized IgG1 mAb that specifically recognizes blood DC antigen 2 (BDCA2), which is uniquely expressed on the surface of human pDCs. Recently, in a phase I, randomized, double blind, placebo-controlled clinical trial, anti-BDCA2 showed potential efficacy in SLE patients with active CLE lesions. Among the 8 CLE patients who received BIIB059, with ACLE (n=4), SCLE (n=1), and DLE (n=3), after 4 weeks of one dose of 20 mg/kg, all patients with ACLE (4/4) and SCLE (1/1) but only 1 of 3 with DLE showed a decrease in CLASI activity score ≥ 4 points. Of note, improvement in CLASI activity was statistically correlated with reduced level of type I IFN inducible protein MxA, which suggests that type I IFN expression in skin lesions reflects cutaneous disease activity[149][149]. Further studies are needed to assess whether anti-BDCA2 mAb may be a promising drug in CLE.

6.3 Targeting cytokines and their receptors

6.3.1 Ustekinumab

Ustekinumab is an mAb targeting IL-12 and IL-23 and is approved for treating plaque psoriasis, psoriatic arthritis, and Crohn's disease[150,151]. Recently, in a phase II RCT, ustekinumab in addition to standard of care treatment resulted in better efficacy in clinical and laboratory parameters than placebo in the treatment of SLE. In this study, among patients with a baseline CLASI activity score ≥ 4 , the proportion with at least 50% improvement in CLASI activity score from baseline was 17/32 (53%) with ustekinumab versus 6/17 (35%) with placebo ($p=0.032$)[25]. Moreover, the efficacy of ustekinumab for treating SCLE[152] and DLE[153] has been suggested in some case reports. Results of the phase III study will be important to assess the potential role of ustekinumab in CLE treatment.

6.3.2 Low-dose IL-2

A loss of the healthy balance of activity between effector and regulatory CD4+ T cells is associated with the development of SLE[154]. In mice and humans, IL-2 can enhance Treg cell development and suppress the differentiation of T follicular helper and T helper 17 cells[154,155]. In a recent phase II study of 40 SLE Chinese patients receiving 3 cycles of low-dose IL-2 at a dose of 1 million IU every other day for 2 weeks followed by a 2-week break, an improvement in skin lesions (20/24) and alopecia (13/14) was observed at week 12. Of note, CLASI activity score was not used in this study, and other studies are needed to assess the role of low-dose IL-2 as potential treatment of CLE[156].

7. Conclusions and perspectives

Overall, recent improvements in the management of CLE have included the development and validation of specific tools to assess skin activity (CLASI[22], RCLASI[157]) as well as the publication of European CLE guidelines[15]. However, there are still several unmet needs.

- Most current therapeutic trials are designed for only SLE, with skin assessment as secondary outcomes. For example, belimumab is not approved for isolated CLE. Therefore, future treatments, particularly biological therapies, should include specific trials of isolated patients in their development plan.
- Second, although some recent trials used CLASI to assess skin improvement, this is not always the case. For example, the recent baricitinib phase II studies focused on skin lesions and articular involvement. However, resolution of SLEDAI-2K arthritis or rash were primary outcomes instead of CLASI score [140]. Among dermatologists and rheumatologists who were present at the recent 2018 international CLE meeting, there

was 100% agreement that the CLASI should be used in evaluating the skin in CLE [158]. Moreover, CLE subtypes are never reported. Of note, we and others reported that response to treatment is widely heterogeneous among CLE subtypes[19,159]. Therefore, future trials with a specific design for CLE and a focus on CLE subtypes are needed to improve management of CLE.

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Table 1. Systemic treatments available for cutaneous lupus erythematosus (CLE) with focus on dosage and monitoring of adverse events

First-line treatment		
Drugs	Dosage	Monitoring of adverse events
HCQ	≤ 5 mg/kg/day of real bodyweight* 400 mg/day is acceptable except for extreme low weight	Ophthalmological examination according to the 2016 American Academy of Ophthalmology guidelines[70] Laboratory tests and electrocardiogram are not systematically recommended
CQ	≤ 2.3 mg/kg/day off real body weight** 250 mg/day is acceptable except for extreme low weight	
QC	100 mg/day	Laboratory tests are not systematically recommended
Second-line treatment		
Drugs	Dosage	Monitoring of adverse events
Methotrexate	Usually 15-25 mg/kg/week (0.2-0.3 mg/kg body weight/week) Per os, SC or IM (SC Concomitant prescription of folic acid	Pre-treatment: complete blood count, renal function, liver enzymes, PIIINP, pregnancy test, hepatitis B/C serology During treatment: complete blood count, renal function, liver enzymes, PIIINP
Retinoids	Acitretin 0.2-1.0 mg/kg/day Isotretinoin 0.5-1 mg/kg/day Concomitant prescription of adequate contraception is mandatory	Pre-treatment and during treatment: Pregnancy test, liver enzymes, lipid profile Continue contraception after treatment: (isotretinoin = 1 month; acitretin = 3 years)
Dapsone	Starting dose of 50 mg/day, then usually 100-150 mg/day maximum 400 mg/day or 2 mg/kg/day in children	Pre-treatment: G6PD activity, complete blood count including reticulocyte, methemoglobin level, liver and renal function During treatment: methemoglobin level (D8-14), complete blood count, reticulocyte, +/- liver and renal function, haptoglobin
Third-line treatment		
Drugs	Dosage	Monitoring of adverse events
Thalidomide [†]	We suggest a starting dose of 50 mg/day Increase at 100 mg/day if persistent activity after 1 month After improvement: decrease to reach a minimal effective dose	Pre-treatment and during treatment: Complete blood count, thyroid-stimulating hormone, liver and renal function, pregnancy test

	<ul style="list-style-type: none"> - Concomitant prescription of adequate contraception is mandatory - We suggest concomitant prescription of low-dose aspirin 	Clinical neurological exam +/- electrophysiologic monitoring based on clinical examination
Lenalidomide	<p>We suggest a starting dose of 5 mg/day Increase at 10 mg/day if persistent activity after 3 months After improvement: minimal effective dose</p> <ul style="list-style-type: none"> - Concomitant prescription of adequate contraception is mandatory - We suggest concomitant prescription of low-dose aspirin 	Pre-treatment and during treatment: Complete blood count, thyroid-stimulating hormone, liver and renal function, pregnancy test, electrocardiography
MMF and MPA	<p>MMF: 1000-3000 mg/day MPA: 1440-2160 mg/day</p>	Pre-treatment and during treatment: complete blood count, liver and renal function
Azathioprine	1- 2.5 mg/kg/day usually 100-150 mg/day	<p>Pre-treatment: enzyme thiopurine methyltransferase activity, complete blood count, hormone, liver and renal function</p> <p>During treatment: complete blood count, hormone, liver and renal function, lipase</p>
IVIgs	1 g/kg/day for 2 days	Pre-treatment: complete blood count, liver and renal function, electrocardiogram

HCQ: hydroxychloroquine, CQ: chloroquine, QC: quinacrine, AAO: American Academy of Ophthalmology, PIIINP: N-terminal propeptide of type III Collagen, MMF: mycophenolate mofetil, MPA: mycophenolic acid, IVIGs: intravenous immunoglobulins

* Delivered dose by pharmacists (not prescribed dose) of ≥ 5 mg/kg of real body weight [69] is associated with an increased risk of retinopathy

** by analogy regarding bioequivalence between HCQ and CQ[†] used as second-line agent in France