

# Current Insights Into The Management Of Discoid Lupus Erythematosus

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**Abstract:** Discoid lupus erythematosus is the most disfiguring and common presentation of chronic cutaneous lupus erythematosus. Although most patients will respond to lifestyle measures and topical treatment, a non-negligible number of patients will require systemic and physical therapy, either alone or in combination. We performed a review of the available evidence on the discoid lupus erythematosus treatment. Lifestyle measures and topical treatment (corticosteroids and topical calcineurin inhibitors) remain the therapeutic strategies with the highest evidence level. Within systemic treatment approaches, antimalarial drugs are still the first-line therapy, while other systemic and physical therapies have highly variable evidence. Hence, we propose a therapeutic algorithm based on the strength of recommendations of the different treatment modalities, focusing on the refractory disease.

**Keywords:** discoid lupus erythematosus, cutaneous lupus erythematosus, disease management

## Introduction

Discoid lupus erythematosus (DLE) is the most disfiguring form of cutaneous lupus erythematosus (CLE). Recurrent outbreaks of inflammatory lesions usually affecting photo exposed areas (face, ears) and scalp, lead to a prominent scarring that might have a high impact on the quality of life of the patients. Therefore, early treatment is mandatory to minimize these undesirable consequences. Most patients with DLE will respond to strict photoprotection, smoking cessation and topical treatment (corticosteroids, calcineurin inhibitors). Antimalarial drugs are considered the first-line systemic treatment. Refractory DLE may benefit from other systemic therapies, although data on their effectiveness are limited to small open-label studies, retrospective reviews, case series, and case reports.

## Methodology

We carry out a search in the PubMed, Web of Science and Embase databases that include all articles published before January 2018, in the English and Spanish languages.

In each of the databases we use the appropriate vocabulary to perform the search. We also reviewed some papers included in the bibliography of the previous reviews. The keywords and search methods used for the Pubmed database were as follows:

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Discoid lupus erythematosus  
Intervention OR therapy OR treatment  
#1 AND #2

After conducting the exhaustive search, 324 articles were suggestive of being reviewed. In a first screening we found 27 repeated articles and 54 works whose main objective was not focused on the treatment of DLE. The remaining 243 articles were thoroughly reviewed, of which 150 were suppressed for different reasons. Finally, 95 articles were included to carry out this review.

The strength of recommendation and the level of evidence were established for each therapy (Tables 1–3)

**Table 1** Strength Of Recommendation And Level Of Evidence

Treatment	Strength Of Recommendation	Level Of Evidence
<b>Lifestyles measures</b>		
Photoprotection	A	I++
Smoking cessation	A	I++
<b>Topical treatment</b>		
Topical and intralesional corticosteroids	A	I+
Topical calcineurin inhibitors	A	I+
Topical retinoids	D	3
Tocoretinate	D	3
R-salbutamol	D	I-
<b>Systemic therapies</b>		
Antimalarials	B	2++
Azathioprine	D	3
Systemic retinoids	C	2+
Methotrexate	C	2+
Fumaric acid esters	C	2+
Mycophenolate mofetil	D	3
Thalidomide,	C	2+
Lenalidomide		
Systemic corticosteroids	D	3
Clofazimine	C	I+
<b>Biological therapies</b>		
Apremilast	D	3
Ustekinumab	D	3
Anti-JAK	D	3
<b>Alternative therapies</b>		
Laser	C	2+
Photodynamic therapy	D	3
Intravenous	D	3
Immunoglobulin		

**Table 2** Strength Of Recommendation (NICE, National Institute For Health And Clinical Excellence; RCT, Randomised Controlled Trial)

Class	Evidence
A	At least one meta-analysis, systematic review or RCT rated as I++, and directly applicable to the target of population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as I+, directly applicable to the target of population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target of population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as I++ or I+
C	A body of evidence including studies rated as 2+, directly applicable to the target of population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

according to the NICE (National Institute for Health and Clinical Excellence) guidelines.

### Lifestyles Measures

#### Photoprotection (Strength Of Recommendation A, Level Of Evidence I++)

Ultraviolet exposure is the most important precipitating factor of CLE flares. Daily photoprotection is essential to prevent the appearance of skin lesions, because UVA and UVB are known to cause CLE flares.<sup>1</sup> Basic recommendations for patients include: avoid sunlight during peak day light hours, as well as artificial ultraviolet light used in tanning booths. It is essential to use sunscreen properly. Based on a randomized, controlled, double-blind clinical trial of 25 patients with CLE, it is recommended to apply a sufficient amount of 50 SPF sunscreen (at least 2mg/cm<sup>2</sup> of body surface) 20–30 mins before exposure. Taking these factors into account, the authors of the trial published a total protection against UVA and UVB irradiation.<sup>2</sup> Physical filters are recommended over chemical filters because they cover a broad radiation spectrum. In addition, the risk of vitamin D deficiency must be considered in patients who avoid sun exposure due to DLE. In these cases it is recommended to perform

**Table 3** Level Of Evidence (RCT, Randomized Controlled Trial; A. Studies With A Level Of Evidence “-” Should Not Be Used As A Basis For Making A Recommendation)

Level Of Evidence	Type Of Evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCT with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCT with a very low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCT with a high low risk of bias <sup>A</sup>
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal <sup>A</sup>
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

screening of 25-hydroxyvitamin D, and in cases of deficiency provide supplements of vitamin D3 or cholecalciferol (especially in countries with few sunlight hours).<sup>3</sup>

Recently, a survey on the habits of prophylactic measures in patients with CLE has been published.<sup>4</sup> The results highlight that most of the physicians surveyed provided information about UV danger in CLE patients. They also provided prophylactic advice such as using topical photoprotector or wearing protective clothes. Interestingly, some notable differences were found, such as that physicians from Japan recommended sunscreens less frequently than in the USA or Europe.

### Smoking Cessation (Strength Of Recommendation A, Level Of Evidence 1++)

Smoking is another cause of CLE worsening. Chasset et al conducted a study in patients with DLE and healthy controls.<sup>5</sup> Their results showed a higher rate of smokers in individuals with DLE. Other studies have reported worse quality of life and greater severity of the disease (CLASI index) in smoking patients. There are also concerns about the decrease of antimalarials efficacy.

The former survey reported interesting results regarding smoking. Comparing with advice on sun exposure, smoking was a less discussed topic among physicians and CLE patients.<sup>4</sup> The results showed that almost half of the participant physicians incentivized patients to quit smoking. However, 13.3% recommended it rarely and 2% never mentioned it.

## Topical Treatment

### Topical And Intralesional Corticosteroids (Strength Of Recommendation A, Level Of Evidence 1+)

Topical corticosteroids are often the first step in the treatment of DLE, but they are commonly insufficient in isolation.<sup>6</sup> They exert their effect on both B and T cells, and decrease immunoglobulins and TNF alpha production.<sup>7</sup> In the review of the literature, we have found only one clinical trial that tests its efficacy in CLE. This is a 12-week crossover study with a total of 78 patients in whom healing or very good response was evidenced in 27% of the subjects randomized with fluocinonide 0.05% cream, with respect to 10% of the patients treated with hydrocortisone 1% cream at 6 weeks.<sup>6</sup> These results highlight the convenience of using high-potency topical corticosteroids over medium- or low-potency topical corticosteroids in DLE patients. Most authors recommend the use of high-potency corticosteroids in acute flares, especially in cases of severe disease. It is important to know and warn patients of possible side effects if these drugs are used for long periods of time (skin atrophy, telangiectasia, striae, solar purpura and hypertrichosis). In patients with chronic DLE lesions not resolved with corticosteroids or topical calcineurin inhibitors, treatment with intralesional corticosteroids may be performed.<sup>8</sup>

### Topical Calcineurin Inhibitors (Strength Of Recommendation A, Level Of Evidence 1+)

They are frequently used in thin skin areas such as the facial region, or in skin damaged by chronic treatment with topical corticosteroids. They decrease or block cytokine production by activated T lymphocytes. Currently there are two commercial preparations: pimecrolimus 1% cream and tacrolimus 0.03% or 0.1% ointment. Pothinamthong et al demonstrated good response with the combination of twice-daily tacrolimus 0.1% and once-daily clobetasol 0.05% in the treatment of DLE.<sup>9</sup> Another randomized study in which 14 of 38 patients were diagnosed with DLE, proved better response in those treated with 0.1% tacrolimus ointment twice-daily

for 3 months over patients treated with vehicle.<sup>10</sup> Barikbin et al performed a comparative study (10 patients with DLE) between pimecrolimus 1% cream twice-daily and betamethasone 0.1% cream twice daily for 8 weeks. With both treatments they obtained similar responses improving the clinical severity.<sup>11</sup> In a case series of 3 patients with scarring alopecia caused by DLE, the usefulness of the combination of a 0.3% tacrolimus lotion with oral anti-malarial therapy was demonstrated. In these patients they achieved hair regrowth.<sup>12</sup>

### Topical Retinoids (Strength Of Recommendation D, Level Of Evidence 3)

The mechanism of action of topical retinoids is based on the increase of collagen synthesis and epidermal turnover, as well as the inhibition of melanogenesis and inflammation.<sup>13</sup> There are some clinical cases that have proven the efficacy of tretinoin and tazarotene in the treatment of DLE and hypertrophic lupus erythematosus. Edwards et al reported the complete resolution of facial lesions secondary to DLE in a woman, performing treatment with topical tazarotene 0.05% gel daily at night for several weeks.<sup>14</sup>

### Tocoretinate (Strength Of Recommendation D, Level Of Evidence 3)

Tocoretinate or tretinoin tocopheryl is an alpha-tocopherol ester of all trans-retinoic acid (ATRA or tretinoin). With this combination we achieve the therapeutic effects of retinoids with less skin irritation. A two-case DLE report was published showing successfully treatment with topical tocoretinate. The first patient is a 43-year-old woman with erythematous-desquamative plaques with pigmentary changes and cutaneous atrophy located on the cheeks and ears. Topical tocoretinate twice daily was started. The authors describe improvement of pigmentation in 3 months and improvement of atrophy in 12 months. The second patient is a 37-year-old man with erythematous and erosive plaques on his temple. After 2 weeks of treatment with topical tocoretinate the lesions improved significantly. At 11 months, cutaneous atrophy was much less evident.<sup>15</sup>

### R-Salbutamol (Strength Of Recommendation D, Level Of Evidence 1-)

R-Salbutamol is a beta2-adrenergic receptor agonist; this receptor is present in the outer membrane of several cell types. The binding of R-salbutamol to the receptors produces an inhibition of the inflammatory response that includes cytokines such as interleukin-2 and interferon- $\gamma$ .<sup>16</sup> Jemec et al designed a randomized clinical trial to assess the efficacy

of R-salbutamol in the treatment of DLE. They included 37 patients diagnosed with DLE: 19 were treated with R-salbutamol 0.5% cream twice-daily for 8 weeks, and the rest received placebo. In the R-salbutamol group authors demonstrated overall improvement both in the intensity of the lesions and in the symptoms.<sup>16</sup> However, no subsequent studies have been published, so the treatment recommendation is controversial.

## Systemic Therapies

### Antimalarial Drugs (Strength Of Recommendation B, Level Of Evidence 2++)

Antimalarial drugs were initially used for cutaneous lupus erythematosus (CLE) and later for systemic disease.<sup>17</sup> The mechanism by which they are effective is still controversial. However, the last theories point to a reduction of the lysosomal pH and the chemotaxis/phagocytosis of immune cells, inducing an autoantigen presentation blockage. They also induce anti-inflammatory function, inhibiting cytokines (IL-1, IL-2, INF- $\gamma$ , INF- $\alpha$ ) and antagonizing the prostaglandin effects.<sup>18</sup> Hydroxychloroquine (HCQ) is considered the first line oral treatment for DLE. Wahie et al designed a multicenter retrospective cohort study in 200 patients diagnosed with DLE who received long-term HCQ (more than 6 months).<sup>19</sup> An adequate clinical response based on protocolized retrospective designation of response in medical case notes was achieved in 60% of patients within the first 6 months, which decreased to 45% after this date. 1 out of 5 responders lost their response after a median interval of 2 years, but they often regained disease control with a combination of HCQ and mepacrine. Non-responders within the first systemic frequently underwent oral corticosteroid therapy. Variable outcomes from different HCQ combinations with systemic therapies (immunosuppressive therapies, retinoids) or either phototherapy have been reported. Predictive variables of poor response to HCQ are disseminated disease and systemic involvement.<sup>20</sup> One study evaluated the safety of chloroquine (CQ) and HCQ by describing the adverse reactions (including ocular toxicity) and the reasons for antimalarial suspension in patients with SLE and DLE. Among 504 patients who had received antimalarial therapy (1.4% HCQ, 88.5% CQ, 10.1% both therapies but not concomitantly), less than 20% reported adverse reactions. Withdrawal of therapy was decided in less than 10% of patients in an average duration of 7 years of treatment (both temporary and definitive), whose main cause were ophthalmic effects, followed by skin rashes

and gastrointestinal symptoms. While the latter are considered mild adverse reactions, treatment withdrawal is mandatory when retinal, neuromuscular and cardiological involvement are present.<sup>21–23</sup> Skin reactions include hyperpigmentation, urticaria, pruritus, annular erythema, morbilliform rash, exfoliative dermatitis and xerosis.<sup>24,25</sup> Ocular symptoms do not always correlate with retinal toxicity, which has a low incidence and is more frequent and severe in patients taking CQ.<sup>22</sup> Antimalarial drugs bind to melanin of the macular pigment epithelium, but the mechanism of toxicity is still unclear. The daily dose (> 5 mg/kg and >2,3 mg/kg of HCQ y CQ for ideal weight, respectively), antimalarial treatment during more than 5 years, renal failure, concomitant use with tamoxifen and previous macular damage are major risk factors for developing retinal toxicity. The American Academy of Ophthalmology screening guidelines recommend a baseline evaluation for all patients before initiating antimalarial therapy or within the first year (fundus examination, visual fields and at least one objective test), and then annually after the 5th year of treatment. In high risk-patients (see above), the evaluation should be performed every 6 months.<sup>26</sup> Several studies have shown the safety of antimalarials in pregnancy.<sup>27</sup> The main strategy employed following failure of antimalarial monotherapy is switching to another antimalarial agent. A multicenter retrospective observational study in 64 patients with CLE who underwent antimalarial switching between HCQ and CQ both for inefficacy (48/62) and adverse effects (16/64), revealed that cutaneous improvement was detected in 50% of cases after 3 months, although the response used to be transient. The effectiveness of the switching was better (sustained response) when the first antimalarial agent withdrawal was for adverse effects.<sup>28</sup>

#### **Azathioprine (Strength Of Recommendation D, Level Of Evidence 3)**

Azathioprine (AZT) is a purine synthesis inhibitor with immunosuppressive effect. It has been effective for the treatment of DLE in some case reports.<sup>29–31</sup> However, other case reports exhibited partial or no response.<sup>32</sup> Therefore, the evidence of the use of AZT in DLE is limited. In addition, the possible side effects of treatment should be considered, including myelosuppression and the possibility of developing malignant tumors. The active substance thiopurine methyltransferase (TPMT) must be measured before starting treatment. If there are low levels of TPMT, AZT is contraindicated.<sup>33</sup>

#### **Systemic Retinoids (Strength Of Recommendation C, Level Of Evidence 2+)**

Retinoids act by modifying the function of the epidermal keratinocytes through their binding as ligands to the nuclear transcription factors. In a study the efficacy of isotretinoin was evaluated in 10 patients with CLE (9 with DLE). Patients received 80 mg daily of treatment for 16 weeks. Very good response was obtained in 80% (the other 2 patients lost the follow-up). No serious side effects were reported, except for xerosis.<sup>34</sup> With respect to alitretinoin, Kuhn et al reported therapeutic success in 3 patients with CLE, so it could be a therapy to be considered in DLE, although specific studies are needed.<sup>35</sup> It should be borne in mind that retinoids are teratogenic agents, so the use of contraceptive methods in women of childbearing age is mandatory. In addition, retinoids can alter the liver profile and raise cholesterol and triglycerides, so analytical tests are necessary during treatment.<sup>36,37</sup>

#### **Methotrexate (Strength Of Recommendation C, Level Of Evidence 2+)**

Methotrexate (MTX) is a folic acid antagonist that has been used since the 1960s for systemic lupus erythematosus. Proposed mechanisms for its therapeutic properties in connective tissue diseases include anti-inflammatory effects secondary to increased production of adenosine, inhibitory action on lymphocytes and neutrophils, and suppression of antibody production. Bottomley and Goodfield first described its use in 4 cases of refractory DLE in 1995, with great improvement in two of them.<sup>38</sup> Since then, few studies have been reported about use of MTX in DLE. The most relevant is a retrospective study of 43 patients with refractory CLE, 12 of them with DLE, treated 7,5–25 mg/week methotrexate. A good response in DLE patients, especially in those with localized disease was observed.<sup>39</sup> Even if the well-known side effects (gastrointestinal reactions, elevation of liver enzymes and pancytopenia) require monitoring blood tests, methotrexate is a well-tolerated and safety drug when used at standard doses.

#### **Fumaric Acid Esters (Strength Of Recommendation C, Level Of Evidence 2+)**

Fumaric acid esters (FAEs) inhibit the transcription factor NF- $\kappa$ B activity, as well as the production of proinflammatory cytokines by T lymphocytes. FAEs have been used for years in the treatment of plaque psoriasis. There is published in the literature a clinical trial of 11 patients with recalcitrant DLE (a patient also with SCLE) to evaluate

the effectiveness of FAEs.<sup>40</sup> The results demonstrated that the mean activity of the disease according to RCLASI (Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index) decreased significantly at 24 weeks of treatment. No serious side effects were reported.

### **Mycophenolate Mofetil (Strength Of Recommendation D, Level Of Evidence 3)**

Mycophenolate mofetil (MMF) is a reversible inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme of the biosynthesis of new guanosine triphosphate (GTP) used for B and T lymphocytes proliferation.<sup>41</sup> MMF has shown effectiveness in the treatment of all subtypes of CLE in small case series. Goyal et al reported very good clinical response in 2 patients with DLE and systemic lupus erythematosus who presented palmoplantar lesions resistant to other treatments.<sup>42</sup> In contrast, Pisoni et al administered MMF to 6 patients with therapy-resistant CLE. Five patients did not obtain response and only 1 achieved partial response. Therefore, the authors recommend limiting its use to severe CLE.<sup>43</sup>

### **Lenalinomide And Thalidomide (Strength Of Recommendation C, Level Of Evidence 2+)**

Thalidomide has been used in refractory cutaneous lupus erythematosus due to its effect inhibiting the production of inflammatory cytokines and preventing keratinocyte apoptosis induced by UVB light. Frankel et al treated 5 patients with refractory CLE with low-dose thalidomide (50 mg/d). 80% of patients partially or completely resolved after an average of 5,5 weeks of therapy.<sup>44</sup> These results are similar to previous retrospective studies using classical doses of 100mg/d.<sup>45,46</sup> Low dose was not related with a lower incidence of neuropathy (80% patients), which resolved after drug withdrawal. Although thalidomide is an effective therapy, teratogenic activity and deep venous thrombosis limit its use. It should be noted that patients with DLE have higher recurrence rates after cessation of the drug with respect to other variants of CLE.<sup>47</sup> Lenalinomide, a synthetic analogue of thalidomide with a similar mechanism of action, has proved to be a useful treatment in several studies, including a prospective phase II pivotal study.<sup>48-51</sup> It is usually administered at doses of 5–10 mg/day, with a lower incidence of neuropathy than thalidomide, but similar recurrence rates of DLE lesions.<sup>51</sup> The main adverse effect of lenalinomide are cytopenias, which rarely require treatment withdrawal, while blood test monitoring is mandatory.<sup>48</sup>

### **Systemic Corticosteroids (Strength Of Recommendation D, Level Of Evidence 3)**

Systemic corticosteroids have a limited effect on chronic forms of lupus. They are usually used in the opening phase of treatment, when the lesions have a high inflammatory activity.<sup>52</sup> They can also be used in combination with other immunosuppressants in the induction phase. The usual dose is 0.5 to 1 mg/kg/day orally, with a subsequent decrease after 2 to 4 weeks or 3 g/day in pulses intravenously, as described for SCLE.<sup>52</sup> Its routine use is not recommended due to adverse effects.

### **Clofazimine (Strength Of Recommendation C, Level Of Evidence 1+)**

Clofazimine inhibits mycobacterial growth by binding to DNA. Clofazimine also exerts antiinflammatory properties. Bezerra et al conducted a randomized clinical trial in which 17 patients with CLE (12 with DLE) were treated with chloroquine (250 mg daily) and 16 patients with CLE (14 with DLE) were treated with clofazimine (100 mg daily) added to sunscreen and oral prednisone. At 6 months, 82.4% of the patients in the clofazimine group experienced complete or almost complete resolution of the skin lesions, compared with 75% in the chloroquine group.<sup>53</sup>

## **Biological Therapies**

### **Apremilast (Strength Of Recommendation D, Level Of Evidence 3)**

Apremilast is a phosphodiesterase-4 (PDE4) inhibitor drug. Its main mechanism of action focuses on nulling Th1- and Th17-mediated immune activity. Currently there are numerous studies that support its effectiveness in psoriasis. Considering its mechanism of action could also be effective in other inflammatory diseases such as DLE. De Souza et al designed a study in which 8 patients were treated with apremilast (20 mg, every 12 hrs) for 85 days. A significant reduction in the disease activity was observed according to CLASI. The most common drug-related adverse events were nausea, headache and diarrhea. These events were classified as mild to moderate in severity and were transient in time, resolving after the initial 1 to 6 days of the study drug dosing.<sup>54</sup>

### **Ustekinumab (Strength Of Recommendation C, Level Of Evidence 3)**

Ustekinumab is a monoclonal antibody that binds to the p40 subunit common to IL-12 and IL-23, inhibiting the Th1 and Th17 pathways of inflammation. IL-17 (produced by Th17 lymphocytes) is elevated in the skin of patients with DLE.<sup>55</sup>

The use of ustekinumab in DLE has anecdotal evidence in the literature, mainly clinical cases in patients with concomitant psoriasis.<sup>56–60</sup> Our experience is based on a patient with facial refractory DLE previously treated with classic therapies and rituximab, who achieved good response with ustekinumab (45 mg/12 weeks), first associated with methotrexate and intralesional corticosteroids for 30 months and then in monotherapy.<sup>61</sup> Combination might have been a therapeutic clue in disease control. Ustekinumab has a good safety profile and dermatologists have experience and expertise in treating psoriasis.

### Anti-JAK (Strength Of Recommendation D, Level Of Evidence 3)

Kahn et al performed a literature review of the role of the JAK-STAT signalling pathway in the pathophysiology of DLE.<sup>62</sup> JAK inhibitors (tofacitinib, ruxolitinib) could be useful in reducing the disease activity, that would correlate with a reduction of the epidermal hyperplasia and the inflammatory infiltrate. The main adverse reactions are infections, headaches and diarrhea. Further studies are needed to determine their efficacy in the clinical practice.

## Alternative Therapies

### Laser (Strength Of Recommendation C, Level Of Evidence 2+)

Contrary to the latest recommendations for the management of CLE developed by the European Dermatology Forum in collaboration with the European Academy of Dermatology and Venereology, laser devices have proven to be useful in active CLE lesions.<sup>63–65</sup> Photosensitivity should not be a contraindication for laser application since it is related to UV lights. Of note, pulsed dye lasers, the most common used device, emit pulses of visible light (wavelength of 585–595 nm). Their effectiveness in DLE is based on the selective photothermolysis of the oxyhemoglobin, which induces thermal damage on the dermal microvasculature (a key point in the pathogenesis of CLE).<sup>66–68</sup> This would lead to a modulation of inflammation and a subsequent reduction of the dermal infiltration. Several cases of successful treatment of DLE with PDL and IPL have been reported.<sup>64,67,69–72</sup> A retrospective study of 16 patients with refractory DLE described the response to treatment with low-fluence PDL and IPL.<sup>73</sup> A satisfactory clinical response was observed in all patients both in symptoms and appearance (desquamation, erythema and scar improvement). Laser PDL parameters used were 585nm, 5 mm spot, 0.45 ms, fluence 5.75–6.75

J/cm<sup>2</sup> and 595 nm, 7 mm spot 0.45 ms–1.5 ms and 30/20 DCD (Dynamic Cooling Device) fluence 7.5–9 J/cm<sup>2</sup>. The average number of sessions was 5. IPL was preferred to PDL for telangiectasia treatment. Hyperpigmentation was the unique side effect, which occurred in one patient. No iatrogenic scars were appreciated. Therefore, the safety profile of the above-mentioned lasers is higher than less selective devices (CO<sub>2</sub> and argon laser).<sup>74</sup> Patients should be educated about photoprotection and informed of the possibility of recurrence. In conclusion, laser is a valuable and safety alternative to systemic therapy, and its early use may be useful in reducing scarring.<sup>75</sup>

### Photodynamic Therapy (Strength Of Recommendation D, Level Of Evidence 3)

Photodynamic therapy (PDT) is a physical treatment widely used in dermatology, especially in non-melanoma skin cancer. The mechanism of action consists in the topical application of a photosensitizer, that accumulates in certain cells and once illuminated (in presence of oxygen), produces a selective cell destruction. In recent years it is being used in inflammatory pathologies with variable results. This therapy produces a local immunosuppression that results in a decrease in the number of Langerhans cells. This fact could explain its function in immunomediated skin pathologies.<sup>76</sup> To date, two case reports have described DLE remission following PDT treatment. Fernández-Guarino et al treated a 45-year-old woman with eight weekly sessions of MAL-PDT showing clinical resolution. After 6 months, the patient remained free of lesions.<sup>77</sup> Later, Debu et al reported a 72-year-old man with right cheek DLE lesions. They performed 5 sessions of MAL-PDT (every 2–3 weeks) with progressive improvement of the erythema, with respect to the left cheek (which authors used as control).<sup>76</sup> In contrast to these reports, Romero-Maté et al reported PDT failure in two patients with recalcitrant DLE lesions. They performed three and two sessions (one per month) of 5-ALA-PDT (20% 5-aminolevulinic acid), respectively. Maybe the use of ALA instead of MAL played its part in the final result.<sup>78</sup>

### Intravenous Immunoglobulin (Strength Of Recommendation D, Level Of Evidence 3)

Intravenous immunoglobulin (IGIV) is a combination of polyclonal immunoglobulins of plasmatic origin.<sup>79</sup> They are commonly used in humoral immunodeficiencies, but also empirically as an immunosuppressant in various autoimmune processes, especially in the field of

dermatology.<sup>80,81</sup> Specifically, for the treatment of DLE Piette et al reported 5 patients treated with IVIG (dose of 1g/kg/day for 2 consecutive days of each month). In 3 individuals, a complete clinical response was obtained between 3 and 12 weeks after the last infusion of IVIG. However, they registered relapses between 2 and 10 months after the infusion (in one of them they disappeared when the treatment was restarted).<sup>82</sup> Because there are just a few cases published in this pathology and the treatment schedule varies according to the different authors, it is not possible to recommend a routine use of IVIG in DLE.

## Other Possible Treatments

Other drugs (that have not demonstrated specifically efficacy in the treatment of DLE) have been used successfully in other forms of CLE or in SLE. All of them could be future therapies to be explored in DLE. Also, there are some drugs that have a good response in DLE, but they could produce flares of SLE, so treatment with them is not recommended.

### Dapsone

Dapsone is an antibiotic from the sulphonamide group. Its mechanism of action is based on the inhibition of dihydropteroate synthase, a critical enzyme in bacterial development. Its anti-inflammatory properties prompted its wide use in dermatology. There are case reports postulating its effectiveness in several types of cutaneous lupus, including DLE, with a clinical resolution percentage of 55% in 55 patients.<sup>83</sup> This drug can produce hematological alterations (such as methemoglobinemia and agranulocytosis), therefore, during treatment, blood count and hepatic activity must be monitored. Due to the possible hemolysis dapsone should not be administered in patients with glucose-6-phosphate dehydrogenase deficiency.

### Acitretin

Acitretin is a second-generation retinoid (derived from etretinate) commonly used for psoriasis. Ruzicka et al designed a randomized clinical trial in 20 patients for the treatment of CLE. The authors report excellent results in 15 patients, especially in SCLE (in this subtype 5/6 individuals presented complete resolution after 2–4 weeks of treatment).<sup>84</sup>

### Phenytoin

Phenytoin or diphenylhydantoin is a commonly used anticonvulsant drug that works by blocking voltage-sensitive

sodium channels. Rodriguez-Castellanos et al carried out a clinical trial in which 93 patients with DLE were included. The results were very satisfactory, with a 90% clinical resolution (relapse of 15.7% at 6–12 months).<sup>85</sup> However, the risk of development of systemic lupus erythematosus due to phenytoin is described, so its use is not recommended in DLE.

### Sulfasalazine

Sulfasalazine (SSZ) is a drug of the sulfonamide group with anti-inflammatory effects. It is composed of a combination of sulfapyridine and a compound similar to aspirin (5-aminosalicylic acid). Case reports have investigated the efficacy of sulfasalazine in treating DLE.<sup>86</sup> There are some clinical cases published for the treatment of DLE. However, it can also produce drug-induced lupus.

### Rituximab

Rituximab is a chimeric monoclonal antibody (murine and human). It is a glycosylated immunoglobulin with activity against the CD20 antigen, located in the surface of lymphocytes. Several clinical cases have investigated its use in SCLE and in SLE patients with cutaneous lesions.<sup>87</sup> However, there are no reported cases in DLE. Also, due to the cost of treatment, lack of further studies and possible side effects, its use is only recommended for selected cases.

### Anti-IL-6 Antibodies

Interleukin 6 (IL-6) is a glycoprotein secreted by macrophages, T cells, endothelial cells and fibroblasts. Located on chromosome 7, its release is induced by IL-1 and increases in response to TNF $\alpha$ . Therefore, it is essentially a proinflammatory cytokine. Tocilizumab is the first monoclonal antibody with anti-IL-6 activity. An open-label phase 1 demonstrated good results in SLE.<sup>88</sup> In recent years, another anti-IL-6 monoclonal antibody (with high affinity and specificity) called sirukumab has been developed. Based in SLE results with tocilizumab, a clinical trial was designed to evaluate the pharmacokinetics and safety of sirukumab in 31 patients with CLE (39% DLE) and in 15 patients with SLE. The treatment was well tolerated in both CLE and SLE patients, so this drug could be an alternative to DLE disease.<sup>89</sup>

### Anti-TNF-Alpha Inhibitors

Although experimental analyses have insinuated the theoretical efficacy of anti-TNF $\alpha$  drugs in severe CLE, current research suggests that these treatments may be responsible for flares of the disease. Levine et al reported a patient



with persistent DLE exacerbated by adalimumab. In addition, in their review of the literature they found 128 cases in which these drugs could produce drug-induced lupus.<sup>90</sup>

### Current/Upcoming Clinical Trials

There are currently several clinical trials aimed at treating different forms of CLE. These new molecules are mainly directed to the proinflammatory cytokine pathways. Specifically, monoclonal antibodies against IFN $\alpha$  are being investigated for DLE. In this pathway, the AMG 811<sup>91</sup> and PD-0360324<sup>92</sup> molecules have shown changes in biomarkers and signaling pathways, although patients with DLE have not presented clinical improvement.

**Table 4** Proposal Of Treatment Algorithm. Combination Between Medical (topical, Systemic Or Both) And Physical (laser, Photodynamic Therapy) Therapies In Refractory Lesions Should Be Considered

Proposal of Treatment	
Lifestyles measures Mandatory	Photoprotection Smoking cessation
First-line therapies	Topical and intralesional corticosteroids Topical calcineurin inhibitors
Second-line therapies	1° Hydroxychloroquine 2° Chloroquine Switching between them
Third-line therapies	Methotrexate Systemic retinoids Fumaric acid esters Thalidomide, lenalinomide Clofazimine Laser Ustekinumab Others: azathioprine, mycophenolate mofetil, systemic corticosteroids, apremilast, photodynamic therapy, intravenous immunoglobulin
Experimental therapies	Dapsone Rituximab Anti-IL-6 antibodies Anti-JAK

In addition, a clinical trial with etanercept was recently been completed in 25 patients; results have not yet been published.

Lastly, from our point of view it would be interesting to investigate the new biological drugs (anti-IL-17 or anti-IL-23 antibodies) employed in other inflammatory cutaneous pathologies such psoriasis.

## Conclusion

In conclusion, classic recommendations on photo protection, smoking cessation and topical therapy remain the most evidence-based approaches for the majority of DLE patients. Refractory DLE may benefit from systemic therapy, thereby we propose a therapeutic algorithm based on the strength of recommendations of the multiple treatment options (Table 4). Even if antimalarial drugs are still considered the first-line systemic therapy in non-responder to lifestyle measures and topical treatment, a combination of both systemic and physical therapies might eventually reach better results than antimalarial monotherapy (e.g. HCQ and laser in refractory individual lesions). Further studies are needed to assess the benefits of treatment combination, which we hypothesize would be the better option in refractory DLE.

## Disclosure

Dr Alberto Romero-Maté reports personal fees from Celgene Corp., during the conduct of the study. The authors report no other conflicts of interest in this work.

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