

# Recent Insight on the Management of Lupus Erythematosus Alopecia

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**Abstract:** Lupus erythematosus (LE) is a chronic autoimmune condition with a wide spectrum of clinical presentations. Alopecias, both non-scarring and scarring, frequently occur in the context of LE and can assume several different patterns. Furthermore, alopecia occurring with LE may be considered LE-specific if LE-specific features are present on histology; otherwise, alopecia is considered non-LE-specific. Non-scarring alopecia is highly specific to systemic LE (SLE), and therefore has been regarded as a criterion for the diagnosis of SLE. Variants of cutaneous LE (CLE), including acute, subacute, and chronic forms, are also capable of causing hair loss, and chronic CLE is an important cause of primary cicatricial alopecia. Other types of hair loss not specific to LE, including telogen effluvium, alopecia areata, and anagen effluvium, may also occur in a patient with lupus. Lupus alopecia may be difficult to treat, particularly in cases that have progressed to scarring. The article summarizes the types of lupus alopecia and recent insight regarding their management. Data regarding the management of lupus alopecia are sparse and limited to case reports, and therefore, many studies including in this review report the efficacy of treatments on CLE as a broader entity. In general, for patients with non-scarring alopecia in SLE, management is aimed at controlling SLE activity with subsequent hair regrowth. Topical medications can be used to expedite recovery. Prompt treatment is crucial in the case of chronic CLE due to potential for scarring and irreversible damage. First-line therapies for CLE include topical corticosteroids and oral antimalarials, with or without oral corticosteroids as bridging therapy. Second and third-line systemic treatments for CLE include methotrexate, retinoids, dapsone, mycophenolate mofetil, and mycophenolate acid. Additional topical and systemic medications as well as physical modalities used for the treatment of lupus alopecia and CLE are discussed herein.

**Keywords:** discoid, hair loss, cicatricial, scarring, non-scarring

## Introduction

Lupus erythematosus (LE) is a chronic autoimmune condition with a wide spectrum of clinical presentations, ranging from isolated cutaneous lesions (cutaneous lupus erythematosus or CLE) to systemic disease (systemic lupus erythematosus or SLE) that can involve almost any organ system.<sup>1-3</sup> Alopecias, both non-scarring and scarring, frequently occur in the context of LE<sup>4</sup> and can assume several different patterns.<sup>5-9</sup> Hair loss has been noted in up to 85% of SLE patients.<sup>7,8</sup> In fact, non-scarring alopecia has been included as a criterion for the diagnosis of SLE according to the latest Systemic Lupus International Collaborating Clinics (SLICC) classification criteria based on its high specificity to SLE at 95.7%.<sup>5,10</sup> Chronic CLE is an important cause of primary cicatricial alopecia,<sup>11</sup> the classical example being scalp discoid LE.<sup>5</sup>

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Other types of hair loss not specific to LE may also occur.<sup>5,8</sup> Alopecia occurring in the context of LE may be difficult to treat, particularly in cases that have progressed to scarring. The objective of this review article is to summarize recent insight regarding the management of lupus alopecia.

## Materials and Methods

We ran a literature search of PubMed/MEDLINE that included studies, reviews, and case reports/series addressing treatments for lupus erythematosus alopecia. Keywords used in various combinations in the literature search included: lupus erythematosus, alopecia, cutaneous, scarring, cicatricial, non-scarring, hair, treatment, therapy, management. Relevant articles published in English were selected based on recent date of publication, report of high-quality data, and/or specific mention of lupus alopecia.

## Types of LE Alopecia

Alopecias occurring with LE may be non-scarring or scarring, and they may be considered LE-specific or non-LE-specific. Alopecias are considered LE-specific when they exhibit LE-specific features on histology.<sup>5</sup>

## LE-Specific Alopecia

### Discoid Lupus Erythematosus (DLE)

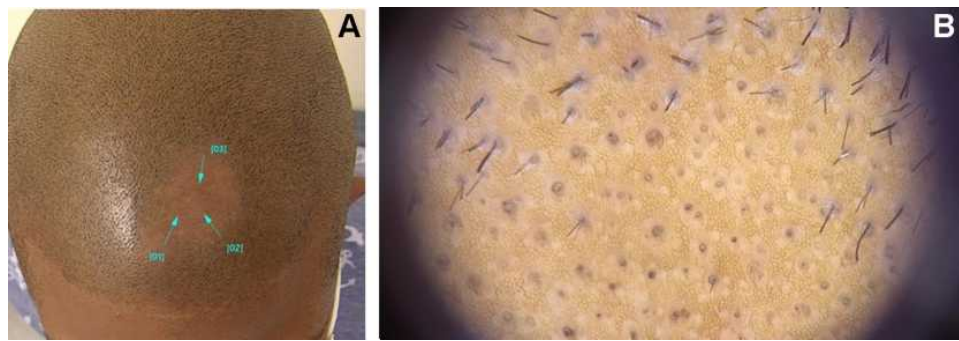
DLE is a variant of chronic CLE and a common cause of scarring alopecia.<sup>5,12,13</sup> DLE is considered as a separate criterion from non-scarring alopecia in the SLICC classification criteria.<sup>5,10</sup> Though DLE lesions are non-scarring

in early stages, they can progress towards permanent scarring and result in irreversible hair loss.<sup>2,5,14</sup>

DLE is characterized clinically by erythematous, scaly papules and plaques with follicular plugging, hypo- and hyperpigmentation, variable atrophy, and telangiectasia (Figure 1A).<sup>2,11,14</sup> We have described cases presenting as brown patches without atrophy or scarring that may be confused with melanocytic lesions, especially if presenting as individual lesions<sup>15</sup> (Figure 1B). This phenotype may be similar to the hyperpigmented canine generalized discoid LE and may have a better prognosis regarding progression.<sup>16</sup> Lesions may be pruritic, tender, or burning.<sup>5,11</sup> Trichoscopy exam should start with dry trichoscopy as using an immersion fluid hydrates the scale. Trichoscopy reveals thick arborizing vessels, follicular keratotic plugs, follicular red dots, peripilar scale, and peripilar erythema<sup>5,11,17</sup> (Figure 2). Blue gray speckled dots and blue-white veil are two features observed in patients with Fitzpatrick skin type IV–VI.<sup>18,19</sup> Histological features include vacuolar interface alteration of the dermoepidermal junction and the follicular epithelium, perivascular and periadnexal lympho-plasmacytic infiltrate, thickening of the basement membrane, pigmentary incontinence, reduced sebaceous glands, increased dermal mucin, and follicular hyperkeratosis.<sup>2,11,14</sup> The inflammation may target both the upper and lower portions of the hair follicle, eventually resulting in follicular destruction, fibrosis, and follicular dropout on histology.<sup>14,20</sup> Horizontal sections reveal two common patterns: alopecia areata (AA)-like pattern (52%)



**Figure 1** (A) Discoid lupus erythematosus (DLE) may present as patchy areas with atrophy and hyperpigmentation. (B) Individual hyperpigmented patches and plaques in discoid lupus erythematosus (DLE) may lack atrophy and simulate pigmented lesions.



**Figure 2 (A and B)** Trichoscopy points to keratotic plugs in this case of early discoid lupus erythematosus (DLE) that has been previously diagnosed and treated as alopecia areata (FotoFinder Systems, x40).

characterized by deep inflammatory infiltrate, increased catagen/telogen count and pigmented casts (Figure 3), and lichen planopilaris (LPP)-like pattern (18%) that shows the inflammatory infiltrate and perifollicular fibrosis at the upper follicular level.<sup>14</sup> Direct immunofluorescence (DIF) of lesional skin is positive for a lupus band in 60% to 80% of cases.<sup>2,5,11</sup>

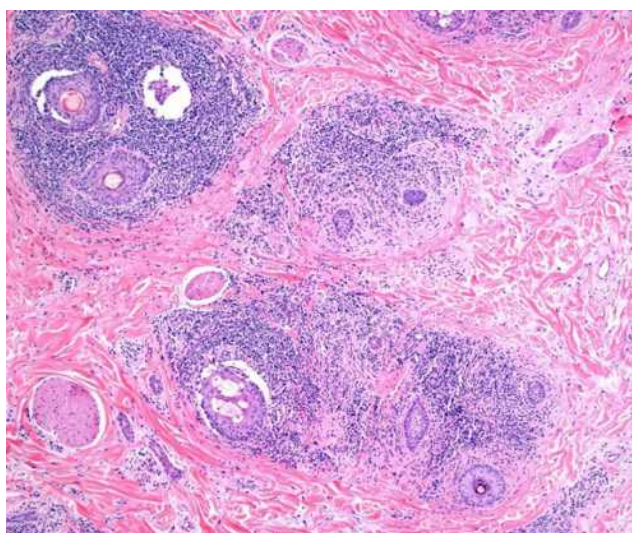
### Non-Scarring Alopecia in SLE

Non-scarring alopecia in SLE is frequently referred to in the literature as a LE non-specific cutaneous finding.<sup>2,7</sup> However, recent studies have shown that non-scarring alopecia in SLE often demonstrates LE-specific changes on histology and DIF.<sup>4,5,8</sup> While it has been suggested that non-scarring alopecia in SLE may represent early DLE,<sup>5,8</sup> the authors of the current review regard non-scarring alopecia in SLE as a distinct, independent entity based on its

clinical course, trichoscopic, and histologic features. Histological changes in non-scarring alopecia of SLE are more comparable to acute CLE than DLE.<sup>21</sup> Additionally, non-scarring alopecia in SLE manifests abruptly and predominantly in patients with severe, uncontrolled SLE, and it has been demonstrated to correlate with underlying disease activity prevalence of proteinuria ( $>1$  g/d<sup>8</sup>). It has a good prognosis and usually resolves when systemic disease is controlled.<sup>2,4,5,8,9,21,22</sup> In a recent study, the presence of certain trichoscopic features in patients with SLE was found to correlate with disease severity; patients with hair shaft changes (including decreased number of hairs, decreased diameter, and hypopigmentation) had more active systemic disease, as determined by significantly higher mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, than those without these trichoscopic features.<sup>23</sup>

Non-scarring alopecia of SLE may assume a diffuse, patchy, or “lupus hair” pattern.<sup>5</sup> It therefore must be distinguished from telogen effluvium or AA which may also occur concomitantly with SLE. The patchy pattern may be mistakenly diagnosed clinically as AA.<sup>2,22</sup> Erythema and patches of reduced hair density (as opposed to patches of complete hair loss) may help distinguish LE patchy alopecia from AA.<sup>2,5,22</sup> Additionally, trichoscopic findings in SLE have been described that may aid in the diagnosis and include: hair shaft changes (decrease in number/diameter and hypopigmentation), black dots, brown scattered pigmentation, blue-grey pigmentation, and prominent and thick arborizing blood vessels.<sup>4,5,22</sup>

Lupus hair refers to alopecia and dry/coarse appearance of the frontal hairline due to increased hair fragility, a striking sign that can be seen in patients with SLE.<sup>2,5,6,24</sup> Similar to other patterns of non-scarring alopecia in SLE, lupus hair is thought to result from severe inflammation



**Figure 3** Histologic image of the alopecia areata (AA) subtype of discoid lupus erythematosus (DLE) shows significant interface dermatitis involving the follicular epithelium and increased telogen count (hematoxylin and eosin, x10).



promoting a catabolic state and negative nitrogen balance which negatively affects hair growth.<sup>2</sup>

### SCLE

Though SCLE rarely involves the scalp, there have been reports of SCLE causing non-scarring alopecia.<sup>5,25</sup> SCLE is characterized clinically by annular or psoriasiform plaques with psoriasiform hyperplasia and perivascular inflammatory infiltrate on histopathology; a positive lupus band on DIF may help distinguish SCLE from psoriasis.<sup>5,25</sup>

### Tumid LE

Tumid LE is a subtype of chronic CLE and has been reported in rare cases to affect the scalp resulting in non-scarring, patchy hair loss.<sup>5,26,27</sup> Clinically tumid LE is characterized by erythematous, indurated papules and plaques with no surface change, and histopathological evaluation shows no interface dermatitis but significant mucin infiltration in the deep dermis.<sup>5,26,27</sup>

### LE Panniculitis/Profundus

LEP, a rare lesion within the spectrum of chronic CLE, is capable of producing both non-scarring and scarring alopecia when it affects the scalp.<sup>20,28–30</sup> When the inflammation is confined to the lower layers of the skin and affects only the lower portion of the hair follicle (the follicular bulbs), the stem cells of the hair follicle are preserved; therefore, the hair loss is non-scarring.<sup>20,30</sup> Although rare in LEP, if the inflammation affects the dermis surrounding the bulge of the follicle, permanent loss of the hair follicle and irreversible alopecia may ensue.<sup>20,29,30</sup>

Clinically, LEP of the scalp may present as tender, slightly erythematous patches of hair loss, sometimes with overlying ulceration<sup>20,28–30</sup> (Figure 4). Trichoscopic features including large yellow dots, black dots, short vellus hairs, thick arborizing vessels, and diffuse erythema of the inter-follicular areas have been described.<sup>21</sup> Histopathological evaluation shows predominantly lymphocytic infiltration of the subcutaneous lobules (lobular panniculitis) and deep dermis, mucinosis, and hyalinization of the fat.<sup>28,29</sup> LEP has been reported to cause alopecia along Blaschko's lines in East Asian men and that subtype is termed Linear and annular lupus panniculitis of the scalp (LALPS).<sup>28,30</sup> It bears a better prognosis and is less frequently associated with SLE.

### LE Non-Specific Alopecia

Several other non-scarring types of alopecia may occur in patients with LE most likely as a coincidental finding<sup>5,8</sup> since histology fails to show LE-specific features.<sup>5</sup>



**Figure 4** Clinical image demonstrates alopecia in lupus panniculitis of the scalp with notable erythema and lack of keratotic plugs or scale.

### Telogen Effluvium (TE)

TE may complicate SLE as a result of severe inflammation, anemia, physical/mental stress, or medications.<sup>2,5,20</sup> Pro-inflammatory cytokines and severe catabolic effects can negatively affect the hair growth cycle, causing diffuse hair shedding and/or thinning.<sup>2,5</sup> A hair pull test, performed by randomly grasping 50–60 hairs, can aid in the diagnosis of TE when more than 5–6 telogen hairs are pulled.<sup>24</sup>

As previously mentioned, diffuse alopecia occurring during acute exacerbations of SLE is a frequent occurrence.<sup>5,6</sup> The etiology of diffuse alopecia in patients with SLE has been largely attributed to TE;<sup>4,7</sup> however, histopathological examination is often not performed. Specific LE-changes on histology may differentiate TE

from diffuse non-scarring hair loss of SLE.<sup>8</sup> Additionally, TE ensues months after a stressful insult or trigger, whereas LE-specific diffuse alopecia occurs concomitantly with disease flares.<sup>5</sup> Nevertheless, a clear distinction may not always be possible, and in our experience, the dermatological treatment with topical steroids with/without topical minoxidil renders significant improvement in either type.

### Alopecia Areata (AA)

It has been suggested that there is a higher incidence of AA in patients with SLE than among general dermatologic patients, perhaps due to a common autoimmune diathesis.<sup>6,7,14</sup> However, patchy hair loss of SLE may also have been misdiagnosed as AA. Deep dermal mucin in a biopsy of non-scarring alopecia may be a clue to underlying SLE,<sup>2</sup> as this is not a feature of typical biopsies of AA.<sup>31</sup> This diagnostic distinction is important as the prognosis of AA is unpredictable, whereas non-scarring alopecia of SLE should improve with good control of systemic disease.<sup>5</sup>

### Anagen Effluvium (AE)

Certain drugs (namely cytotoxic agents and anti-metabolites) used in LE and occasionally severe systemic inflammation can cause the rapidly dividing matrix cells of anagen hair follicles to suddenly and temporarily stop dividing, resulting in dystrophic AE.<sup>2,5,24</sup> Clinically this presents as scalp/body hair loss and narrowed segments of the hair shaft (Pohl-Pinkus constriction) resulting in hair shaft breakage.<sup>2,5,24</sup> A pull test will be positive for anagen and telogen hairs.<sup>5</sup> AE occurs as early as one week after the triggering insult.<sup>5</sup>

## Management of LE-Specific Alopecia

Data regarding the management of lupus alopecia are sparse and limited to case reports. Thus, many studies included in the current review report the efficacy of treatments on CLE as a broader entity. Systematic reviews have noted a paucity of high-quality evidence for the management of CLE as well.<sup>32,33</sup>

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is often utilized in the literature to assess the clinical response of CLE.<sup>34</sup> The CLASI score can be separated into an “activity” and a “damage” score. The activity score accounts for non-scarring alopecia in addition to erythema, scale/hypertrophy, and mucous

membrane involvement. The damage score comprises dys-pigmentation, scarring, atrophy, and panniculitis: features that may be seen in association with scarring alopecia.

## General Principles

For patients with non-scarring alopecia in SLE (diffuse, patchy, and lupus hair), management is aimed at controlling SLE activity with expected subsequent hair regrowth. Adjuvant topical treatment with high potency steroids, such as clobetasol 0.05%, with or without topical minoxidil can expedite recovery, which usually occurs in 3 months (Figure 5). Management of SLE other than first-line therapy with oral antimalarials<sup>32</sup> is beyond the scope of this review.

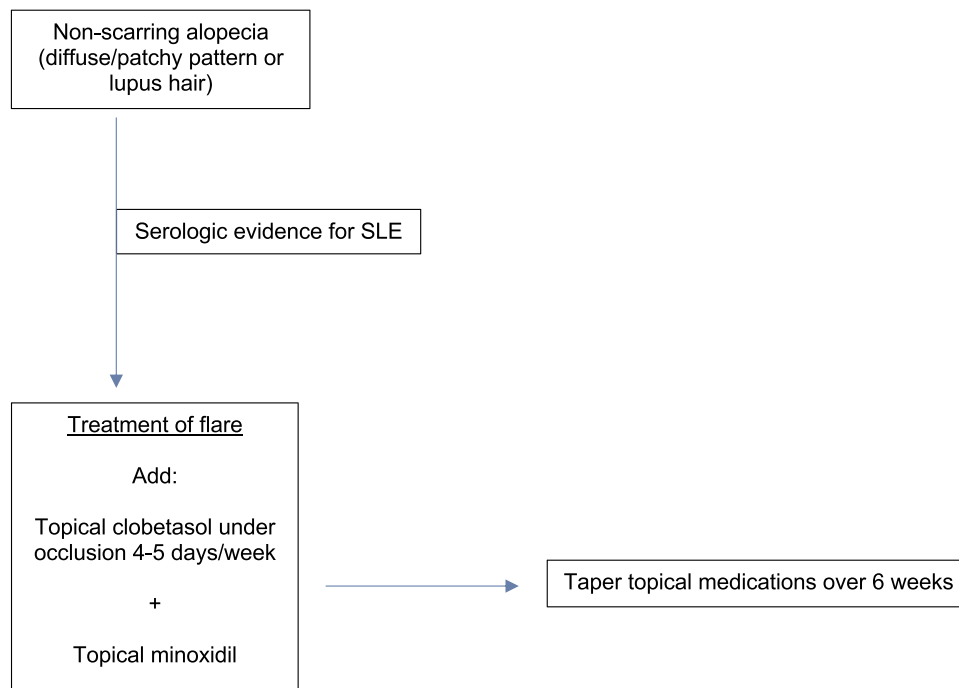
Chronic CLE can cause primary cicatricial alopecia, which is generally considered to be permanent.<sup>13,35</sup> Therefore, prompt treatment is crucial to target early inflammation and prevent irreversible damage.<sup>12,13,30,35</sup> The goal of treatment for any primary cicatricial alopecia is to prevent progression of hair loss, and regrowth should not be expected once scarring has ensued.<sup>11</sup>

Treatments for LE alopecia are summarized in Table 1. According to recent guidelines by the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venerology (EADV), current first-line therapies for CLE include topical corticosteroids for localized disease and systemic treatment with antimalarials for severe/widespread disease.<sup>36</sup> Systemic corticosteroids are often used as a bridging therapy and recommended as first-line treatment in highly active, severe CLE with high-risk of scarring,<sup>36</sup> which includes DLE-associated alopecia (Figure 6). In our experience oral dexamethasone as a mini-pulse of dose 0.1mg/kg on two consecutive days of the week is a well-tolerated alternative to oral prednisone and has negligible mineralocorticoid effects.

Second and third-line systemic treatments for CLE include methotrexate, retinoids, dapsone, mycophenolate mofetil (MMF), and mycophenolate acid (MPA).<sup>36</sup>

## Lifestyle Measures

Sun-exposure is known to exacerbate and precipitate CLE,<sup>2,32,37</sup> and studies have demonstrated decreased interferon-mediated inflammation in biopsies of skin protected by sunscreen.<sup>37,38</sup> Thus, photoprotection and sun avoidance are important preventative measures.<sup>2,11,32</sup> Higher sun protection factor (SPF 60 or greater), broad-spectrum UVA/UVB coverage, and physical protection are recommended.<sup>37</sup>



**Figure 5** Algorithm describes an approach to treatment of discoid lupus erythematosus (DLE) on the scalp.  
**Abbreviations:** SLE, systemic lupus erythematosus; IL, intralesional; IVIG, intravenous immunoglobulin.

Smoking tobacco has been found to be more prevalent among patients with DLE<sup>39</sup> and has been associated with more severe manifestations of CLE<sup>40</sup> as well as decreased

efficacy of treatment.<sup>41</sup> Though the pathomechanism of smoking on the natural history LE is not fully understood, smoking cessation is strongly recommended.<sup>32,37,42,43</sup>

**Table I** Therapies for LE Alopecia

Topical therapies	<b>Corticosteroids*</b> (including intralesional) Calcineurin inhibitors R-salbutamol Retinoids
Systemic therapies	<b>Anti-malarials ± corticosteroids*</b> Retinoids MTX Dapsone MMF/MPA Thalidomide/lenalidomide FAEs Apremilast Azathioprine Cyclosporine IVIG JAK inhibitors Biologics
Physical modalities	Light/laser therapy Hair transplantation

**Note:** Bold asterisk (\*) denotes first-line therapies.

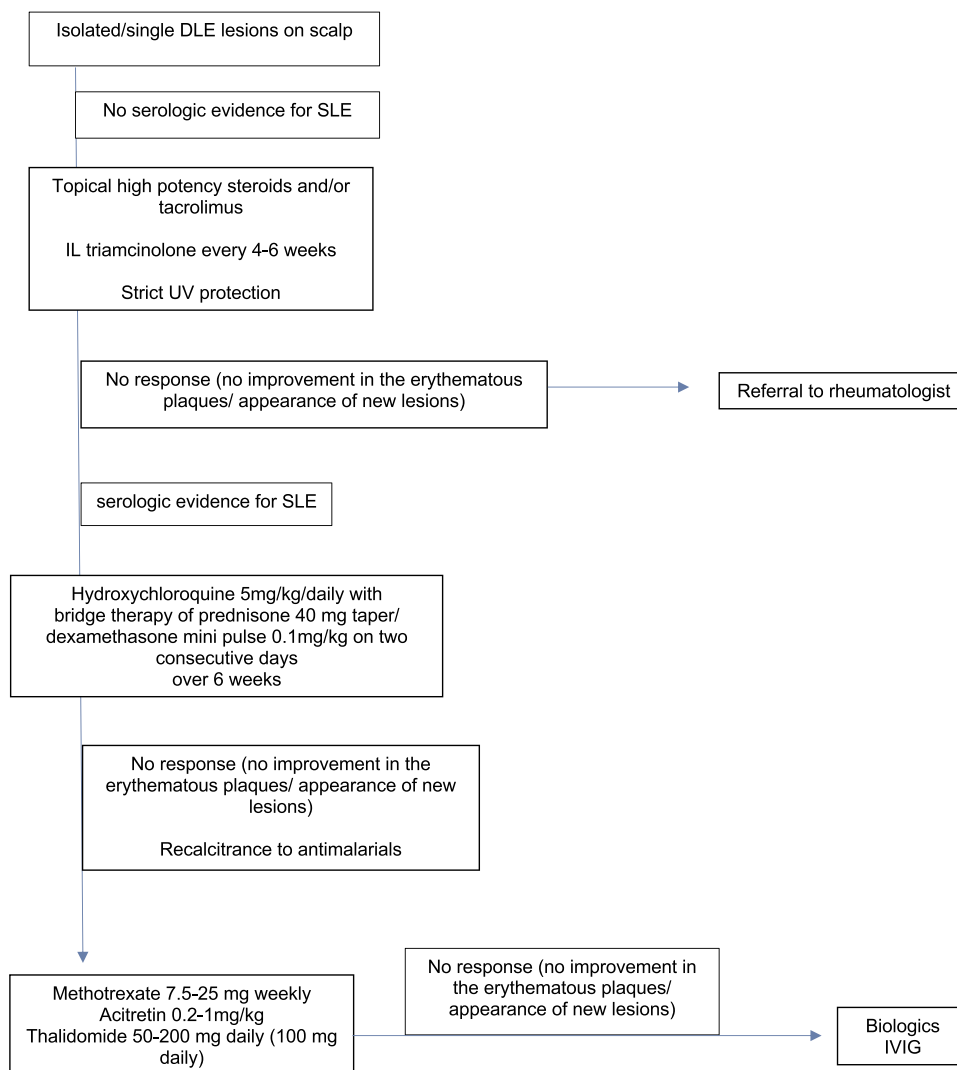
**Abbreviations:** MTX, methotrexate; MMF, mycophenolate mofetil; MPA, mycophenolate acid; FAEs, fumaric acid esters; IVIG, intravenous immunoglobulin; JAK, janus kinase.

## Current First-Line Therapies: Corticosteroids and Antimalarials

In concordance with EDF and EADV guidelines, topical/IL corticosteroids and oral antimalarials are widely recommended as first-line therapies for CLE,<sup>11,37,42,44–49</sup> though approximately 30–40% of CLE cases will remain refractory to standard first-line treatments.<sup>50</sup> Data supports the use of high-potency topical corticosteroids over lower-potency formulations.<sup>2,11,13,33,37</sup> Using high-potency steroids under occlusion can improve efficacy. A stepwise approach is often employed beginning with topical therapies and subsequently introducing oral antimalarials.<sup>12,37</sup> However, an aggressive multi-modal approach is often necessary to prevent irreversible alopecia in patients with chronic CLE<sup>12,30,43,51</sup> including oral corticosteroids as bridging therapy.<sup>11,12,37,51</sup>

Long-term systemic therapy with antimalarials is indicated for non-scarring alopecia in SLE, and topical/intralesional (IL) steroids may hasten hair regrowth.<sup>2</sup>

Hydroxychloroquine (HCQ) has demonstrated efficacy in treating CLE/DLE and is traditionally used as a first-line



**Figure 6** Algorithm describes an approach to treatment of non-scarring alopecia in systemic lupus erythematosus (SLE).

antimalarial.<sup>11,32,33,52</sup> HCQ is the hydroxyl derivative of chloroquine, and both are antimalarial agents that have proven useful in the treatment of autoimmune diseases, including SLE and rheumatoid arthritis.<sup>53</sup> Unlike other immunomodulatory therapies, HCQ treatment has actually been associated with a reduction in infections.<sup>53</sup> Though few hypotheses exist, the precise mechanism of action of HCQ remains elusive.<sup>53</sup> Early HCQ treatment may delay the occurrence of cutaneous damage in patients with SLE.<sup>54</sup> However, in one study, less than 50% of patients with DLE maintained long-term clinical response to hydroxychloroquine.<sup>55</sup> Combination therapy with HCQ and quinacrine may be more effective than HCQ monotherapy, particularly in patients who fail the latter.<sup>56</sup> HCQ can also be replaced by chloroquine.<sup>11</sup>

The efficacy of HCQ in treating individual cutaneous manifestations, including alopecia, is not well reported. In case reports, treatment with HCQ as monotherapy or in combination with other treatments resulted in improvement in alopecia secondary to variants of CLE, including DLE, LEP, and tumid LE.<sup>12,20,28,30,44,57-59</sup> It is important to note that HCQ above a dose regimen of 5 mg/kg is associated with significant ocular toxicity and should be avoided.<sup>60</sup>

## Topical Therapies

### Topical Calcineurin Inhibitors (TCIs)

Randomized comparative trials and other studies have demonstrated the efficacy of TCIs (tacrolimus and pimecrolimus) in the treatment of CLE,<sup>32,61,62</sup> though clinical



improvement was not always sustained with longer periods of follow-up.<sup>63</sup> TCIs are considered first- or second-line agents for CLE<sup>11,36,37,49</sup> and may exhibit comparable efficacy to topical corticosteroids<sup>62</sup> with an improved side effect profile.<sup>13,32,37,62,63</sup> Case reports have documented the success of topical tacrolimus in promoting significant hair regrowth in 4 patients with recalcitrant alopecia secondary to DLE, both as monotherapy (using 0.1% ointment)<sup>64</sup> and as an adjunct to oral antimalarial (using compounded 0.3% lotion).<sup>13</sup>

### R-Salbutamol

R-salbutamol is a beta-2-adrenergic receptor agonist that has shown efficacy as a topical formulation in the treatment of CLE.<sup>32,43,65</sup> A randomized controlled trial (RCT) involving 37 patients with DLE found statistically significant improvement in scaling/hypertrophy, induration, patient global assessment, and lesional size when treated with R-salbutamol topically.<sup>66</sup> A prospective study that examined the use of topical R-salbutamol on patients with SCLE and treatment-resistant DLE found improvement in both subtypes of CLE but a better response in SCLE.<sup>67</sup> However, topical R-salbutamol is not currently commercially available,<sup>43</sup> and new data have not been published since 2009.<sup>65</sup>

### Retinoids

Topical retinoids (tazarotene and tocoretinate) have also been used to successfully treat refractory DLE lesions in case reports.<sup>68,69</sup> Tocoretinate (a synthetic esterified compound of tocopherol and retinoic acid) improved erosions and erythema due to DLE as well as signs of damage (dyspigmentation and atrophy) in a case series.<sup>69</sup>

## Systemic Therapies

### Retinoids

Systemic retinoids are considered second-line treatment options for CLE,<sup>36,46,47,68,70</sup> and a RCT suggested that acitretin may be equally as effective as HCQ in improving/clearing erythema, infiltration, and scaling of CLE lesions,<sup>33,71</sup> though more frequent and severe adverse events occurred with acitretin. In a more recent case series, 3 patients with different forms of CLE (including DLE and SCLE) refractory to various other topical and systemic agents demonstrated excellent clinical improvement with alitretinoin and suffered minimal side effects.<sup>47</sup> Oral isotretinoin has also been effective in refractory CLE, including ACLE, SCLE, and DLE.<sup>11,70,72,73</sup> An important

consideration is that systemic retinoids are associated with reversible alopecia.<sup>2</sup>

### Methotrexate (MTX)

In a retrospective study of 43 patients with CLE, low-dose MTX, as both monotherapy and adjunctive therapy, resulted in significant improvement in activity of cutaneous lesions in 98% of patients. Alopecia was not explicitly considered in the Cutaneous Lupus Activation Index (CLAI) which was used to assess disease activity and clinical response.<sup>3</sup> In fact, of non-antimalarial treatments, thalidomide and methotrexate were the most effective options in CLE recalcitrant to antimalarials, according to a recent retrospective study.<sup>74</sup> These data are supported by a previous retrospective analysis that demonstrated clinical improvement in approximately 83% of patients with refractory CLE (including DLE, SCLE, LEP) and complete response in 50% with low-dose MTX. In a randomized comparative trial, low-dose MTX was found to be equally effective as chloroquine in clearance of skin rash associated with SLE.<sup>75</sup> MTX is associated with severe toxicities, namely bone marrow suppression and hepatotoxicity, which occasionally required discontinuation of treatment in these studies.<sup>3,75</sup>

### Dapsone

In a retrospective analysis of 34 patients with CLE, dapsone with or without antimalarials resulted in clinical improvement in more than 58% of patients and complete remission in approximately 17%.<sup>76</sup> In a case report, dapsone resulted in rapid clinical improvement of recalcitrant scarring alopecia due to chronic CLE after a biopsy demonstrated neutrophils in the inflammatory infiltrate.<sup>77</sup> This case illustrates the utility of histology-guided treatment, a recommended principle for the management of cicatricial alopecia.<sup>11</sup>

### Mycophenolate Mofetil (MMF) and Mycophenolate Acid (MPA)

In non-comparative studies and case series, MMF or MPA resulted in clinical improvement in 90–100% of patients with variants of CLE.<sup>78–80</sup> However, in another study, 5 out of 7 patients with therapy-resistant cutaneous manifestations of SLE achieved no clinical improvement with MMF.<sup>81</sup>

### Thalidomide and Lenalidomide

Thalidomide, a glutamic acid derivative with anti-tumor and immunomodulatory properties, and its synthetic



analog lenalidomide have demonstrated success in treating refractory CLE.<sup>32,42,45,50,82</sup>

A meta-analysis found an overall response rate of 90% in 548 chronic CLE patients with thalidomide treatment, with similar efficacy among severe CLE subtypes.<sup>42</sup> In observational studies and case reports, thalidomide therapy has resulted in a significant and rapid clinical improvement of recalcitrant active CLE lesions in at least 80–90% of patients.<sup>50,82,83</sup> Thalidomide has also been reported to significantly improve alopecia associated with DLE in a pediatric patient.<sup>59</sup> However, its use is limited by severe side effects, including teratogenicity, peripheral neuropathy, and thrombosis, as well as frequent relapses after withdrawal of therapy.<sup>42,50,82–84</sup>

In several non-comparative trials and observational studies, lenalidomide proved efficacious in treating refractory CLE, without inducing or worsening peripheral neuropathy.<sup>45,50,84,85</sup> 77–100% of patients in different studies achieved clinical response,<sup>45,50,84,85</sup> and at least 43–86% achieved complete response as determined by a CLASI activity score of 0.<sup>45,50,85</sup> Lenalidomide was found to be safe and effective in the treatment of refractory cutaneous manifestations of SLE in pediatric patients; in a retrospective study of 10 adolescents, 100% of patients achieved complete or near complete resolution at 6 months of treatment, including hair regrowth in patients with extensive alopecia.<sup>86</sup> Similar to thalidomide, however, lenalidomide was associated occasionally with arterial thromboses<sup>85</sup> and frequent relapse upon dose reduction or discontinuation.<sup>50,85</sup>

### Fumaric Acid Esters (FAEs)

FAEs are approved for the treatment of psoriasis and multiple sclerosis, and they are thought to exert immunomodulatory activity through inhibition of the transcription factor nuclear factor (NF)-κB and T-cell mediated inflammation.<sup>1,65,87</sup> In a Phase II non-comparative trial, treatment with FAEs resulted in significant decrease in mean revised-CLASI activity scores in patients with recalcitrant CLE (DLE and SCLE).<sup>1</sup> Reductions in mean R-CLASI damage scores were noted, though they were not statistically significant.<sup>1</sup> Side effects included abdominal pain and headaches; no severe adverse events occurred.<sup>1</sup> Recent case reports have also documented the efficacy of FAEs as an adjuvant to other systemic therapies in treating severe, recalcitrant cutaneous manifestations of SLE, with favorable tolerability.<sup>87,88</sup>

### Apremilast

In a phase II open-label pilot trial, treatment with apremilast as monotherapy resulted in significant decline in both CLASI activity and damage scores in patients with DLE.

Adverse events were mild and transient.<sup>89</sup>

Apremilast is a phosphodiesterase-4 inhibitor with immunomodulatory activity, particularly with regard to Th-1 and Th-17 mediated activity.<sup>65</sup> Though data are currently very limited, apremilast may be a viable and safe therapeutic option in CLE.<sup>32,65,89</sup>

### Azathioprine

Azathioprine has been reported to be effective as adjuvant therapy in difficult cases of CLE, including DLE and SCLE. It is also associated with occasionally severe side effects including myelosuppression and malignancy, among others.<sup>11,32,65,90</sup> It is not recommended for CLE according to the European guidelines in the absence of associated SLE.<sup>36,43</sup>

### Cyclosporine

Very scarce documentation exists on the use of cyclosporine to treat CLE.<sup>11,32</sup> In two cases of refractory SCLE, cyclosporine A in conjunction with MTX was effective,<sup>46</sup> but in other cases of chronic CLE, cyclosporine has been ineffective.<sup>91</sup>

### Intravenous Immunoglobulin (IVIG)

Few heterogenous studies and case reports have documented the efficacy of IVIG in the treatment of CLE, including DLE and SCLE, though some conflicting data exist.<sup>32,49,65,92</sup> A recent proof-of-concept study reported overall clinical improvement with reduction in CLASI-A scores, low rates of relapse, and no serious adverse effects in patients with recalcitrant CLE when treated with IVIG as monotherapy.<sup>93</sup>

### Janus Kinase (JAK) Inhibitors

JAK inhibitors are being studied for their efficacy in many autoimmune and inflammatory disease processes, including SLE.<sup>9</sup> Various JAK inhibitors including tofacitinib, ruxolitinib, and baricitinib have demonstrated promising results in the treatment of AA.<sup>9</sup>

Baricitinib is an inhibitor of JAK 1 and 2, approved for the treatment of rheumatoid arthritis. In a phase II study, baricitinib significantly improved the severity of rash and arthritis in patients with active SLE refractory to standard therapy.<sup>94</sup> In a recent case report, introduction of baricitinib resulted in significant improvement in diffuse

non-scarring alopecia in a patient with SLE that was refractory to several lines of therapy.<sup>9</sup> Given limited data on the use of JAK inhibitors in SLE and SLE alopecia, authors are cautiously optimistic.<sup>9</sup> Notably, JAK inhibitors are occasionally associated with severe adverse effects, including infection and thrombosis.<sup>95</sup>

### Belimumab

Belimumab is the only biological therapy approved by the FDA to treat SLE;<sup>43,96</sup> however, data to support its efficacy in CLE are more limited.<sup>32,43</sup> Belimumab targets soluble B-lymphocyte stimulator (BLyS), which was found to be significantly more expressed in lesional biopsies of all CLE subtypes compared to controls.<sup>97</sup> In a large, multicentric retrospective analysis of 11 prospective cohorts, median CLASI-activity scores significantly decreased overtime with belimumab treatment.<sup>96</sup> A post hoc analysis of combined data from two Phase III clinical trials comparing belimumab to placebo found that significantly more patients in the treatment group had improvement in their mucocutaneous manifestations of SLE.<sup>98</sup> A recent study aimed to evaluate efficacy of belimumab specifically on refractory, severe CLE and found that belimumab therapy resulted in dramatic improvement in CLASI-activity scores (and no worsening of CLASI damage scores) in a small cohort of patients.<sup>99</sup> Additionally, belimumab is associated with a very good safety profile, with low rates of infusion reactions as well as other severe adverse events.<sup>96</sup>

### Rituximab

Phase III trials investigating the efficacy of rituximab in SLE did not meet their endpoint.<sup>43</sup> However, some observational studies have supported its efficacy in improving CLE, particularly ACLE.<sup>32,43,65</sup> A retrospective cohort study analyzed the efficacy of rituximab in SLE patients with several subtypes of CLE, including ACLE, SCLE, CCLE, and non-specific LE (NSLE). NSLE included alopecia. Rituximab therapy (with or without cyclophosphamide) resulted in clinical improvement with all subtypes, but more so in patients with ACLE and NSLE.<sup>100</sup>

Another prospective study involving SLE patients receiving rituximab therapy found that patients with ACLE responded favorably whereas those with chronic CLE did not respond; rather, new chronic CLE lesions emerged in some patients while on rituximab.<sup>101</sup> Authors of this report surmise that inflammation in CLE is B-cell independent.<sup>101</sup>

### Ustekinumab

In a recent phase II RCT, ustekinumab in addition to standard-of-care therapy was more effective than placebo in treating SLE and resulted in significant improvement in CLASI-activity scores.<sup>102</sup> In case reports, ustekinumab has been effective in treating severe and recalcitrant CLE, including ACLE, SCLE, and DLE.<sup>103–106</sup> Ustekinumab inhibits the p40 subunit shared by the cytokines IL-12 and IL-23, and IL-23 plays an important role in the expansion and survival of pathogenic IL-17-producing cells.<sup>102,103</sup> These cytokines have been found to be elevated in the serum of patients with SLE,<sup>103</sup> and IL-17A has been found to be significantly elevated in the skin of patients with CLE.<sup>107</sup> Ustekinumab has a very favorable safety profile and may play a role in the treatment of CLE, pending further studies.<sup>43,65,102</sup>

### Anti-Tumor Necrosis Factor (TNF)-Alpha Biologics

Anti-TNF-alpha inhibitors, though theoretically could be efficacious in treating CLE, have not been effective in observational studies.<sup>11,65</sup> On the contrary, available data have raised concerns that these drugs may actually trigger and/or exacerbate LE.<sup>11,65</sup> However, a recent retrospective analysis found that only 1/20 patients with concomitant LE and psoriatic disease experienced a clinical flare of lupus while on treatment, translating to an incidence of clinical flares of 0.92% events per patient-year.<sup>106</sup>

### Other Biologics

Limited data suggest the potential utility of other biological agents in the treatment of CLE.<sup>32,43,65</sup> BIIBB059 is a monoclonal antibody that targets blood dendritic cell antigen 2, a plasmacytoid dendritic cell-specific receptor. In a RCT involving 12 patients with SLE, single doses of BII059 resulted in decreased CLASI-activity scores and reduced inflammatory infiltrates in skin lesions.<sup>108</sup> A post hoc analysis on data from an RCT<sup>109</sup> that demonstrated the efficacy of anifrolumab (anti-interferon-alpha receptor monoclonal antibody) in SLE noted statistically significant improvements in rash versus placebo.<sup>110</sup> Similarly, a phase II RCT that investigated the efficacy of another anti-interferon-alpha monoclonal antibody, Sifalimumab, noted improvements in CLASI scores in the treated group compared to placebo.<sup>111</sup>

Interferon-gamma is implicated in the pathogenesis of DLE; however, a Phase I RCT showed no clinical benefit in patients with DLE when treated with AMG 811, an anti-interferon-gamma antibody.<sup>112</sup>

## Physical Modalities

### Laser and Light Therapy

Laser and light therapies, including pulse-dye laser (PDL) and intense pulsed light (IPL) among others, have demonstrated success in treating both the activity and damage of DLE lesions,<sup>48,113–118</sup> sometimes with confirmed histologic improvement and reduction of inflammation.<sup>117,118</sup> Most data support the efficacy of PDL with a wavelength of 585–595.<sup>32,37</sup> A recent RCT aimed to investigate the efficacy of PDL (595 nm) in the treatment of DLE and found that lesions treated with PDL demonstrated significant reductions in erythema, texture, and physician global assessment compared to controls.<sup>117</sup> Improvement in modified CLASI scores was not significant. Side effects in treating CLE with PDL are often minimal and included dyspigmentation and transient pain: scarring was rare.<sup>32,113</sup> Despite limited data suggesting the efficacy of light/laser therapies in CLE, European guidelines<sup>36</sup> recommend against the use of UV light and laser treatments in patients with CLE due to photosensitivity and risk of koebnerization.<sup>36,65</sup>

### Hair Transplantation

A recent systematic review noted the scarcity of documentation on hair transplantation in patients with scarring alopecia, particularly in patients with chronic CLE.<sup>119</sup> An old study noted positive results for 8 patients with DLE who underwent punch graft transplants (an average of 72% graft survival).<sup>120</sup> However, graft destruction has been reported in patients with other forms of primary cicatricial alopecia.<sup>11,119</sup> Cutaneous LE and any underlying SLE if present must be controlled before considering hair transplantation surgery<sup>2,11,119</sup> due to risk of koebnerization.<sup>2</sup> A general recommendation, though not well substantiated by data, is that underlying disease should be inactive for at least two years prior to surgery.<sup>11,119</sup>

## Conclusion

Data regarding the specific effect of treatment regimens on the reversal of LE alopecia are severely lacking. Though often not reported, it may be inferred that the treatment of SLE will also improve associated non-scarring alopecia.

Presence of chronic CLE often warrants early, aggressive, multi-modal intervention due to the risk of scarring resulting in irreversible hair loss. Close collaboration with a rheumatologist should be implemented in the care of patients with LE. Currently, topical/IL corticosteroids and oral antimalarials are the mainstay of therapy for CLE.

A recent systematic review of RCTs highlighted the lack of evidence for many drugs other than topical steroids, hydroxychloroquine, and acitretin in the treatment of DLE.<sup>33</sup>

TCI's have demonstrated efficacy in treating CLE and LE alopecia specifically, and other topical treatment options include retinoids and R-salbutamol. Second-line and third-line systemic therapies for CLE include methotrexate (MTX), retinoids, dapsone, mycophenolate mofetil (MMF)/mycophenolate acid (MPA), and thalidomide.<sup>36</sup> Systemic therapy with lenalidomide, FAEs, azathioprine, apremilast, IVIG, and biologicals (including ustekinumab, rituximab and belimumab) have also been efficacious in individual reports and small series. Oral and topical minoxidil may be used adjuvant treatments to support hair growth.<sup>11,35</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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