Portuguese Journal of Dermatology and Venereology

Permanyer

Check for updates

Port J Dermatol and Venereol.

REVIEW ARTICLE

Cutaneous lupus erythematosus: a review of new and emerging therapies

Lúpus eritematoso cutâneo: revisão de novas terapêuticas emergentes

Joana Xará[1] and Margarida Gonçalo[1,2]*

[1]Department of Dermatology, University Hospital, Coimbra Local Health Unit and Faculty of Medicine; [2]Department of Dermatology, Faculty of Medicine, University of Coimbra. Coimbra, Portugal

Abstract

Cutaneous lupus erythematosus (CLE) is an autoimmune connective tissue disorder with heterogenous skin manifestations. According to the current therapeutic guidelines for the treatment of CLE, short courses of topical corticosteroids remain the first-line treatment for localized disease, while topical calcineurin inhibitors offer a safer alternative with lower side effects. Regardless of CLE subtype, antimalarials are the first-line systemic treatment for disfiguring and widespread skin lesions and prevent systemic involvement. In addition, the use of systemic corticosteroids should be restricted to patients with highly active and/or severe CLE. Second-line treatments include methotrexate, retinoids, and dapsone, while mycophenolate mofetil is considered third-line option. Moreover, thalidomide should be reserved for use in recalcitrant CLE patients, preferably in combination with antimalarials. Despite the considerable impact of CLE on quality of life, therapeutic options remain insufficient and, aside from hydroxychloroquine and corticosteroids, no other systemic treatments are approved. This review offers a brief overview of CLE pathogenesis and the current development landscape for new and emerging systemic therapies, highlighting promising targeted drugs such as anifrolumab (anti-type 1 interferon), deucravacitinib (allosteric tyrosine kinase 2 inhibitor), litifilimab (plasmacytoid dendritic cell-targeted therapy), iberdomide (cereblon-targeting ligand), and belimumab (B-cell targeted therapy), among others.

Keywords: Cutaneous lupus. Clinical trials. Anifrolumab. Iberdomide. Litifilimab. Belimumab.

Resumo

O lúpus eritematoso cutâneo (LEC) é uma doença autoimune do tecido conjuntivo que se apresenta com manifestações cutâneas muito heterogéneas. De acordo com as diretrizes terapêuticas atuais, ciclos curtos de corticosteróides tópicos mantém-se como tratamento de 1ª linha na doença localizada, enquanto os inibidores da calcineurina tópicos são uma alternativa mais segura, com menos efeitos secundários. Independentemente do subtipo de LEC, os antimaláricos são o tratamento sistémico de primeira linha nos casos de lesões cutâneas generalizadas e desfigurantes e na prevenção do envolvimento sistémico. Além disso, o uso de corticóides sistémicos deve ser restrito a doença com atividade severa. Os tratamentos de segunda linha incluem metotrexato (MTX), retinóides e dapsona, enquanto o micofenolato de mofetil (MFM) é considerado uma opção de terceira linha. Além disso, a talidomida deve ser reservada para casos de LEC refratários a outros tratamentos, preferencialmente em combinação com antimaláricos. Apesar do impacto considerável na qualidade de vida, as opções terapêuticas no LEC permanecem insuficientes e, além da hidroxicloroquina e dos corticóides, nenhum outro tratamento

***Correspondence:**
Joana Xará
E-mail: joanaresendexara@gmail.com

Received: 21-10-2024
Accepted: 05-11-2024
DOI: 10.24875/PJDV.24000082

Available online: 12-12-2024
Port J Dermatol and Venereol. 2024;82(4):229-240
www.portuguesejournalofdermatology.com

sistémico está aprovado. Esta revisão oferece uma breve visão geral da patogénese do LEC e do panorama atual do desenvolvimento de novos tratamentos sistémicos, destacando terapêuticas dirigidas promissoras como anifrolumab (anti-interferão tipo 1), deucravacitinib (inibidor alostérico da tirosina cinase 2), litifilimab (terapêutica dirigida às células dendríticas plasmocitóides), iberdomide (ligante modulador dirigido ao cereblon) e belimumab (terapêutica dirigida às células B), entre outros.

Palavras-chave: Lúpus cutâneo. Ensaios clínicos. Anifrolumab. Iberdomide. Litifilimab. Belimumab.

Introduction

Cutaneous lupus erythematosus (CLE) is an autoimmune connective tissue disorder with heterogenous manifestations, which may present with exclusively skin involvement or as part of systemic lupus erythematosus (SLE).

According to the 2004 classification system modified by Düsseldorf, CLE is divided into four distinct subtypes even though patients may exhibit overlapping features: acute CLE (ACLE), subacute CLE (SCLE), chronic CLE (CCLE), and intermittent CLE (ICLE) or lupus erythematosus tumidus (LET). These heterogeneous skin presentations are grouped under the umbrella of CLE based on the characteristic clinical and histologic features and their ability to present concomitantly with SLE despite significant interindividual variation[1].

CCLE can be further divided into chronic discoid lupus erythematosus (CDLE), lupus erythematosus profundus (LEP), and chilblain lupus erythematosus (ChLE), with CDLE being the most common subtype of CCLE[2]. ACLE and SCLE often present with widespread maculopapular to annular skin lesions, mainly on sun-exposed areas, whereas CDLE is characterized by scattered, disc-like scarring plaques[3]. Histopathologically, CLE is marked by the presence of lymphocytic infiltrates, deeper and denser in CDLE compared to SCLE, and necroptotic keratinocytes at the dermo-epidermal junction[4]. However, the classification of CLE subtypes should be considered flexible, as overlapping clinical and histological features are common.

Furthermore, the risk of developing systemic disease varies with different clinical subtypes of CLE. ACLE is associated with a higher risk of SLE, occurring in about 80% of cases, whereas localized CDLE is associated with SLE in only about 5% of cases[4,5]. The current evidence suggests that CLE and SLE are closely related yet distinct diseases with different courses[4].

CLE is a significant cause of morbidity, potentially affecting psychological well-being and quality of life to an extent similar to or greater than chronic hypertension, congestive heart failure, type 2 diabetes, and heart attacks[6].

The only US Food and Drug Administration (FDA)-approved drugs for CLE are hydroxychloroquine and glucocorticoids, which were approved under earlier regulations before the current clinical trial standards[7,8]. Off-label treatments include other antimalarials such as chloroquine and quinacrine, as well as immunosuppressants such as methotrexate and mycophenolate mofetil. Additional treatment options include dapsone, retinoids (such as acitretin, isotretinoin, and alitretinoin), thalidomide, and lenalidomide[7,8]. No systemic treatments for CLE have been approved by the FDA in over 60 years, but, recently, new targeted therapies for SLE, such as belimumab and anifrolumab, have recently received approval from the (FDA) and European Medicines Agency (EMA) and their specific effect on cutaneous lesions is also being evaluated.

Most information on the pathogenesis, clinical trials, and new drugs for CLE comes from studies based on SLE, with limited involvement of dermatologists and often without properly distinguishing CDLE from acute and subacute variants.

Patients included in SLE clinical trials must have a diagnosis of SLE, including a positive ANA, according to the most recent ACR/EULAR classification criteria. As a result, this requirement excludes the majority of CLE patients who have negative ANA and do not have concomitant SLE, despite the potential benefit from targeted treatments also for CLE[9]. Moreover, the outcome measures typically include only a few non-specific skin assessments, such as “rash” or “alopecia”, and many trials do not consider the use of the Cutaneous Lupus Erythematosus Disease Activity Index (CLASI) as a primary endpoint[9,10]. SLE patients with skin manifestations do not accurately represent CLE patients, and assessing cutaneous improvement in these trials with CLE-Investigator’s Global Assessment criteria is insufficient for evaluating skin disease activity[9].

Consequently, drugs that may be effective for CLE but do not demonstrate efficacy for SLE may not receive approval. Therefore, clinical trials dedicated to

CLE patients are needed to directly assess the efficacy of new tailored treatment options.

This review provides a brief overview of CLE pathogenesis and the current landscape of development for new and emerging systemic therapies for CLE.

Pathogenesis

Chronic inflammation, which creates a positive feedback loop involving both the innate and adaptive immune systems, is a characteristic feature across all CLE subtypes[1,7].

A complex interaction between genetic variants traits, epigenetic modifications, and environmental triggers underlies the pathogenesis. Environmental triggers such as ultraviolet light exposure, smoking, or certain drugs can lead to cellular damage in individuals with a susceptible genetic and epigenetic background[11,12]. Involved genes encode proteins that participate in cell signaling, cell death cascades (apoptosis and ubiquitination), DNA degradation (such as DNAse/TREX1 defects), clearance of cell debris (immune complexes), as well as cellular adhesion and the activation or regulation of the immune system, including innate immune system activation and B-cell/T-cell function[1,13].

Keratinocyte apoptosis and secondary necroptosis release cytosolic and nuclear debris into the extracellular space and instigate an inflammatory response with the release of damage-associated molecular pattern molecules, such as high mobility group box 1 protein, autoantigens such as Ro52 and Ro60, and cytokines such as CXCL chemokines, interleukins (ILs), and interferons (IFNs)[1,13,14]. It is also known that elevated expression of type I interferon (IFN-I) plays a central role in the pathogenesis of LE by creating an inflammatory loop[15]. This further amplifies the autoimmune response by recruiting plasmacytoid dendritic cells (pDCs) and enhancing antigen presentation. Upon activation, B cells produce autoantibodies against nuclear components, while cytotoxic T cells target basal keratinocytes, leading to interface dermatitis, particularly in CLE subtypes with superficial involvement[1,17]. Cytotoxic markers like granzyme B, expressed by CD8+ T cells, are found in CLE skin lesions and are likely induced by INF-I[18] (Fig. 1).

Until recently, it was believed that IFN-I was produced by recruited pDCs. However, recent data indicate that pDCs in the lesional skin and peripheral blood of CLE patients may not be the main producers of IFN-I, whereas in the skin keratinocytes might produce high amounts of INF-I[1,16]. Recent trials of drugs targeting pathways involving IFN-I have shown promising results in CLE, but the role of pDCs and INFs in the pathogenesis of CLE requires further investigation.

Targeted therapeutic agents

Based on CLE pathogenesis, potential therapeutic targets include different inflammatory cytokines and their receptors or intracellular targets and different cells involved in CLE pathogenesis, namely plasmacytoid DC, B, and T cells. Here, we review the new and emerging potential treatments in CLE focusing on each specific target (Table 1).

IFN-targeted therapies

INF RECEPTOR INHIBITION

Anifrolumab

Anifrolumab is a fully human, effector-null, IgG1κ monoclonal antibody directed against the INF-α/β/ω receptor subunit 1 (IFNAR1), providing a total inhibition of all IFN-I (IFNα, IFNβ, IFNε, IFNκ, and IFNω) and thereby interrupting the positive feedback loop of inflammation and keratinocyte damage[19,20]. Compared to skin tissue from other autoimmune diseases, the involved skin of patients with SLE exhibits one of the highest signatures for INF activity[20]. Similarly, Merola et al. demonstrated this finding using RNA tape sampling analyses in chronic lupus erythematosus[21].

Anifrolumab has been approved by the FDA since 2021 and by the EMA since 2022 for the treatment of SLE, based on data from one phase II (MUSE) and two phase III (TULIP-1, TULIP-2) clinical trials.

In all published phase II and III clinical trials, CLASI was used to assess changes in skin manifestations. In TULIP-1 trial, no differences in CLASI scores were found between patients receiving anifrolumab and those on placebo. In contrast, TULIP-2 trial showed a statistically significant difference, with 49% of anifrolumab-treated patients achieving a ≥ 50% improvement in CLASI-A compared to 25% in the placebo group[22,23]. In addition, the *post hoc* analysis of the MUSE phase 2 trial indicated that anifrolumab was more effective in treating skin lesions that in addressing arthritis, particularly among patients with a strong IFN signature[20]. A 3-year extension of the TULIP-2 trial has demonstrated a favorable long-term safety profile for anifrolumab. The most common side effects were mild to moderate respiratory infections, with a slightly

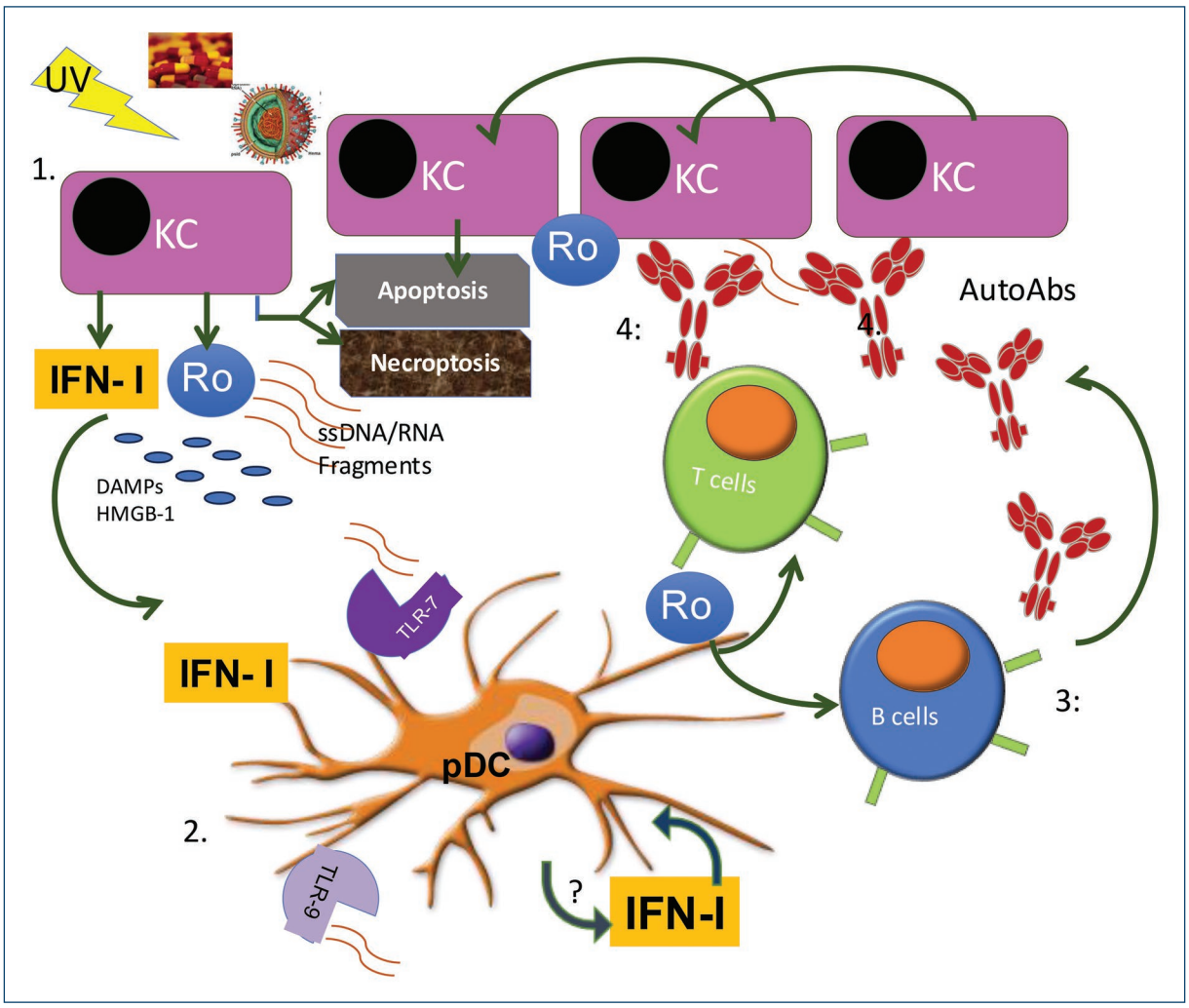

Fig. 1. Schematic presentation of the circular pathomechanisms involved in cutaneous lupus erythematosus (CLE), showing the contribution of both the innate and acquired immune response involving keratinocytes (KC), plasmocytoid dendritic cells (pDC), B and T cells, even though other cells are also involved, namely neutrophils. 1: in susceptible individuals, keratinocytes respond in an exaggerated way to the effect environmental factors such as ultraviolet light, smoke, drugs, or virus and enter a process of apoptosis or necroptosis, releasing cytosolic and nuclear debris into the extracellular space, namely RNA fragments and ribonucleoproteins (Ro52/60) that, upon deficiency of degradation, will be recognized as autoantigens. Keratinocytes also release damage-associated molecular patterns (DAMPs), such as high mobility group box 1 protein (HMBG-1), and pro-inflammatory mediators such as chemokines, interleukins, and especially type I interferons (IFN-I). 2: Toll-like receptors 7/9 (TLR-7/9) present on pDC can recognize RNA fragments and under the influence of INF-I will be activated to enhance antigen presentation to T and B cells. 3: B cells produce autoantibodies that will bind circulating or free autoantigens. 4: T cells, particularly cytotoxic T cells, target basal keratinocytes inducing their necroptosis/apoptosis with further contribution to the reinitiation the inflammatory cycle. The elevated expression of IFN-I plays a central role in the initiation and perpetuation of an inflammatory loop in CLE.

elevated risk of viral infections such as varicella-zoster and herpes zoster, and also influenza, nasopharyngitis, and bronchitis. Less common side effects included mucosal candidiasis and joint or muscle pain[46,47].

A multicenter, randomized, double-blind, placebo-controlled, phase III study (LAVENDER) is ongoing to evaluate the efficacy and safety of anifrolumab in adults with refractory CCLE and/or SCLE. The results of this study will further elucidate the potential benefits of anifrolumab in patients with isolated CLE.

Real-life observational studies support the efficacy of anifrolumab in treating refractory mucocutaneous

Table 1. Main therapeutic targets in development for cutaneous lupus erythematosus and respective drugs

Therapeutic target	Drug	Administration
Type I interferon		
Interferon-α/β/ω receptor subunit 1	Anifrolumab*†	i.v./s.c.
Interferons	Rontalizumab and sifalimumab	i.v./s.c.
TYK2	Deucravacitinib†	Oral
PanJAK1	Tofacitinib†	Oral
JAK1/2	Baricitinib†	Oral
JAK1	Upadacitinib†	Oral
PanJAK	Delgocitinib†	Topical
JAK1/2	Ruxolitinib†	Topical
Plasmacytoid dendritic cells		
Blood dendritic cell antigen 2	Litifilimab	s.c.
Immunoglobulin-like transcript 7	Daxdilimab	s.c.
Cereblon-targeting ligands	Iberdomide	Oral
B cells		
B-cell activity factor	Belimumab*	i.v.
CD20	Rituximab*	i.v.
BTK	Fenebrutinib and branebrutinib	Oral
T cells		
CD40 ligand	Dapirolizumab	i.v.
CD28	Lulizumab	s.c.
Interleukins 12/23	Ustekinumab†	s.c.
TNF-alfa	Etanercept	s.c.
Others		
Extracellular RNA	RSLV-132	i.v.
TLR-7	DS-7011a	i.v./s.c.

*Approved for SLE.
†Approved for other indications and available in the European and/or American market.
TYK: tyrosine kinase; JAK: janus kinase; BTK: Bruton tyrosine kinase; TNF: tumor necrosis factor; TLR: toll-like receptor; i.v: intravenous; s.c.: subcutaneous.

manifestations in patients with CLE[24-45]. A review on the real-world efficacy of anifrolumab in 137 SLE patients showed promising results across almost all CLE variants, including DLE, ACLE, SCLE, ChLE, LET, lupus panniculitis (*"lupus profundus"*), and lupus pernio. Rapid improvement was observed within 4 weeks, with fewer than 20% of patients being non-responders[46]. These results may suggest that patients with skin-limited lupus may also significantly benefit from anifrolumab treatment.

Rontalizumab and sifalimumab

Rontalizumab and sifalimumab, two others humanized IgG1 anti-IFN-α monoclonal antibodies targeting multiple IFN-α subtypes, showed mixed results in phase II trials and have not progressed to phase III trials[48].

The ROSE trial evaluated the efficacy of rontalizumab in 238 patients with moderate-to-severe SLE but failed to meet its primary and secondary endpoints in both overall patient group and on those with a high IFN signature. Nevertheless, an exploratory analysis found unexpectedly higher benefits for patients with low IFN scores, emphasizing the importance of stratifying lupus patients based on their IFN signature[48].

Sifalimumab, tested in a phase IIb trial in 431 patients with active SLE, showed a greater percentage of patients reaching the primary endpoint compared to placebo, with consistent improvements across various measures, including CLASI[49]. However, higher herpes zoster infection rates and a decision to prioritize the more promising anifrolumab led to the discontinuation of further sifalimumab studies[49].

Janus kinase/signal transducers and activators of transcription (JAK/STAT) inhibitors

Deucravacitinib

Deucravacitib is an oral selective allosteric tyrosine kinase-2 (TYK2) inhibitor approved for the treatment

of moderate-to-severe plaque psoriasis[50]. The mechanism of action involves suppressing the downstream effects of various cytokines, including IL-10, IL-12, IL-23, and IFN-I. This cytokine profile is involved in SLE and DLE pathogenesis[51].

Recently, there have been promising results for TYK-2 inhibitors in the management of LE. In the PAISLEY phase II trial for SLE, 69.6% of patients with a baseline CLASI-A score of ≥ 10 showed a CLASI-50 response at week 48 in the 3 mg BID group, compared to 16.7% in the placebo group[52]. This supports the potential benefit of deucravacitinib across various SLE skin manifestations. There are already some case reports indicating the efficacy of deucravacitinib in treating recalcitrant LET, SCLE, and DLE[49,53-55]. In addition, a reduction in IFN-I signaling was observed at all dosage levels[52].

Most of adverse events described were mild-to-moderate with upper respiratory tract infections, urinary tract infections, nasopharyngitis, and headaches being the most frequently reported[52].

At present, two phase III studies for deucravacitinib in SLE (NCT05617677 and NCT05620407) and a phase II trial focusing on patients with active DLE/SCLE are ongoing (NCT04857034).

Baricitinib

Baricitinib, an oral selective JAK1 and JAK2 inhibitor approved for rheumatoid arthritis, atopic dermatitis, and alopecia areata, showed promising results as a treatment for SLE in phase 2 trials and the SLE-BRAVE-I study[56]. In this latter study, the primary endpoint (SLE Responder Index 4 at week 52) was achieved in the 4 mg group[56]. However, these positive results were not confirmed in the SLE-BRAVE-II trial, where baricitinib failed to meet the primary efficacy endpoint and major secondary endpoints[57]. Nevertheless, there are a few reports showing efficacy in CLE, namely in lupus panniculitis and linear CLE[58,59].

Tofacitinib

The phase II pilot study was discontinued due to low recruitment. However, preliminary results showed that among the five DLE patients who received 5 mg of oral tofacitinib twice daily, two experienced a 75% improvement in their CLASI-A scores by week 24[7,60]. Results from the phase Ib/II trial in CLE are not yet available (NCT03288324).

In addition, case reports demonstrated that tofacitinib-induced rapid remission in seven out of ten patients with active skin and/or musculoskeletal disease, as well as significant improvement in three patients with recalcitrant cutaneous SLE[61,62].

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor used in the treatment of rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, and ulcerative colitis. In a phase II double-blind trial including 341 SLE patients, both the combination therapy of elsubrutinib and upadacitinib, as well as upadacitinib monotherapy, significantly improved disease activity and reduced the risk of relapse[61].

There are few case reports indicating significant improvement in cutaneous lesions associated with SCLE, LET, and DLE[63-65].

Filgotinib and lanraplenib

Filgotinib, a JAK1 inhibitor, and lanraplenib, a spleen TYK inhibitor, were tested in a phase II trial in patients with moderate-to-severe CLE[7]. The trial failed to meet its primary endpoint of change in the CLASI-A score at week 12 and one serious adverse event occurred in the filgotinib group[61,66].

Delgocitinib

Delgocitinib, a TYK2 and pan-JAK inhibitor, was assessed in a phase II trial (NCT03958955) that was discontinued due to insufficient recruitment[1,7]. The trial did not achieve its primary endpoint at week 6[7]. However, a recent case report described the successful treatment of facial SCLE lesions using delgocitinib 0.5% ointment[67].

Ruxolitinib

Ruxolitinib, a JAK 1/2 inhibitor, is effective in the treatment of several immunologic skin diseases, including alopecia areata and atopic dermatitis, and has also been shown to control skin lesions in a case of ChLE[68]. Using *in vitro* models, including a 3D epidermal model stimulated by nucleic acid fragments, ruxolitinib was shown to decrease levels of CXCL10, a key chemokine induced by IFN-I[68,69].

Currently, an open-label phase II trial is underway to evaluate the efficacy of ruxolitinib 1.5% cream in adults with DLE.

pDC-targeted therapies

Litifilimab

The blood dendritic cell antigen 2 (BDCA2), a receptor specific to the surface of pDCs, acts as a negative regulator of INF-I production, a well-known key factor in the pathogenesis of SLE[70]. Litifilimab is a subcutaneous humanized IgG1 monoclonal antibody that binds to BDCA2, causing its rapid internalization from the surface of pDCs. This process results in the subsequent downregulation of signaling through toll-like receptor (TLR) 7/9 that recognizes nucleic acid fragments and subsequent reduction in the production of all type I and III IFNs, IL-6, and several chemokines[9,70].

In the phase I trial (NCT02106897), which involved 54 healthy controls and 12 SLE patients, single doses of litifilimab showed a favorable safety profile. Furthermore, serum concentrations of litifilimab were correlated with decreased expression of IFN, as well as reduction in CLASI-A scores and skin IFN-I –induced proteins in skin[7,70]. Of the eight patients who received a single dose, six showed a reduction of at least 4 points in their CLASI-A score at week 4 and/or week 12, which was corroborated by decreased IFN-I–induced proteins levels in lesional biopsies[7,70].

LILAC was a phase II, multicenter, placebo-controlled, two-part trial, which evaluated the efficacy of litifilimab in patients with SLE. The Part A of the study involved 110 patients with SLE and showed that litifilimab at a dose of 450 mg was superior to placebo in joint involvement, but secondary outcomes, as the CLASI-50 response at week 24 and changes in CLASI-A score at weeks 12, 16 and 24, did not show statistically significant differences between treatment and placebo groups[7,71]. In Part B that enrolled 132 participants with moderate-to-severe SCLE and/or DLE, the percentage change in CLASI-A from baseline at 16 weeks showed significant improvements in all litifilimab dosing groups (50, 150, and 450 mg arms) compared to placebo. Subsequent analysis confirmed a statistically significant dose-response effect for this primary endpoint, but, due to limited statistical power, the study could not effectively evaluate secondary endpoints[7,71,72].

Most adverse events in the litifilimab group were mild or moderate, with diarrhea, nasopharyngitis, urinary tract infections, falls, and headaches being the most frequently reported, occurring in ≥ 5% of the participants. In addition, viral infections, namely three cases of influenza, two cases of herpes zoster, one case of herpes keratitis, and one case of viral gastroenteritis, including four serious adverse events, occurred in the litifilimab groups[71,72].

A phase II Part A/phase III Part B multicenter, randomized, double-blind trial (AMETHYST, NCT05531565) evaluating litifilimab in SCLE and CCLE is currently underway.

Future studies should investigate whether treatment of CLE patients with litifilimab can prevent progression to SLE or development of lupus nephritis.

Daxdilimab

Daxdilimab is a monoclonal antibody that targets immunoglobulin-like transcript 7, leading to the depletion of pDCs. Following a favorable improvement in the CLASI-A response observed in its phase I trial, recruitment is underway for a phase II trial focusing on patients with moderate-to-severe DLE (NCT05591222)[73].

Cereblon-targeting ligands

Iberdomide

The protein cereblon (CRBN) is a substrate receptor of the cullin 4-really interesting new gene (RING)-E3 ubiquitin ligase complex $CRL4^{CRBN}$, which mediates selective protein ubiquitination and degradation through the proteasome[74,75]. Iberdomide, a high-affinity CRBN ligand, inhibits this complex, promoting polyubiquitination and proteasomal degradation of hematopoietic transcription factors Ikaros (IKZF1) and Aiolos (IKZF3). This results in the suppression of pDCs and IFN-I response, reduction in B cells and anti-dsDNA antibodies, and an increase in IL-2 production and regulatory T (Treg) cells[74,75].

A phase II randomized, double-blind, placebo-controlled, ascending-dose trial evaluated iberdomide safety and efficacy in active SLE patients. At week 24, the 0.45 mg iberdomide dose achieved a 54% SRI-4 response rate compared to 35% with placebo, with higher responses in patients with a high IFN-I or Aiolos gene signature. These responses were maintained or improved over 52 weeks among all dosing groups. Secondary outcomes showed that the 0.45 mg dose had significant CLASI-50 response differences from placebo in SCLE and CCLE, but not in ACLE[76].

Gastrointestinal events and infections, mostly mild or moderate and dose-dependent, were the most common adverse events[76].

Iberdomide has not undergone a skin-specific trial and no phase III trials are currently planned.

B-cell–targeted therapies

Belimumab

Belimumab is a fully humanized IgG1γ monoclonal antibody that inhibits selectively the B-cell activity factor (BAFF), a crucial cytokine that regulates B-cell survival and activation. BAFF is a member of the tumor necrosis factor ligand superfamily primarily found on hematopoietic cells, but also expressed in epithelial cells, adipocytes, and keratinocytes[77]. Studies showed that BAFF overexpression and elevated serum levels were linked to increased SLE disease activity and, for this reason, belimumab became the first biological treatment to be tested and subsequently approved for SLE treatment[77].

A *post hoc* analysis of pooled data from five phase III randomized, placebo-controlled trials (BLISS-76, BLISS-52, North East Asia, BLISS-SC, and EMBRACE) assessed the effects of belimumab on SLE disease activity focusing on specific mucocutaneous manifestations and vasculitis in 3086 patients. At week 52, belimumab group showed significant improvements over placebo in four SELENA-SLEDAI items (vasculitis, rash, alopecia, and mucosal ulcers) and in nine BILAG items (mild maculopapular eruption, localized active discoid lesions, mild alopecia, small mucosal ulceration, malar erythema, subcutaneous nodules, swollen fingers and cutaneous vasculitis), with the largest treatment difference in vasculitis[78]. Improvement in skin disease activity was also confirmed in the Belimumab in Real-Life Setting Study (BeRLiSS-JS)[79]. Current evidence shows that belimumab takes about 20 weeks to achieve a significant clinical response, with its maximum effect seen at 1 year[7,77]. In addition, belimumab has been associated with increased risk of depression, self-injury, and suicide, so it should be used with caution in psychiatric patients[77].

A phase III, multicenter 24-week trial (BELI-SKIN, EUDRA-CT: 2017-003051-35) is now underway to assess efficacy of belimumab in refractory cutaneous manifestations.

Rituximab

Rituximab is a monoclonal antibody directed against the CD20 antigen, leading to B cell depletion. At present, it is recommended in SLE guidelines for cases resistant to standard immunosuppressors. However, rituximab failed to achieve efficacy in improving skin activity in two large randomized controlled trials in SLE patients (EXPLORER and LUNAR trials)[80].

Subsequent studies have demonstrated mixed results, with a retrospective study suggesting that rituximab may be effective in the treatment of severe CLE in some patients with systemic disease, especially those with acute and non-specific types[81]. Moreover, a prospective study in SLE patients described new-onset CCLE or SCLE flares with rituximab treatment in patients with no baseline skin activity[82].

Fenebrutinib and branebrutinib

Fenebrutinib and branebrutinib are selective Bruton's tyrosine kinase inhibitors that target B cells and myeloid cells involved in the pathogenesis of SLE. In a phase II trial, fenebrutinib failed to demonstrate efficacy in patients with moderate to severe active SLE. The trial results revealed no significant difference in the SRI-4 between fenebrutinib-treated group and placebo group[83]. A phase II trial showed that branebrutinib was not superior to placebo in the percentage of patients achieving a ≥ 50% decrease from baseline mCLASI activity score at week 24, which measured skin erythema and scale/hypertrophy and inflammation of the scalp[7].

T-cell–targeted therapies

Dapirolizumab

Dapirolizumab is an antibody fragment that targets the CD40 ligand (CD40L), mainly expressed on activated T cells and platelets. CD40L has long been an attractive therapeutic target due to its crucial role in adaptive immune activation and driving pathological processes in SLE. However, previous studies with a prior anti-CD40L prototype showed increased thrombo-embolic events, possibly due to platelet aggregation resulting from fragment crystallizable (Fc)-mediated cross-linking[84,85]. Therefore, dairolizumab was developed without a functional Fc domain to mitigate this effect.

In a phase II randomized, placebo-controlled study of dapirolizumab for SLE, secondary outcomes showed that dapirolizumab group had greater improvements in CLASI activity scores at week 24 compared to the placebo, with continued superiority at week 48. Although

infection rates were higher in these patients, there was no increased risk of thromboembolism[85].

A phase III trial (NCT04294667) in SLE is ongoing but does not include any skin-specific primary or secondary outcome measures.

Lulizumab

Lulizumab is a monoclonal antibody that targets CD28, a crucial T cell costimulatory molecule, thereby preventing the activation of pathogenic T cells involved in autoimmune diseases[86].

In a 24-week randomized, multicenter, double-blind study of 349 patients with SLE, lulizumab did not meet its primary endpoint of BICLA response rates. Additional efficacy outcome measures, which included CLASI-20 and CLASI-50, also did not reveal significant differences between groups[86].

Other targets

Ustekinumab

Ustekinumab is a monoclonal antibody inhibiting the p40 subunit of IL-12 and IL-23, approved for the treatment of psoriasis, psoriatic arthritis, and inflammatory bowel disease. Increased levels of these ILs in serum and tissue samples from patients with SLE, have sparked interest in ustekinumab for treating SLE and potentially CLE[87].

A *post hoc* analysis of the CLASI-50 response at week 24 demonstrated that ustekinumab was superior to placebo. Although these results seemed robust, in the phase III LOTUS study, there were no significant differences between treatment groups in the response rates for SRI-4 at week or CLASI activity improvement at week 52. The primary and secondary endpoints were not achieved, and the study was discontinued[88].

Etanercept

Etanercept is a TNF-α inhibitor that potentially treats active lesions with a reduced risk of systemic TNF effects, such as disease flares and drug-induced SCLE. In a phase II trial (NCT02656082) evaluating the efficacy and safety of intra-dermal injection of etanercept in discoid lupus erythematosus, 52% achieve a 20% decrease in the modified limited Score of Activity and Damage in DLE (ML-SADDLE) at week 12[7].

RSLV-132

Circulating extracellular RNA is the primary trigger of IFN-I in SLE, which plays a central role in the SLE pathogenesis. RSLV-132 is a novel catalytically active human RNase molecule fused to human IgG1 Fc that digests extracellular RNA, thereby inhibiting immune activation through Toll-like receptors and IFN pathways[89].

A phase II trial involving SLE patients with moderate-severe cutaneous disease activity showed no significant improvement in CLASI score after 6 months of RSLV-132 therapy. However, a trend toward clinical improvement was observed in participants with higher SLEDAI and CLASI scores, potentially suggesting that patients with more active systemic disease are most likely to benefit from RNase therapy[89].

DS-7011a

DS-7011a is a monoclonal antibody against TLR7 which is thought to contribute to the lupus pathogenesis[77]. Currently a phase 1b/2 randomized, double-blind, placebo-controlled, randomized trial is ongoing to assess the efficacy of DS-7011a in SLE and active CLE.

Other cytokines

Other considered therapies included BT063 (monoclonal antibody targeting IL-10), vobarilizumab (nanobody against IL-6), PF-04236921 (IL-6 monoclonal antibody), and avizakimab (anti-IL-21 monoclonal antibody). However, results from phase II studies were disappointing[7].

Conclusion

CLE is a significant cause of morbidity with a high risk for permanent scarring and depigmentation, which could negatively impact psychological well-being and quality of life of the patients. Treatment of CLE remains challenging due to the insufficient current available therapeutic options and recalcitrant disease, often requiring several immunosuppressive drugs with significant risk of systemic side effects. Therefore, this shortfall in effectively managing the disease highlights the need to develop new and improved treatment options.

While there have been exciting advances in new drugs for SLE, it remains crucial to develop tailored clinical trials focused on CLE patients with validated measures specific to skin disease, at to its different

subtypes. SLE patients with skin involvement do not accurately represent CLE patients, and the outcome measures of SLE trials are insufficient for capturing meaningful changes in skin activity. The identification of selective biomarkers, such IFN signature pointed out in some studies, is fundamental for individualized therapy by classifying potential responders and should be a focus of future research.

New emerging treatments targeting specific pathways involved in CLE pathogenesis, with recent phase II and III trials for anifrolumab, litifilimab, and deucravacitinib, have shown the most promising results, but there is still a long way to find highly efficacious and safe drugs for CLE.

Funding

None.

Conflicts of interest

J. Xará: none; M. Gonçalo has participated in lectures, advisory boards and/or clinical trials from Abbvie, Almirall, Amgen, Astra-Zeneca, Biogen, Leo Pharma, Lilly, Novartis, Pfizer, Sanofi, Takeda.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Niebel D, de Vos L, Fetter T, Brägelmann C, Wenzel J. Cutaneous lupus erythematosus: an update on pathogenesis and future therapeutic directions. Am J Clin Dermatol. 2023;24:521-40.
2. Kuhn A, Landmann A. The classification and diagnosis of cutaneous lupus erythematosus. J Autoimmun. 2014;48-9:14-9.
3. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. Nat Rev Rheumatol. 2019;15: 519-32.
4. Fetter T, Braegelmann C, de Vos L, Wenzel J. Current concepts on pathogenic mechanisms and histopathology in cutaneous lupus erythematosus. Front Med (Lausanne). 2022;9:915828.
5. Vera-Recabarren MA, García-Carrasco M, Ramos-Casals M, Herrero C. Comparative analysis of subacute cutaneous lupus erythematosus and chronic cutaneous lupus erythematosus: clinical and immunological study of 270 patients. Br J Dermatol. 2010;162:91-101.
6. Klein R, Moghadam-Kia S, Taylor L, Coley C, Okawa J, LoMonico J, et al. Quality of life in cutaneous lupus erythematosus. J Am Acad Dermatol. 2011;64:849-58.
7. Xie L, Lopes Almeida Gomes L, Stone CJ, Faden DF, Werth VP. An update on clinical trials for cutaneous lupus erythematosus. J Dermatol. 2024;51:885-94.
8. Kuhn A, Aberer E, Bata-Csörgő Z, Caproni M, Dreher A, Frances C, et al. S2k guideline for treatment of cutaneous lupus erythematosus - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2017;31:389-404.
9. Cho SK, Vazquez T, Werth VP. Litifilimab (BIIB059), a promising investigational drug for cutaneous lupus erythematosus. Expert Opin Investig Drugs. 2023;32:345-53.
10. Chakka S, Krain RL, Concha JS, Chong BF, Merola JF, Werth VP. The CLASI, a validated tool for the evaluation of skin disease in lupus erythematosus: a narrative review. Ann Transl Med. 2021;9:431.
11. Meller S, Winterberg F, Gilliet M, Müller A, Lauceviciute I, Rieker J, et al. Ultraviolet radiation-induced injury, chemokines, and leuko- cyte recruitment: an amplification cycle triggering cutaneous lupus erythematosus. Arthritis Rheum. 2005;52:1504-16.
12. Rodríguez RD, Alarcón-Riquelme ME. Exploring the contribution of genetics on the clinical manifestations of systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2024;15:101971.
13. Tsokos GC. Autoimmunity and organ damage in systemic lupus erythematosus. Nat Immunol. 2020;21:605-14.
14. Stannard JN, Kahlenberg JM. Cutaneous lupus erythematosus: Updates on pathogenesis and associations with systemic lupus. Curr Opin Rheumatol. 2016;28:453-9.
15. Crow MK. Type I interfern in the pathogenesis of lupus. J Immunol. 2014;192:5459-68.
16. Vazquez T, Patel J, Kodali N, Diaz D, Bashir MM, Chin F, et al. Plasmacytoid dendritic cells are not major producers of type 1 interferon in cutaneous lupus: an in depth immunoprofile of subacute and discoid lupus. J Invest Dermatol. 2023;144:1262-1272.e7.
17. Grassi M, Capello F, Bertolino L, Seia Z, Pippione M. Identification of granzyme B-expressing CD-8-positive T cells in lympho- cytic inflammatory infiltrate in cutaneous lupus erythematosus and in dermatomyositis. Clin Exp Dermatol. 2009;34:910-4.
18. Wenzel J, Uerlich M, Wörrenkämper E, Freutel S, Bieber T, Tüting T. Scarring skin lesions of discoid lupus erythematosus are characterized by high numbers of skin-homing cytotoxic lymphocytes associated with strong expression of the type I interferon-induced protein MxA. Br J Dermatol. 2005;153:1011-5.
19. Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KC, Vital EM, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol. 2019;1:e208-19.
20. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis Rheumatol. 2017;69:376-86.
21. Merola JF, Wang W, Wager CG, Hamann S, Zhang X, Thai A, et al. RNA tape sampling in cutaneous lupus erythematosus discriminates affected from unaffected and healthy volunteer skin. Lupus Sci Med. 2021;8:e000428.
22. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med. 2020;382:211-21.
23. Merrill JT, Furie R, Werth VP, Khamashta M, Drappa J, Wang L, et al. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. Lupus Sci Med 2018;5:e000284.
24. Plüß M, Piantoni S, Wincup C, Korsten P. Rapid response of refractory systemic lupus erythematosus skin manifestations to anifrolumab-a case-based review of clinical trial data suggesting a domain-based therapeutic approach. J Clin Med. 2022;11:3449.
25. Blum FR, Sampath AJ, Foulke GT. Anifrolumab for treatment of refractory cutaneous lupus erythematosus. Clin Exp Dermatol. 2022;47:1998-2001.
26. Shope C, Andrews L, Cunningham M, Connett J. A case of Rowell syndrome with excellent improvement following anifrolumab. JAAD Case Rep. 2022;31:27-30.
27. Trentin F, Tani C, Elefante E, Stagnaro C, Zucchi D, Mosca M. Treatment with anifrolumab for discoid lupus erythematosus. J Am Acad Dermatol. 2023;159:224-6.
28. Trentin F, Tani C, Cauli A, Ceccarelli F, Ciccia F, Conti F, et al. AB0558 Anifrolumab in refractory systemic lupus erythematosus: a real-life, multicenter study. Ann Rheum Dis. 2023;82:1476.

29. Schaeffer M, Lipsker D. Paradoxical joint and muscle pain in a patient treated with anifrolumab and belimumab. J Eur Acad Dermatol Venereol. 2023;37:e1198-9.
30. Shaw K, Sanchez-Melendez S, Taylor D, Barker J, LaChance A, Shahriari N, et al. Assessment of clinical response to Anifrolumab in patients with refractory discoid lupus erythematosus. J Am Acad Dermatol. 2023;159:560-3.
31. Shaw K, Taylor D, Sanchez-Melendez S, Barker J, Lonowski S, Shahriari N, et al. Improvement in mucosal discoid lupus erythematosus with anifrolumab. Clin Exp Dermatol. 2023;27:llad190.
32. Kowalski EH, Stolarczyk A, Richardson CT. Successful treatment of severe chronic cutaneous lupus with anifrolumab: A series of 6 cases. JAAD Case Rep. 2023;4:21-9.
33. Carter LM, Wigston Z, Laws P, Vital EM. Rapid efficacy of anifrolumab across multiple subtypes of recalcitrant cutaneous lupus erythematosus parallels changes in discrete subsets of blood transcriptomic and cellular biomarkers. Br J Dermatol. 2023;189:210-8.
34. Viedma-Martínez M, Garrido-Gamarro B, Villegas-Romero I, Millán-Cayetano FJ, Jimenez-Gallo D, Linares-Barrios M. Real-life experience of anifrolumab for cutaneous lupus erythematous. J Eur Acad Dermatol Venereol. 2023;38:e576-e583.
35. Günther C, Wolf C, Fennen L, Rösing S, Beissert S, Aringer M, et al. Case report: response of cutaneous lupus lesions in SLE to interferon receptor blockade parallels reduction of interferon score in blood. Front Immunol. 2023;14:1253279.
36. Woodbury MJ, Smith KN, Smith JS, Merola JF. Anifrolumab for the treatment of refractory chilblain lupus erythematosus. JAAD Case Rep. 2023;48:69-71.
37. Chasset F, Jaume L, Mathian A, Abisror N, Dutheil A, Barbaud A, et al. Rapid efficacy of anifrolumab in refractory cutaneous lupus erythematosus. J Am Acad Dermatol. 2023;89:171-3.
38. Martín-Torregrosa D, Mansilla-Polo M, Lasheras-Pérez MA, Botella-Estrada R, Torres-Navarro I. Refractory cutaneous lupus erythematosus successfully treated with anifrolumab: a case series. Int J Dermatol. 2024;63:368-70.
39. Han S, Ferrer J, Bittar M, Jones A. Alopecia secondary to severe discoid lupus responding to anifrolumab. Int J Womens Dermatol. 2023;9:e098.
40. Khan MA, Khan FH, Khan HB, Saadeh C, Davey N. Role of anifrolumab in refractory cutaneous manifestations of lupus erythematosus: a case series and literature review. Cureus. 2023;15:e39553.
41. Bao A, Petri MA, Fava A, Kang J. Case series of anifrolumab for treatment of cutaneous lupus erythematosus and lupus-related mucocutaneous manifestations in patients with SLE. Lupus Sci Med. 2023;10:e001007.
42. Paolino G, Ramirez GA, Calabrese C, Moroni L, Bianchi VG, Bozzolo EP, et al. Anifrolumab for moderate and severe muco-cutaneous lupus erythematosus: a monocentric experience and review of the current literature. Biomedicines. 2023;11:2904.
43. Miyazaki Y, Funada M, Nakayamada S, Sonomoto K, Tanaka H, Hanami K, et al. Safety and efficacy of anifrolumab therapy in systemic lupus erythematosus in real-world clinical practice: LOOPS registry. Rheumatology (Oxford). 2024;1; 63:2345-2354.
44. Flouda S, Emmanouilidou E, Karamanakos A, Koumaki D, Katsifis-Nezis D, Repa A, et al. Anifrolumab for systemic lupus erythematosus with multi-refractory skin disease: a case series of 18 patients. Lupus. 2024;33:1248-53.
45. Karagenova R, Vodusek Z, Krimins R, Krieger A, Timlin H. Treatment with voclosporin and anifrolumab in a patient with lupus nephritis and refractory discoid lupus erythematosus: a case report and literature review. Cureus. 2024;16:e55321.
46. Díaz-Planellas S, Katsifis-Nezis D, Fanouriakis A. Clinical trials of interferon inhibitors in systemic lupus erythematosus and preliminary real-world efficacy of anifrolumab. Mediterr J Rheumatol. 2024;35:381-91.
47. Cingireddy AR, Ramini N, Cingireddy AR. Evaluation of the efficacy and safety of anifrolumab in moderate-to-severe systemic lupus erythematosus. Cureus. 2024;16:e63966.
48. Kalunian KC, Merrill JT, Maciuca R, McBride JM, Townsend MJ, Wei X, et al. A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2016;75:196-202.
49. Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, et al. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016;75:1909-16.
50. Ezeh N, Vleugels RA, Shahriari N. Discoid lupus erythematosus successfully treated with deucravacitinib. JAAD Case Rep. 2024;49:59-61.
51. Morand E, Merola JF, Tanaka Y, Gladman D, Fleischmann R. TYK2: an emerging therapeutic target in rheumatic disease. Nat Rev Rheumatol. 2024;20:232-40.
52. Morand E, Pike M, Merrill JT, van Vollenhoven R, Werth VP, Hobar C, et al. Deucravacitinib, a tyrosine kinase 2 inhibitor, in systemic lupus erythematosus: a phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2023;75:242-52.
53. Zhang A, Gaffney RG, Merola JF. Treatment of recalcitrant lupus erythematosus tumidus with deucravacitinib. JAAD Case Rep. 2024;45:110-2.
54. Bouché N, Al-Saedy MA, Song EJ. Successful treatment of refractory subacute cutaneous lupus erythematosus with deucravacitinib. JAAD Case Rep. 2023;39:93-5.
55. Kurz B, Ivanova I, Drexler K, Berneburg M, Gunther F, Niebel D. Rapid clinical improvement of refractory subacute cutaneous lupus erythematosus with oral tyrosine kinase 2 inhibitor deucravacitinib: a case report. J Eur Acad Dermatol Venereol. 2024;38:e434-6.
56. Morand EF, Vital EM, Petri M, van Vollenhoven R, Wallace DJ, Mosca M, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE- BRAVE-I). Lancet. 2023;401:1001-10.
57. Petri M, Bruce IN, Dörner T, Tanaka Y, Morand EF, Kalunian KC, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). Lancet. 2023;401:1011-9.
58. Chen J, Luo Y, Duan Y, Wang L, Long H, Liu Y, et al. A double-blind pilot study of oral baricitinib in adult patients with lupus erythematosus panniculitis. J Dermatol. 2024;51:1434-40.
59. Zhan J, Chen F, Jin Y, Yan L, Cao J, Xuan X, et al. Blaschko linear lupus erythematosus treated with baricitinib: a case report. J Dermatol. 2023;50:e213-5.
60. Alsukait S, Learned C, Rosmarin D. Open-label phase 2 pilot study of oral tofacitinib in adult subjects with discoid lupus erythematosus (DLE). J Drugs Dermatol. 2023;22:425-7.
61. Moysidou GS, Dara A. JAK inhibition as a potential treatment target in systemic lupus erythematosus. Mediterr J Rheumatol. 2024;35:37-44.
62. You H, Zhang G, Wang Q, Zhang S, Zhao J, Tian X, et al. Successful treatment of arthritis and rash with tofacitinib in systemic lupus erythematosus: the experience from a single Centre. Ann Rheum Dis. 2019;78:1441-3.
63. Ninkov T, Chan J, Von Nida J. A case of terbinafine-induced subacute cutaneous lupus erythematosus rapidly resolving with upadacitinib. Clin Exp Dermatol. 2024;49:1241-3.
64. Maione V, Bighetti S, Bettolini L, Incardona P, Calzavara-Pinton P. Efficacy of upadacitinib in a case of resistant lupus erythematosus tumidus. J Eur Acad Dermatol Venereol. 2024;38:e335-6.
65. Hu W, Zhang S, Lian C. Treatment of discoid lupus erythematosus with upadacitinib: a case report. Clin Cosmet Investig Dermatol. 2023;16:2793-800.
66. Werth VP, Fleischmann R, Robern M, Touma Z, Tiamiyu I, Gurtovaya O, et al. Filgotinib or lanraplenib in moderate to severe cutaneous lupus erythematosus: a phase 2, randomized, double-blind, placebo-controlled study. Rheumatology (Oxford). 2022;61:2413-23.
67. Maruyama A, Katoh N. Subacute cutaneous lupus erythematosus successfully treated with topical delgocitinib. J Dermatol. 2023;50:e110-1.
68. Park JJ, Little AJ, Vesely MD. Treatment of cutaneous lupus with topical ruxolitinib cream. JAAD Case Rep. 2022;28:133-5.
69. Klaeschen AS, Wolf D, Brossart P, Bieber T, Wenzel J. JAK inhibitor ruxolitinib inhibits the expression of cytokines characteristic of cutaneous lupus erythematosus. Exp Dermatol. 2017;26:728-30.
70. Furie R, Werth VP, Merola JF, Stevenson L, Reynolds TL, Naik H, et al. Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. J Clin Invest. 2019;129:1359-71.
71. Furie RA, van Vollenhoven RF, Kalunian K, Navarra S, Romero-Diaz J, Werth VP, et al. Trial of anti-BDCA2 antibody litifilimab for systemic lupus erythematosus. N Engl J Med. 2022;387:894-904.
72. Werth VP, Furie RA, Romero-Diaz J, Navarra S, Kalunian K, van Vollenhoven RF, et al. Trial of anti-BDCA2 antibody litifilimab for cutaneous lupus erythematosus. N Engl J Med. 2022;387:321-31.
73. Karnell JL, Wu Y, Mittereder N, Smith MA, Gunsior M, Yan L, et al. Depleting plasmacytoid dendritic cells reduces local type I interferon responses and disease activity in patients with cutaneous lupus. Sci Transl Med. 2021;13:eabf8442.
74. Furie RA, Hough DR, Gaudy A, Ye Y, Korish S, Delev N, et al. Iberdomide in patients with systemic lupus erythematosus: a randomised, double-blind, placebo-controlled, ascending-dose, phase 2a study. Lupus Sci Med. 2022;9:e000581.
75. Lipsky PE, Vollenhoven RV, Dörner T, Werth VP, Merrill JT, Furie R, et al. Biological impact of iberdomide in patients with active systemic lupus erythematosus. Ann Rheum Dis. 2022;81:1136-42.
76. Merrill JT, Werth VP, Furie R, van Vollenhoven R, Dörner T, Petronijevic M, et al. Phase 2 trial of iberdomide in systemic lupus erythematosus. N Engl J Med. 2022;386:1034-45.
77. Jafari AJ, McGee C, Klimas N, Hebert AA. Monoclonal antibodies for the management of cutaneous lupus erythematosus: an update on the current treatment landscape. Clin Exp Dermatol. 2024;7:llae374.
78. Manzi S, Sanchez-Guerrero J, Yokogawa N, Wenzel J, Ocran-Appiah J, Khamashta M, et al. Belimumab effects on skin in patients with systemic lupus erythematosus: a pooled *post hoc* analysis of five phase 3, randomized, placebo-controlled clinical trials. Arthritis Rheumatol. 2022;74:1933-5.
79. Zen M, Gatto M, Depascale R, Regola F, Fredi M, Andreoli L, et al. Early and late response and glucocorticoid-sparing effect of belimumab in patients with systemic lupus erythematosus with joint and skin manifestations: results from the belimumab in real life setting study-joint and skin (BeRLiSS-JS). J Pers Med. 2023;13:691.

80. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62:222-33.
81. Verdelli A, Corrà A, Mariotti EB, Aimo C, Ruffo di Calabria V, Volpi W, et al. An update on the management of refractory cutaneous lupus erythematosus. Front Med (Lausanne). 2022;9:941003.
82. Vital EM, Wittmann M, Edward S, Yusof MY, MacIver H, Pease CT, et al. Brief report: responses to rituximab suggest B cell- independent inflammation in cutaneous systemic lupus erythematosus. Arthritis Rheumatol. 2015;67:1586-91.
83. Isenberg D, Furie R, Jones NS, Guibord P, Galanter J, Lee C, et al. Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2021;73:1835-46.
85. Furie RA, Bruce IN, Dörner T, Leon MG, Leszczyński P, Urowitz M, et al. Phase 2, randomized, placebo-controlled trial of dapirolizumab pegol in patients with moderate-to-severe active systemic lupus erythematosus. Rheumatology (Oxford). 2021;60:5397-407.
86. Boumpas DT, Furie R, Manzi S, Illei GG, Wallace DJ, Balow JE, et al. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. Arthritis Rheum. 2003;48:719-27.
87. Merrill JT, Shevell DE, Duchesne D, Nowak M, Kundu S, Girgis IG, et al. An anti-CD28 domain antibody, lulizumab, in systemic lupus erythematosus: results of a phase II study. Arthritis Rheumatol. 2018; 70:903-10.
88. Dai H, He F, Tsokos GC, Kyttaris VC. IL-23 Limits the production of IL-2 and promotes autoimmunity in lupus. J Immunol. 2017;199: 903-10.
89. van Vollenhoven RF, Kalunian KC, Dörner T, Hahn BH, Tanaka Y, Gordon RM, et al. Phase 3, multicentre, randomised, placebo-controlled study evaluating the efficacy and safety of ustekinumab in patients with systemic lupus erythematosus. Ann Rheum Dis. 2022;81: 1556-63.
90. Burge DJ, Werth VP, Merrill JT, Boackle S, Posada J. Evaluation of RNase therapy in systemic lupus erythematosus: a randomized phase 2a clinical trial of RSLV-132. Lupus Sci Med. 2024;11:e001113.