

SEMMELWEIS EGYETEM
DOKTORI ISKOLA

Ph.D. értekezések

3554.

BOKOR LAURA ANNA

Bőrgyógyászat és venerológia
című program

Programvezető: Dr. Sárdy Miklós, egyetemi tanár
Témavezetők: Dr. Hidvégi Bernadett Éva, egyetemi docens és
Dr. Bánvölgyi András, egyetemi docens

CUTANEOUS LUPUS ERYTHEMATOSUS: FROM IMMUNOMETABOLISM TO THERAPY

Ph.D. Thesis

Laura Anna Bokor, M.D.

Translational Medicine Program

Károly Rácz Conservative Medicine Division

SEMMELWEIS UNIVERSITY



Supervisors:

Bernadett Hidvégi, M.D., Ph.D.

András Bánvölgyi, M.D., Ph.D.

Official reviewers:

Gabriella Emri, M.D., Ph.D.

Szabolcs Bozsányi, M.D., Ph.D.

Head of the Complex Examination Committee:

Prof. Gábor Varga, M.D., Ph.D.

Members of the Complex Examination Committee:

Stefania Bunduc, M.D., Ph.D.

Mahmoud Obeidat, M.D., MSc, Ph.D.

Bianca Golzio Navarro Cavalcante, Ph.D.

Budapest

2026

**“Science is not only a disciple of reason but, also,
one of romance and passion.”**

Stephen Hawking

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS	6
2. STUDENT PROFILE	10
2.1. Vision and mission statement, specific goals	10
2.2. Scientometrics	10
2.3. Future plans	11
3. SUMMARY OF THE PH.D.	12
4. GRAPHICAL ABSTRACTS OF THE STUDIES	13
4.1. Study I	13
4.2. Study II	13
5. INTRODUCTION	14
5.1. Overview of the topic	14
5.1.1. What is the topic?	14
5.1.2. What is the problem to solve?	14
5.1.3. What is the importance of the topic?	14
5.1.4. What would be the impact of our research results?	15
5.2. The clinical characterization and disease burden of CLE	16
5.3. Immunopathogenesis of CLE	20
5.4. The role of immunometabolism in the pathogenesis of CLE	25
5.5. Therapeutic strategies in CLE: from conventional to targeted approaches	31
6. OBJECTIVES	34
6.1. Study I – Investigating the role of glucose metabolism in CLE	34
6.2. Study II – Investigating the efficacy and safety of novel therapeutic options in CLE	34
7. METHODS	35
7.1. Study I	35
7.1.1. Patient selection and sample collection	35
7.1.2. Immunohistochemistry	35
7.1.3. Evaluation of immunohistochemistry	36
7.1.4. In silico correlation analysis of SLC2A1 and MX1 mRNA expression	36

7.1.5. Statistical analysis	36
7.2. Study II	38
7.2.1. Study design and protocol registration	38
7.2.2. Systematic literature search strategy and eligibility criteria	38
7.2.3. Study selection and data extraction	39
7.2.4. Quality assessment	39
7.2.5. Statistical analysis	40
8. RESULTS	41
8.1. Study I	41
8.1.1. Demographic and clinical characteristics of the study cohort	41
8.1.2. GLUT1 and MxA expression in lesional CLE skin	45
8.1.3. Correlations of GLUT1 expression, IFN-I activity, and disease activity	49
8.1.4. In silico validation of SLC2A1 and MX1 co-expression across independent transcriptomic datasets	49
8.2. Study II	51
8.2.1. Search results, study selection, and study characteristics	51
8.2.2. Efficacy of novel therapeutic interventions in CLE	53
8.2.3. Qualitative synthesis of non-pooled efficacy data	56
8.2.4. Analysis of adverse events	56
8.2.5. Analysis of serious adverse events	57
8.2.6. Qualitative synthesis of non-pooled safety data	57
8.2.7. Quality assessment	59
9. DISCUSSION	60
9.1. Summary of findings, international comparisons	60
9.1.1. Study I	60
9.1.2. Study II	62
9.2. Strengths	63
9.2.1. Study I	63
9.2.2. Study II	64

9.3. Limitations	65
9.3.1. Study I	65
9.3.2. Study II	65
10. CONCLUSION	66
10.1. Study I	66
10.2. Study II	66
11. IMPLEMENTATION FOR PRACTICE	67
11.1. Study I	67
11.2. Study II	67
12. IMPLEMENTATION FOR RESEARCH	68
12.1. Study I	68
12.2. Study II	68
13. IMPLEMENTATION FOR POLICYMAKERS	69
14. FUTURE PERSPECTIVES	70
15. REFERENCES	71
16. BIBLIOGRAPHY	99
16.1. Publications related to the thesis	99
16.2. Publications not related to the thesis	99
17. ACKNOWLEDGEMENTS	100

1. LIST OF ABBREVIATIONS

2-DG	2-deoxyglucose
ACLE	acute cutaneous lupus erythematosus
ACR	American College of Rheumatology
AE	adverse event
AIM2	absent in melanoma 2
ANOVA	Analysis of Variance
BCR	B-cell receptor
BDCA2	blood dendritic cell antigen 2
BLyS	B-lymphocyte stimulator
CCLE	Cancer Cell Line Encyclopedia
cGAS-STING	cyclic GMP-AMP synthase - stimulator of interferon genes
CHLE	chilblain lupus erythematosus
CI	confidence interval
CINeMA	Confidence in Network Meta-Analysis
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity
CLASI-D	Cutaneous Lupus Erythematosus Disease Area and Severity Index – Damage
CLE	cutaneous lupus erythematosus
DAMP	damage-associated molecular pattern
DC	dendritic cell
DLE	discoid lupus erythematosus
DMR	differentially methylated region
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
dsDNA	double-stranded DNA
EULAR	European League Against Rheumatism
FDA	U.S. Food and Drug Administration
GC	germinal center

GEO	Gene Expression Omnibus
GLUT	glucose transporter
GTPase	guanosine triphosphatase
HIF-1α	hypoxia-inducible factor 1-alpha
IFN-I	type I interferon
IFN-γ	interferon gamma
IFN-κ	interferon kappa
IFN-λ	interferon lambda
IFNAR	interferon- α/β receptor
IFNLR	interferon lambda receptor
IL-12	interleukin 12
IL-17	interleukin 17
IL-1β	interleukin 1 beta
IL-22	interleukin 22
IL-23	interleukin 23
IL-6	interleukin 6
IRF5	interferon regulatory factor 5
ISG	interferon-stimulated gene
ITGAM	integrin alpha M
JAK	Janus kinase
LE	lupus erythematosus
LEP	lupus erythematosus profundus/panniculitis
LET	lupus erythematosus tumidus
MD	mean difference
MDA5	melanoma differentiation-associated protein 5
MHC	major histocompatibility complex
MINORS	Methodological Index for Non-Randomized Studies
mRNA	messenger ribonucleic acid
mTOR	mechanistic target of rapamycin

MxA	Myxovirus resistance protein A
NET	neutrophil extracellular trap
NMA	network meta-analysis
OR	odds ratio
OXPHOS	oxidative phosphorylation
PASI	Psoriasis Area and Severity Index
pDC	plasmacytoid dendritic cell
PICO	Population, Intervention, Comparator, Outcome
PKM2	pyruvate kinase M2
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PRR	pattern recognition receptor
PSMB8	proteasome subunit beta type-8
QoL	quality of life
RCT	randomized controlled trial
RIG-I	retinoic acid-inducible gene I
RNA	ribonucleic acid
RoB2	Cochrane Risk-of-Bias tool
ROS	reactive oxygen species
SAE	serious adverse event
SCLE	subacute cutaneous lupus erythematosus
SLE	systemic lupus erythematosus
SNP	single nucleotide polymorphism
SUCRA	surface under the cumulative ranking plots
SYK	spleen tyrosine kinase
TAP1	transporter associated with antigen processing 1
TCR	T-cell receptor
T_{eff}	effector T cell
T_{fh}	follicular helper T cells

Th1	T helper cell 1
Th17	T helper cell 17
Th2	T helper cell 2
TLR	Toll-like receptor
TNF	tumor necrosis factor- α
T_{reg}	regulatory T cell
TREX1	three prime repair exonuclease 1
TYK2	tyrosine kinase 2
UV	ultraviolet
UVB	ultraviolet B

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve the quality of life for patients with cutaneous lupus erythematosus (CLE) by advancing our understanding of its pathophysiology and optimizing its clinical management.



My mission is to deepen our understanding of CLE pathogenesis, identify potential novel therapeutic targets, and synthesize emerging clinical evidence to improve therapeutic decision-making.

My specific goals are to investigate the role of alterations in immunometabolism, particularly glucose metabolism, in CLE pathogenesis and to establish an evidence-based efficacy and safety ranking of novel therapies to optimize the clinical management of CLE.

2.2. Scientometrics

Number of all publications:	4
Cumulative IF:	44.7
Av IF/publication:	11
Ranking (SCImago):	D1: 2, Q1: 1, Q2: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	13.6
Av IF/publication:	6.8
Ranking (SCImago):	D1: 1, Q2: 1
Number of citations on Google Scholar:	70
Number of citations on MTMT (independent):	36
H-index (Google Scholar):	5
H-index (MTMT):	3

The detailed bibliography of the student can be found on page 99.

2.3. Future plans

My future professional goals are gaining clinical expertise in the diagnosis and management of autoimmune skin diseases, with a continued focus on CLE. Alongside clinical practice, I plan to remain actively involved in research and to apply emerging scientific evidence into everyday patient care.

3. SUMMARY OF THE PH.D.

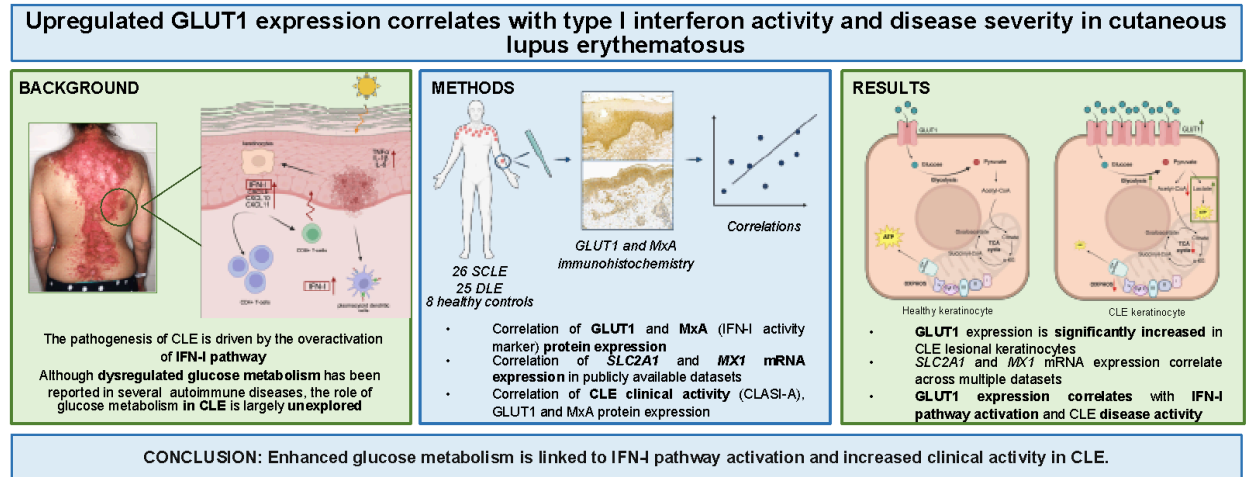
CLE is an autoimmune disease in which the overactivation of the type I interferon (IFN-I) pathway drives and sustains cutaneous inflammation. The heterogeneous and potentially severe skin manifestations may lead to permanent scarring, and a subset of patients face the risk of progression to systemic lupus erythematosus (SLE), profoundly affecting their quality of life. A substantial proportion of patients also fail to respond adequately to available therapies. Despite its considerable clinical impact, the precise immunopathogenesis of CLE remains poorly understood, and managing refractory cases is particularly challenging given the absence of comparative efficacy and safety data on novel therapies and a lack of consensus on their use in everyday practice.

Although alterations in immunometabolism have been implicated in the pathogenesis of several systemic and cutaneous autoimmune and inflammatory diseases, its role in CLE remains poorly characterized. The first study investigated the role of glucose metabolism in CLE through immunohistochemical analysis of glucose transporter 1 (GLUT1) and IFN-I marker myxovirus resistance protein A (MxA) in lesional skin. Both GLUT1 and MxA were significantly elevated in CLE samples compared to healthy controls. Keratinocyte GLUT1 expression showed a significant positive correlation with MxA expression and with Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity (CLASI-A) scores, a validated measure of cutaneous disease activity. These findings were supported by consistent *SLC2A1-MXI* co-expression across multiple independent transcriptomic datasets. In the second study, we conducted a systematic review and network meta-analysis evaluating the efficacy and safety of novel biologics and small molecules in CLE. Deucravacitinib, a selective tyrosine kinase 2 (TYK2) inhibitor, was the most effective therapy, with patients over eight times more likely to achieve a 50% reduction in disease activity compared to placebo. Litifilimab and anifrolumab also demonstrated statistically significant superiority over placebo. The safety profile of these novel therapies was comparable to placebo, with the exception of baricitinib. To our knowledge, this is the first work to establish a link between altered glucose metabolism, IFN-I pathway activation, and disease activity in CLE, thereby contributing to a better understanding of its immunopathogenesis. The first head-to-head comparison of novel therapeutic agents

presented here further supports the optimization of evidence-based clinical decision-making in CLE.

4. GRAPHICAL ABSTRACTS OF THE STUDIES

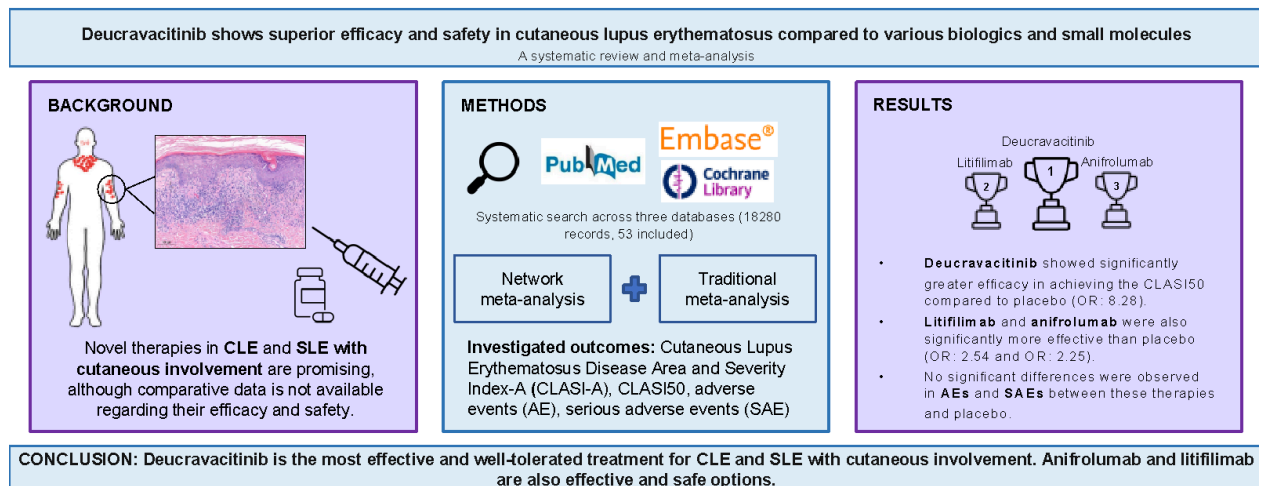
4.1. Study I



Graphical abstract of Study I

Abbreviations: CLE = cutaneous lupus erythematosus; IFN-I = type I interferon; GLUT1 = glucose transporter 1; MxA = Myxovirus resistance protein A

4.2. Study II



Graphical abstract of Study II

Abbreviations: CLE = cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; CLASI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity; AE = adverse event; SAE = serious adverse event; OR = odds ratio

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Our research focuses on the immunopathogenesis and clinical management of CLE. Specifically, it explores the role of glucose metabolism in driving the activation of the type I interferon (IFN-I) pathway and its contribution to overall disease activity. In parallel, we compare the efficacy and safety of novel therapies in CLE.

5.1.2. What is the problem to solve?

Despite recent advances in targeted therapies for SLE and lupus erythematosus (LE) with mucocutaneous involvement, the management of CLE remains a challenge. Nearly 40% of affected patients fail first-line therapy, and 20% are resistant to multiple lines of treatment (1, 2). To date, no therapies have been specifically approved for this disease, and novel treatments for SLE are not yet incorporated into CLE guidelines. There is no consensus or enough clinical experience regarding the integration of these novel interventions into everyday clinical practice, which further complicates therapeutic decision-making. Comparative data on the efficacy and safety of these treatments is also absent. Besides the challenges of CLE management, the underlying molecular pathology of the disease has not yet been fully characterized, which is essential for identifying novel therapeutic targets and developing effective therapies.

5.1.3. What is the importance of the topic?

CLE is an autoimmune skin disease that imposes a significant, frequently underestimated burden on both individuals and healthcare systems. The symptoms might heal with irreversible scarring despite adequate treatment, and a subset of patients faces the additional risk of progression to a multi-organ disease. Despite this profound disease burden, fundamental gaps remain in both the pathophysiological understanding and the clinical management of CLE. Addressing these gaps, therefore, represents both a scientific and a clinical necessity.

5.1.4. What would be the impact of our research results?

The impact of this research is twofold: it addresses critical gaps in both the pathophysiological understanding and the clinical management of CLE. Elucidating the role of glucose metabolism in the activation of the IFN-I system, one of the most prominent drivers of inflammation in CLE, and its contribution to disease severity may deepen our understanding of CLE immunopathogenesis and thereby facilitate the identification of novel therapeutic targets. Furthermore, a head-to-head comparison of existing novel therapies regarding their efficacy and safety profiles may aid clinical decision-making when selecting a therapy for CLE patients, and could contribute to the update of regional and international treatment recommendations.

5.2. The clinical characterization and disease burden of CLE

Cutaneous lupus erythematosus (CLE) is an autoimmune disease characterized by the overactivation of the IFN-I system and a broad spectrum of clinical manifestations. These symptoms can range from localized cutaneous symptoms to disseminated skin lesions and multi-organ involvement (SLE). The annual incidence of CLE is estimated at 2.9 to 4.3 cases per 100,000 individuals. Nearly a quarter (24%) of patients already have an established diagnosis of SLE at the time of their initial CLE presentation. While many cases remain localized to the skin, prospective longitudinal studies reveal that one in five patients (18.7%) will progress to systemic disease within three years of their initial diagnosis (3-6).

According to the widely accepted Düsseldorf classification, the cutaneous manifestations of CLE are categorized primarily based on clinical, histological, serological, and genetic findings (7, 8). This system distinguishes acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus, a heterogeneous subgroup encompassing discoid lupus erythematosus (DLE), lupus erythematosus profundus/panniculitis (LEP), and chilblain lupus erythematosus (CHLE) (Table 1). Most recently, intermittent cutaneous lupus erythematosus (ICLE) was introduced as a new distinct subtype to specifically encompass lupus erythematosus tumidus (LET).

Table 1. Düsseldorf classification of cutaneous lupus erythematosus

Acute cutaneous lupus erythematosus (ACLE)
Subacute cutaneous lupus erythematosus (SCLE)
Chronic cutaneous lupus erythematosus - Discoid lupus erythematosus (DLE) - Lupus erythematosus profundus/panniculitis (LEP) - Chilblain lupus erythematosus (CHLE)
Intermittent cutaneous lupus erythematosus (ICLE) - Lupus erythematosus tumidus (LET)

DLE is the most prevalent subtype of CLE. This form typically affects the face, scalp, and ears. Lesions present as well-circumscribed, disc-shaped erythrosquamous plaques with adherent scaling and infiltrated hyperpigmented borders. The central areas characteristically show atrophy, telangiectasia, and hyperkeratosis. DLE lesions resolve with residual hypopigmentation and scarring (Figure 1) (9).

Another major clinical subset of CLE is SCLE, which predominantly affects photoexposed skin. It occurs in two morphological variants, annular and papulosquamous. The annular variant presents as polycyclic scaly lesions with central clearing, whereas the papulosquamous form features psoriasiform papules and plaques. In contrast to DLE, SCLE lesions resolve without scarring, leaving residual, vitiligo-like hypopigmentation (Figure 2) (10).

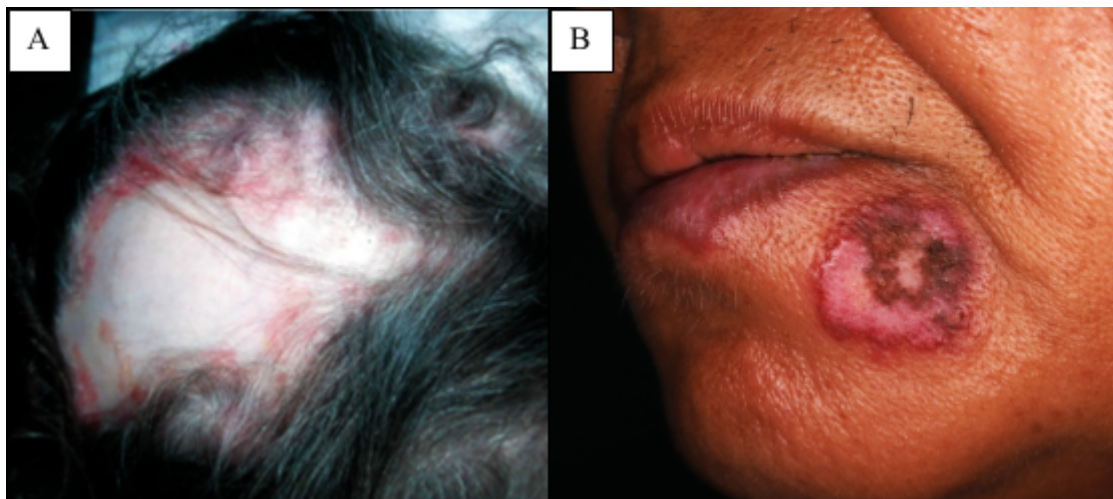


Figure 1. Different clinical presentations of discoid lupus erythematosus

(A) Scarring alopecia. (B) DLE plaque on the face. The images are from the archive of the Department of Dermatology, Venereology and Dermatooncology, Semmelweis University.



Figure 2. Different clinical presentations of subacute cutaneous lupus erythematosus

The images are from the archive of the Department of Dermatology, Venereology and Dermatoooncology, Semmelweis University.

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is a standard, validated instrument for the quantification of disease severity (11). This scoring system assesses cutaneous involvement, integrating both the anatomical distribution and the morphological characteristics of the lesions. It consists of two domains, activity (CLASI-A), scoring the presence of erythema, scaling, mucosal lesions, and non-scarring alopecia, and damage (CLASI-D), measuring scarring and cutaneous atrophy. In recent clinical trials, the CLASI50 has been used as a standardized outcome measure to represent a clinically significant response to treatment, defined as the proportion of patients achieving at least a 50% reduction in their baseline CLASI score following the given intervention (12).

CLE imposes a substantial psychosocial burden. Patients report quality of life (QoL) impairments comparable to those of severe cardiovascular and metabolic diseases (13). Chronic lesional damage plays a central role in decreased QoL, as higher damage scores are directly associated with negative effects on body image (14). Although effective

treatment can meaningfully improve emotional and functional QoL, therapy resistance remains a major clinical challenge (15).

5.3. Immunopathogenesis of CLE

The pathomechanism of CLE is characterized by a self-amplifying pro-inflammatory cycle driven by hyperactivation of the IFN-I pathway. This leads to an anti-epithelial cytotoxic immune response in lesional skin, resulting in the release of cellular debris and pro-inflammatory mediators, and subsequent reactivation of innate immune pathways. The central feature of this vicious cycle is the crosstalk between the adaptive and innate immune systems: effector mechanisms of the adaptive immune response continuously re-engage innate immune pathways, sustaining their parallel activation in affected skin and perpetuating the inflammatory cascade (16).

The initial activation of this pro-inflammatory cycle occurs in genetically predisposed individuals upon exposure to external trigger factors. Several single nucleotide polymorphisms (SNPs) have been identified to increase susceptibility to CLE, including sequence variations in major histocompatibility complex (MHC) class I and II alleles, the tumor necrosis factor- α (TNF α) promoter, TYK2, interferon regulatory factor 5 (IRF5), or integrin alpha M (ITGAM) (17-20). Additional SNPs associated with increased CLE risk have been implicated in key pathological processes, including IFN-I pathway activation, antigen presentation, antibody production, clearance of cellular debris, apoptosis, and leukocyte migration (21). Thus far, a single monogenic variant of CLE has been described: a rare familial form of CHLE caused by loss-of-function mutations in the three prime repair exonuclease 1 (TREX1) gene (22). Complementing this genetic predisposition, epigenetic modifications have increasingly been recognized as additional contributors to disease susceptibility. Genome-wide DNA methylation profiling of CD4⁺ T cells in SLE patients with cutaneous involvement revealed DLE-specific hypomethylated differentially methylated regions (DMRs) within transporter associated with antigen processing 1 (TAP1) and proteasome subunit beta type-8 (PSMB8), two genes implicated in antigen processing and presentation (23).

Among external trigger factors, ultraviolet (UV) radiation is the most extensively studied. Photosensitivity is reported in up to 82% of CLE patients, and lesions predominantly affect sun-exposed skin areas in up to 93.4% of cases (24). Consistent with these observations, higher disease activity has been associated with direct UV-induced disease flares (25). UV radiation has been shown to induce keratinocyte apoptosis through multiple distinct cellular mechanisms, including reactive oxygen

species (ROS)-mediated mitochondrial membrane damage, the ligand-independent activation of Fas/Fas Ligand membrane death receptors, and direct structural deoxyribonucleic acid (DNA) damage (26). These findings are further underscored by a prospective gene expression study demonstrating the upregulation of interferon pathway and MHC-related genes in the skin of CLE patients, but not in healthy individuals, following UV irradiation (27).

Alongside UV radiation, cigarette smoking is another prominent environmental trigger in CLE. Active smokers have significantly higher CLASI scores compared to non-smoking patients, and they need higher therapeutic dosages of antimalarials for adequate symptom control, as smoking directly attenuates the efficacy of these agents (28, 29). Mechanistically, smoking promotes multiple pro-inflammatory processes relevant to CLE pathogenesis, including elevated serum levels of pro-inflammatory cytokines, enhanced apoptosis, neutrophil extracellular trap (NET) formation via neutrophil activation, and the release of phototoxic microparticles (30).

Beyond environmental triggers, certain medications represent a well-established etiological factor for LE. Drug-induced SLE has long been associated with procainamide, hydralazine, and quinidine use (31). SCLE in particular can be triggered by a broader range of agents, including calcium channel blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, proton pump inhibitors, antifungals, and statins (32). Notably, monoclonal antibodies have increasingly been implicated in the development of SCLE over recent years, most prominently TNF- α inhibitors and immune checkpoint inhibitors (33).

These trigger factors induce keratinocyte apoptosis and the subsequent release of nuclear components. Beyond the observed accumulation of apoptotic keratinocytes in CLE lesions following UV stimulation, impaired clearance of cellular debris has also been identified (34). This defective clearance has been linked to multiple contributing mechanisms, including reduced phagocytic activity and deficient enzymatic DNA degradation due to mutations in deoxyribonuclease (DNase)-encoding genes such as DNase I and DNase III (35). Consequently, apoptotic cells not adequately removed by macrophages may undergo secondary necroptosis, resulting in the release of pro-inflammatory mediators and potential autoantigens, including nuclear-derived materials and other damage-associated molecular patterns (DAMPs) (36). These

endogenous immunostimulatory nucleic acids drive the activation of pattern recognition receptors (PRRs) on antigen-presenting cells (APCs) and keratinocytes (37). In plasmacytoid dendritic cells (pDCs), Toll-like receptors 7 and 9 (TLR7/9) are the majority of expressed PRRs for the recognition of nucleic acid motifs presented as autoantibody-bound immune complexes (38). In keratinocytes, besides TLRs, nucleic acid sensing is mediated by multiple cytosolic PRRs: the retinoic acid-inducible gene I (RIG-I)-like receptors melanoma differentiation-associated protein 5 (MDA5) and RIG-I, and the cyclic GMP-AMP synthase - stimulator of interferon genes (cGAS-STING) pathway, both driving IFN-I activation (39, 40). Of note, inflammasome activation by cytosolic double-stranded DNA (dsDNA) receptor absent in melanoma 2 (AIM2) has also been reported in keratinocytes (41). Upon PRR activation, keratinocytes and pDCs produce excessive amounts of type I and type III interferons — notably interferon kappa (IFN- κ) and interferon lambda (IFN- λ) — alongside other pro-inflammatory cytokines and chemokines (42, 43). These interferons signal through their cognate receptors: type I IFNs through the heterodimeric IFN- α/β receptor (IFNAR), comprising IFNAR1 and IFNAR2 subunits, and type III IFNs through interferon lambda receptor (IFNLR) (44). Activation of both receptors leads to the phosphorylation of Janus kinase 1 (JAK1) and TYK2, initiating downstream JAK-STAT signaling and inducing the expression of a wide range of IFN-stimulated genes (ISGs) (45). Among these, MxA (encoded by *MX1*) is a cytoplasmic guanosine triphosphatase GTPase, whose expression directly correlates with IFN-I activity (46, 47). ISG upregulation enhances antigen detection and innate immune signaling, amplifies cytokine production in keratinocytes through an autocrine feedback loop, and drives the expression of IFN-regulated chemokines, including CXCL9, CXCL10, and CXCL11 (48). Through CXCL10, type I IFNs recruit CXCR3-expressing T helper cell 1 (Th1) CD4⁺ T cells, cytotoxic CD8⁺ T cells, pDCs, and macrophages into lesional skin (49, 50). CD8⁺ T cells exert cytotoxic effects via the perforin/granzyme B pathway, which leads to keratinocyte apoptosis and the subsequent release of cellular debris (51, 52). Recruited Th1 lymphocytes further produce TNF- α and the type II interferon, interferon gamma (IFN- γ). Both perpetuate the inflammatory cascade by upregulating CXCR3 expression, promoting Th1 differentiation from naïve T cells, and polarizing macrophages toward the pro-inflammatory M1 phenotype (53, 54). Both

IFN- γ and TNF- α have been shown to play pivotal roles in keratinocyte necroptosis, resulting in interface dermatitis, the hallmark histopathological feature of CLE. It is characterized by immune cell infiltration and vacuolar degeneration of the basal keratinocyte layer and the formation of colloid bodies (Civatte bodies) derived from apoptotic and necroptotic keratinocytes (55, 56).

B cells also contribute to CLE pathogenesis. APCs drive the maturation and clonal expansion of naïve B cells, which, following repeated autoantigen presentation, differentiate into plasma cells. This process is facilitated by follicular helper T cells (T_{fh}) residing in the germinal centers of lymph nodes (57). Peripherally, mature B cells cluster with T cells and dendritic cells, forming ectopic lymphoid structures adjacent to cutaneous lesions. These tertiary lymphoid organs provide a sustained pro-inflammatory microenvironment that drives chronic inflammation, as B cells themselves can function as autoantibody- or cytokine-producing cells, active APCs, or co-stimulatory activators of T cells (58). While the precise role of B cells in CLE lesion development remains incompletely understood, their contribution to pathogenesis may be subtype-specific, as recent studies have revealed distinct infiltrating immune cell patterns across different CLE subtypes. B cell numbers and cluster formation were significantly higher in DLE compared to SCLE (59, 60).

Besides the well-established contributions of the adaptive and innate immune system, the role of keratinocytes in CLE pathogenesis has been increasingly reconsidered in recent years. Rather than serving as passive targets of cytotoxic injury, these cells are now recognized as active participants in cutaneous immune responses. They have been shown to function as immune cells, participating in antigen processing and presentation, producing a range of cytokines and chemokines, and regulating innate immune responses (61). Notably, intensive crosstalk has been identified between keratinocytes and multiple dermal cell populations, including fibroblasts, myeloid cells, and T lymphocytes. Ultraviolet B (UVB) radiation-triggered, IFN-I-primed keratinocytes activate neighboring fibroblasts via TNF- α , interleukin 6 (IL-6) and interleukin 1 beta (IL-1 β), inducing the production of CCL2, CCL7 and CCL8 chemokines in vitro, which drives the recruitment of CD14⁺ myeloid cells. These cells in turn secrete type-I interferons and other pro-inflammatory cytokines, facilitating the recruitment of

cytotoxic T cells to the dermal-epidermal junction and sustaining the pro-inflammatory loop beyond the resolution of the initial trigger (62, 63).

Collectively, these findings highlight the active immunological role of keratinocytes in CLE and add a further layer of complexity to an already multifaceted pathomechanism. A deeper understanding of the precise roles of the implicated cell types and cytokines within this complex network of cellular crosstalk is needed to fully characterize the mechanisms sustaining chronic cutaneous inflammation.

5.4. The role of immunometabolism in the pathogenesis of CLE

The research of immunometabolism has expanded considerably over the past decade. This field explores the intricate crosstalk between metabolic regulation and immune cell function. Distinct immune cell populations employ highly specific metabolic programs to meet their bioenergetic and biosynthetic demands to sustain survival, proliferation, and effector responses. Beyond their canonical role in ATP generation, these metabolic pathways produce intermediate metabolites that act as signaling molecules and can directly modulate immune cell function. This homeostatic balance is tightly regulated, and its alterations have been increasingly recognized as a key driver of immune-mediated pathologies. The role of such metabolic reprogramming in disease pathogenesis has been extensively documented across a broad spectrum of disorders, including malignancies, metabolic diseases, and systemic autoimmune conditions (64).

The activation and proliferation of immune cells during an inflammatory response are associated with a substantial increase in energetic demand. Glycolysis and oxidative phosphorylation (OXPHOS) are the two principal pathways that supply this energy. While OXPHOS is considerably more efficient — yielding 36 ATP molecules per glucose molecule compared to only 2 via glycolysis — it requires mitochondrial biogenesis, making it a comparatively slow and complex process to upregulate. Glycolysis, by contrast, can be rapidly induced by the direct activation of glycolytic enzymes and is therefore the preferred metabolic pathway when immune cells are activated. This metabolic switch toward glycolysis enables the rapid generation of ATP and biosynthetic intermediates necessary to support cell growth, proliferation, and effector functions (65).

A critical rate-limiting step of glycolysis is the transport of glucose across the plasma membrane. This process is mediated by the glucose transporter (GLUT) protein family, encoded by the solute carrier family 2 (*SLC2A*) genes, consisting of 14 distinct isoforms that facilitate the diffusion of substrates, including glucose, fructose, urate, and myoinositol. Within this family, GLUT1 (*SLC2A1*) is the ubiquitously expressed isoform, regulating basal glucose uptake in most mammalian cells (66, 67).

Enhanced glycolysis is a hallmark of immune cell activation in a broad range of cell types. Upon activation, CD4⁺ T cells undergo rapid growth, proliferation, and

differentiation into regulatory (T_{reg}) and effector (T_{eff}) subsets. Notably, the metabolic state plays a decisive role in cell fate determination: a glycolytic shift selectively promotes the differentiation and expansion of T_{eff} cells, whereas the differentiation of T_{reg} cells — characterized by low GLUT1 expression and a predominant reliance on fatty acid oxidation — remains unaffected (68, 69). Mature effector T cell subsets — particularly Th1, T helper cell 2 (Th2), and T helper cell 17 (Th17) — exhibit markedly elevated GLUT1 expression upon T-cell receptor (TCR) activation, and depend on glycolysis as their primary catabolic pathway (70). Consistent with this, GLUT1 deficiency in both mouse and human T cells has been shown to impair glucose uptake and glycolytic flux, and to attenuate cell growth and proliferation and decrease survival (71). Additionally, GLUT1-deficient Th1 and Th17 cells demonstrated diminished capacity to produce cytokines, reducing their capability to induce an inflammatory reaction in vivo. Beyond these CD4⁺ T cell subsets, CD4⁺ T_{fh} are also highly glycolytic, and inhibiting glycolysis in these cells led to a significant reduction in their numbers (72). Parallel to the metabolic dichotomy observed between T_{reg} and T_{eff} subsets, CD8⁺ memory T cells preferentially utilize fatty acid oxidation, whereas activated CD8⁺ effectors are highly glycolytic (73, 74). Similarly, in B cells, B-cell receptor (BCR) activation leads to increased GLUT1 expression, and inhibition of glycolysis prevents BCR-triggered protein synthesis and cell growth (75).

GLUT1 upregulation also plays a pivotal role in innate immune cell function. In macrophages, TLR activation and M1 polarization are characterized by a pronounced glycolytic shift, and GLUT1 deletion has been shown to impair macrophage activation and phagocytic capacity (76). Similarly, in dendritic cells (DC), restricting glycolytic substrate availability abrogates maturation and cytokine production and reduces their capacity to prime T cell responses (77, 78).

In addition to supporting immune cell activation and effector function, metabolic reprogramming has emerged as a key determinant of immune cell phenotype. Inhibition of pyruvate kinase M2 (PKM2), a key glycolytic enzyme and upstream regulator of hypoxia-inducible factor 1- α (HIF-1 α), has been shown to shift macrophage polarization from the pro-inflammatory M1 toward the pro-reparatory M2 phenotype (79). Analogous observations have been reported in T cells, where glycolytic inhibition by 2-deoxyglucose (2-DG) promoted the conversion of Th17 into T_{reg} cells (68). These

findings establish a direct connection between cellular metabolism and immune phenotype. Specifically, glycolysis and HIF-1 α activation are associated with pro-inflammatory functions, while OXPHOS and fatty acid oxidation are characteristic of an anti-inflammatory phenotype (69). Beyond glucose and fatty acid metabolism, upregulation of the pentose phosphate pathway and amino acid metabolism has also been implicated in regulating the effector functions of immune cells. The specific metabolic pathways of major immune cell subsets are summarized in Table 2.

Table 2. Characteristic metabolic pathways of major immune cell subsets

Immune cells	Metabolic pathways
CD4+ effector T cells (Th1, Th2, Th17)	- glycolysis (69) - amino acid metabolism (80) - fatty acid synthesis (81)
CD8+ effector T cells	- glycolysis (74) - fatty acid synthesis (82)
Follicular helper T cells	- glycolysis (72)
B cells	- glycolysis (75) - fatty acid synthesis (83)
M1 pro-inflammatory macrophages	- glycolysis (76) - pentose-phosphate pathway (84) - amino acid metabolism (85) - fatty acid synthesis (86)
Dendritic cells	- glycolysis (78) - fatty acid synthesis (87)
Regulatory T cells	- OXPHOS (88) - fatty acid oxidation (69)
CD8+ memory T cells	- OXPHOS (89) - fatty acid oxidation (73)
M2 macrophages	- OXPHOS (90) - fatty acid oxidation (91)

Similar to immune cells, keratinocytes rely predominantly on GLUT1 for glucose uptake, as evidenced by a 95% reduction in keratinocyte glucose transport in GLUT1 knockout mice (92). GLUT1 expression is further upregulated upon keratinocyte activation, playing an essential role in enhanced proliferation, as observed during wound healing and UVB-induced epidermal hyperplasia (93, 94). Accordingly, GLUT1 deletion prevented the physiological epidermal hyperplasia observed following UV irradiation and in wound healing, and impaired keratinocyte proliferation and migration within the wound site (92). GLUT1 deficiency also prevented the development of imiquimod- and interleukin 23 (IL-23)-induced psoriasiform hyperplasia and cutaneous

inflammation. Consistent with this, pharmacological GLUT1 inhibition reduced keratinocyte proliferation, decreased inflammatory cell infiltration in skin biopsies from imiquimod-pretreated mice, and suppressed inflammatory gene expression in samples from psoriatic skin lesions. Interestingly, despite impaired proliferation and signs of metabolic and oxidative stress in GLUT1 $-/-$ primary keratinocytes in vitro, normal skin development was unaffected in GLUT1-deficient mice. These findings suggest a metabolic adaptation via alternative pathways in vivo and indicate that basal epidermal homeostasis does not strictly require GLUT1-mediated glucose uptake. Instead, GLUT1 appears to be selectively indispensable for the elevated metabolic demands of activated and rapidly proliferating keratinocytes, which makes it a promising therapeutic target in hyperproliferative and inflammatory skin diseases.

Consistent with findings from murine models, GLUT1 expression is upregulated in skin biopsies from patients with psoriasis (95, 96). Importantly, GLUT1 expression positively correlated with epidermal thickness, inflammatory cell infiltration density, and the Psoriasis Area and Severity Index (PASI) score — a validated instrument for the measurement of clinical disease activity (97). Beyond psoriasis, increased GLUT1 expression has been reported across a spectrum of inflammatory and autoimmune skin disorders, including chronic spongiotic dermatitis, vitiligo, oral lichen planus, and atopic dermatitis (98-101).

Beyond the systemic diseases outlined above, dysregulated glucose metabolism has been implicated in the pathogenesis of SLE (102). Autoreactive CD4⁺ T cells from both SLE patients and lupus-prone mice exhibit elevated metabolic activity, and glycolysis is their predominant catabolic pathway (103). Consequently, inhibition of glycolysis reduced CD4⁺ T cell activation, proliferation, and IFN- γ production, effectively ameliorating the autoimmune phenotype. In addition, direct GLUT1 inhibition restricted CD4⁺ T cell clonal expansion and favorably modulated T cell polarization by suppressing Th1 and Th17 lineages, while promoting T_{reg} differentiation (104). This highly glycolytic phenotype extends to autoreactive T_{fh} cells (72). In murine lupus models, inhibition of glycolysis suppressed T_{fh} expansion, leading to a downstream reduction in germinal center (GC) B cells and anti-dsDNA IgG autoantibody titers. Crucially, this metabolic intervention was highly selective. It impaired autoreactive T_{fh} cells and autoantibody-producing B cell differentiation, while pathogen-specific GC B

cell responses remained intact, and protective humoral immunity was preserved. In recent years, alterations in immunometabolism have emerged as a critical driver in the pathogenesis of both systemic and cutaneous autoimmune and inflammatory diseases, promoting the aberrant activation of innate and adaptive immune cells as well as keratinocytes. Despite these paradigm-shifting discoveries, the precise pathomechanism underlying CLE remains to be elucidated. In particular, it has yet to be determined whether immune cells and keratinocytes undergo a similar metabolic rewiring and glycolytic shift during CLE pathogenesis, representing a significant gap in our current understanding of the disease.

5.5. Therapeutic strategies in CLE: from conventional to targeted approaches

The therapeutic landscape of CLE is actively evolving from conventional systemic immunosuppressants toward novel, targeted interventions. Despite this advancement, the management of the diverse cutaneous manifestations of this disease remains complex. The clinical evidence supporting these treatments is limited, and the establishment of standardized, evidence-based regimens continues to be a profound clinical challenge. Currently, the management of CLE relies on a limited number of guidelines published in 2021, with a notable absence of recently updated protocols (2, 105, 106). Beyond this, practitioners must extrapolate from broader SLE guidelines addressing mucocutaneous involvement (107-109). To date, there are no U.S. Food and Drug Administration (FDA)-approved therapies explicitly indicated for CLE. Novel agents are evaluated almost exclusively within systemic lupus cohorts and while these trials frequently report significant improvement in cutaneous symptoms, skin-specific responses have largely been assessed as secondary endpoints (110). The recent adoption of the CLASI score as a primary endpoint now allows for targeted evaluation of cutaneous efficacy, robust comparative efficacy and safety data, however, remain unavailable. The emerging therapies have not been incorporated into CLE guidelines, leaving clinicians with few evidence-based options when patients do not respond to standard therapeutic regimens. Nearly 40% of patients fail first-line therapy, with substantial heterogeneity across subtypes, and up to 20% remain resistant to multiple lines of treatment. There is therefore a critical unmet need to refine therapeutic strategies in CLE (1, 2).

According to the aforementioned guidelines, first-line therapy for CLE and SLE with mucocutaneous involvement consists of antimalarials in combination with topical and/or systemic glucocorticoids, as clinically indicated. For localized treatment, topical calcineurin inhibitors serve as a valuable, steroid-sparing alternative, particularly for facial lesions. In cases of severe or disseminated cutaneous involvement, systemic glucocorticoids are recommended in addition to antimalarials and topical treatment. For patients with an inadequate response to first-line therapy, methotrexate or mycophenolate mofetil may be introduced as second-line agents (2, 105, 106).

Recently, the therapeutic landscape of LE has expanded. Several novel biologics and small molecules have been investigated, targeting key signaling pathways implicated in

SLE and CLE pathogenesis. Anifrolumab, a monoclonal antibody targeting IFNAR subunit 1, blocks IFN-I signaling, a major driver of LE inflammation (111-113). Further upstream, litifilimab targets blood dendritic cell antigen 2 (BDCA2) on pDCs, suppressing the release of IFN-I, IL-6, and TNF- α — cytokines that collectively regulate T-, B-, and natural killer cell activity (114-116). B cells are also targeted by several distinct agents: belimumab inhibits B-lymphocyte stimulator (BLyS) to induce apoptosis in autoreactive B cells, while rituximab specifically depletes CD20+ B cells, sparing stem cells and mature plasma cells (117-122). Targeting the immunological crosstalk between T and B cells, dapirolizumab pegol, an anti-CD40 ligand monoclonal antibody, disrupts T cell-B cell interactions and, thereby, prevents B cell proliferation, differentiation, and autoantibody production (123).

Directly targeting pro-inflammatory cytokines provides another therapeutic avenue. Ustekinumab blocks interleukin 12 (IL-12) and IL-23 and prevents CD4+ T cells from differentiating into Th1 and Th17 subsets, while suppressing the secretion of IFN- γ , interleukin 17 (IL-17), and TNF- α (124, 125). Other targeted anti-cytokine therapies include TNF- α inhibitor etanercept and IL-6 inhibitor sirukumab (126, 127). Sirukumab simultaneously impairs B cell differentiation, autoantibody production, and Th17 expansion. Beyond direct cytokine blockade, intracellular signaling pathways have also become major pharmacological targets. Deucravacitinib, a highly selective TYK2 inhibitor, exerts broad inhibitory effects on cellular responses to IFN-I, IL-6, IL-12, IL-17, interleukin 22 (IL-22), and IL-23 (128). Similarly, JAK inhibitors — including baricitinib (JAK1/2), tofacitinib (JAK1/2/3), filgotinib (JAK1), and upadacitinib (JAK1) — block the signal transduction of pivotal cytokines in LE pathogenesis, including IL-12, IL-23, and IFN- α (129-134). Lanraplenib, a spleen tyrosine kinase (SYK) inhibitor, suppresses signaling cascades downstream of activated immunoreceptors across B cells, monocytes, macrophages, and neutrophils (133). Iberdomide modulates the cereblon E3 ubiquitin ligase complex to facilitate the targeted degradation of the Ikaros and Aiolos transcription factors, consequently inhibiting B cell proliferation, plasmablast differentiation, and autoantibody secretion (135, 136). Most recently, enpatoran, a dual TLR7 and TLR8 inhibitor, has emerged as a promising therapeutic agent, blocking key upstream drivers of IFN-I activation and suppressing pro-inflammatory signaling in myeloid cells, B cells, and neutrophils (137, 138).

These rapidly evolving targeted therapies mark a new era in the pharmacological management of autoimmune diseases. To fully realize the clinical potential of these agents, a deeper understanding of the localized molecular mechanisms driving cutaneous inflammation is needed, and a rigorous synthesis of emerging clinical evidence to guide therapeutic decisions is equally required.

6. OBJECTIVES

6.1. Study I – Investigating the role of glucose metabolism in CLE

The precise pathomechanism underlying CLE and its distinct clinical subtypes remains incompletely understood, and the exact molecular mechanisms driving its various clinical presentations are still unclear. While dysregulated immunometabolism has been established as a key driver of inflammation in SLE, its role in CLE is entirely unexplored (102-104). Specifically, it remains to be elucidated how alterations in glucose metabolism influence keratinocyte function and the overactivation of the innate and adaptive immune responses in the CLE. Understanding these pathways is key to the development of targeted therapies for this disease. The aim of this study, therefore, was to characterize the role of glucose metabolism in CLE pathogenesis, with a specific focus on the expression of GLUT1 transporters and their correlation with the overactivation of the IFN-I system and disease activity. Our second objective was to compare alterations in glucose metabolism between DLE and SCLE — the two most prevalent subtypes of CLE — to further define the pathomechanistic similarities and differences underlying their distinct clinical presentations.

6.2. Study II – Investigating the efficacy and safety of novel therapeutic options in CLE

Numerous targeted therapies have been evaluated in LE, however, studies comparing their efficacy and safety profiles in CLE are currently lacking. The available evidence is largely derived from SLE cohorts with heterogeneous disease manifestations, which limits its direct applicability to CLE and LE with predominant mucocutaneous involvement. Consequently, the selection of novel therapeutic agents in clinical practice remains largely empirical. CLE-specific comparative studies are urgently needed to inform evidence-based international treatment recommendations. Therefore, this study aimed to comprehensively evaluate and compare the efficacy and safety of novel therapeutic options in CLE.

7. METHODS

7.1. Study I

7.1.1. Patient selection and sample collection

The study cohort consisted of 51 CLE patients (26 SCLE, 25 DLE) admitted to the Department of Dermatology, Venereology, and Dermatatooncology, Semmelweis University, Budapest, Hungary. All participants were free of systemic immunosuppressive therapy and untreated for CLE at the time of biopsy. Samples were collected from active, untreated lesional skin. An additional 8 samples were obtained from perilesional skin excised alongside benign melanocytic nevi from healthy individuals and served as controls.

Concurrent with tissue sampling, clinical disease severity was assessed for each patient using the activity domain of the CLASI score.

All protocols involving human participants were conducted in strict accordance with the ethical standards set forth by the 1964 Declaration of Helsinki and its later amendments. Ethical approval was issued by the Regional and Institutional Committee of Science and Research Ethics at Semmelweis University (Approval ID: 75/2024; Date of approval: May 14, 2024).

7.1.2. Immunohistochemistry

4 µm thick sections were cut from 4% formaldehyde-fixed, paraffin-embedded skin biopsy blocks and mounted on glass slides for immunohistochemical staining. Standard deparaffinization was performed before heat-induced epitope retrieval. For this, slides were placed in 0.1 M citrate buffer (pH 6.0) in an electric pressure cooker and heated for three consecutive 7-minute cycles. Samples were then allowed to cool gradually to room temperature. Once cooled, the tissue sections were incubated overnight with the primary antibodies (monoclonal rabbit GLUT1 antibody [Abcam, EPR3915, ab115730] prepared at a 1:400 dilution and monoclonal rabbit MX1 antibody [Cell Signaling Technology, D3W7I, 37849S] with a 1:200 dilution). The slides were subsequently incubated with NovoLink post-primary reagent (Leica Biosystems) for 30 minutes, immediately followed by incubation with the NovoLink Polymer detection system (Leica Biosystems) for an additional 30 minutes. Chromogenic development was

performed using a 3,3'-diaminobenzidine (DAB) peroxidase substrate (Dako), and standard hematoxylin was used for nuclear counterstaining. Finally, whole-slide digital imaging was performed by digitizing the stained sections with a Panoramic Scan apparatus (3D Histech, Budapest, Hungary) with Carl Zeiss objective lens (numerical aperture = 0.83; Carl Zeiss MicroImaging Inc., Jena, Germany).

7.1.3. Evaluation of immunohistochemistry

Histopathological grading was performed by two independent dermatopathologists, whose individual scores were averaged to yield a final expression score for each biopsy. For GLUT1, positivity was defined as a membranous staining pattern in the epidermis. GLUT1 expression was assessed across the full thickness and length of the epidermis. For MxA, cytoplasmic staining was considered positive, and expression was graded in both the epidermis and dermal infiltrating lymphocytes. Expression levels were quantified using a semi-quantitative four-tiered scoring system: 0 (absent), + (mild; less than 25% of cells stained), ++ (moderate; 25–75% of cells stained), and +++ (strong; more than 75% of cells stained).

7.1.4. *In silico* correlation analysis of SLC2A1 and MX1 mRNA expression

We analyzed three publicly available transcriptomic datasets to evaluate *SLC2A1* and *MX1* messenger ribonucleic acid (mRNA) expression. We accessed the Cancer Cell Line Encyclopedia (CCLE) dataset from cBioPortal on August 21, 2025. Only complete cases were analyzed (n = 877) (139-142). The GSE109248 dataset was retrieved from the Gene Expression Omnibus (GEO) on July 22, 2025. (143, 144). Keratinocyte bulk ribonucleic acid (RNA)-sequencing data were extracted from the ARCHS4 database on November 14, 2025 (145). We then manually filtered these samples to primary, untreated keratinocytes to avoid confounding from genetic modifications or pharmacological pretreatments. Data preprocessing and normalization were done in Python using the pandas, json, and ARCHS4py modules.

7.1.5. Statistical analysis

Statistical analyses were conducted using GraphPad Prism version 10.5.0 for Windows (GraphPad Software, Boston, MA, USA; www.graphpad.com). Associations between

continuous variables were assessed using Spearman rank correlation for non-parametric data and Pearson correlation for normally distributed variables. Group comparisons were performed using one-way analysis of variance (ANOVA). For all analyses, $p < 0.05$ was considered statistically significant.

7.2. Study II

7.2.1. Study design and protocol registration

The methodological framework for this systematic review and meta-analysis was developed in strict adherence to the Cochrane Handbook for Systematic Reviews of Interventions. Prior to data extraction, the study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (identifier: CRD42023485291). To ensure the capture of rapidly emerging clinical data, a minor deviation from the original protocol was introduced to permit the inclusion of peer-reviewed scientific letters. All analyses and subsequent findings are reported in compliance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

7.2.2. Systematic literature search strategy and eligibility criteria

A systematic literature search was conducted on November 25, 2023, across three major scientific databases: PubMed (MEDLINE), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search key and the number of records retrieved from each database are detailed in the Supplementary Material of the original publication (146).

The PICO (Population, Intervention, Comparator, Outcome) framework was used to define the eligibility criteria for study inclusion: patients with CLE or SLE with mucocutaneous involvement (P), biologic therapy or small molecule (I), placebo or reported pre- and post-intervention outcomes in the absence of a comparator arm (C), efficacy and safety profile (O). The CLASI score, adverse events (AEs), and serious adverse events (SAEs) were the investigated outcomes. All included studies had to report cutaneous efficacy using any validated form of the CLASI score, including absolute CLASI changes or the CLASI50. Only the activity domain (CLASI-A) was considered in the analysis. Eligibility was restricted to peer-reviewed original research articles. Review articles, editorials, abstracts, and comments were excluded. As noted in the protocol deviation above, letters to the editor were additionally considered eligible given their potential to contain reportable clinical outcome data.

7.2.3. Study selection and data extraction

Following database searches, all retrieved records were imported into EndNote 20 for reference management and systematic duplicate removal (147). Subsequently, a two-phase screening process was carried out by two independent reviewers in accordance with the predefined selection strategy: title and abstract screening, followed by full-text assessment. Both phases were conducted using Rayyan Systems (Cambridge, MA, USA) (148). Disagreements at any stage were resolved by a third independent investigator. Inter-reviewer agreement at the full-text selection stage was excellent (Cohen's Kappa = 0.91).

Relevant data were independently extracted by two investigators using a standardized form. The following variables were recorded for each eligible study: study details (first author, year of publication, trial identification number if applicable, study design, and study timeframe), intervention parameters (therapeutic agent, dosing regimen, and route of administration), baseline clinical characteristics (cohort size, patient demographics, baseline CLASI-A scores, concurrent SLE diagnoses, CLE subtypes, and concomitant baseline medications), and study endpoints (follow-up duration, proportion of CLASI50 responders, adverse events, and serious adverse events). Where data were presented exclusively in graphical format, numerical values were extracted using WebPlotDigitizer (149). To prevent statistical error due to overlapping patient populations, duplicate cohorts were identified, and only data from the publication reporting the largest sample size were analyzed.

7.2.4. Quality assessment

The quality assessment of the included studies was performed by two independent reviewers. Risk of bias assessment was carried out using study design-specific tools, in accordance with the principles of the Cochrane Collaboration: randomized controlled trials were evaluated using the revised Cochrane Risk-of-Bias tool (RoB2) (150), non-randomized and single-arm studies were assessed with the Methodological Index for Non-Randomized Studies (MINORS) (151), and case series and case reports were appraised using the Joanna Briggs Institute Critical Appraisal Tools (152, 153). Subsequently, the Confidence in Network Meta-Analysis (CINeMA) framework was used to grade the overall certainty of evidence (154, 155).

7.2.5. Statistical analysis

We used two complementary approaches for quantitative data synthesis. First, we performed a network meta-analysis (NMA) using odds ratios (OR) and mean differences (MD) as effect sizes. In the NMA, we conducted two parallel analyses. In the first, all doses of each therapeutic agent were pooled. In the second one, individual dosing regimens were analyzed separately.

We then performed a traditional pairwise meta-analysis, using proportions and MDs from baseline as effect size measures.

In the NMA, network geometry was assessed for each outcome in advance by constructing network plots to evaluate node connectivity (156). Disconnected treatment arms were excluded following consensus among the authors. To account for multi-arm trial correlations, random-effects network models were applied, assuming a common heterogeneity variance across the entire network (157). Treatment hierarchies were established using P-scores and surface under the cumulative ranking (SUCRA) plots (158). Results are presented as forest plots, P-score rankings, SUCRA plots, and direct evidence plots.

For the standard meta-analysis, proportion-based outcomes were modeled using random-intercept logistic regression (159, 160). Between-study heterogeneity (τ^2) was estimated via maximum likelihood, and individual study 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method (161). For continuous outcomes, MD was calculated as the difference between follow-up and baseline values, pooled using the inverse variance weighting method, and τ^2 was estimated with the restricted maximum likelihood estimator and the Q-profile method (157, 158).

All analyses were performed in R (version 4.2.3; R Core Team, 2023) using the netmeta and BUGSnet packages (162, 163). Further methodological details are provided in the Supplementary Material of the original publication (146).

8. RESULTS

8.1. Study I

8.1.1. Demographic and clinical characteristics of the study cohort

Lesional skin biopsies were obtained from 51 patients with confirmed CLE, of whom 26 had SCLE and 25 had DLE. 98% of the patients were female, and the cohort had a mean age of 66 ± 18 years. Concomitant SLE was diagnosed in 19.6% of the patients (10/51). The SLE diagnosis was established according to the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria (164). Among patients with concurrent SLE, the most frequently documented extracutaneous manifestations were leukopenia, followed by arthritis and hypocomplementemia. Mean baseline cutaneous disease activity, as measured by the CLASI-A score, was 9.8 ± 6.8 in the SCLE group and 6.0 ± 3.2 in the DLE group. All patients were untreated for CLE and free of systemic immunosuppressive therapy at the time of biopsy in order to eliminate pharmacological confounding factors. Comprehensive demographic and clinical characteristics of the cohort are presented in Table 3. Where applicable, concomitant medications with potential immunomodulatory or immunometabolism-modulating properties, namely metformin, statins, montelukast, and sulfasalazine, are also noted in Table 3 (165-168).

Table 3. Baseline characteristics of the study population

Patient number	Age	Sex	CLE subtype	Autoantibody profile	SLE (1 = yes, 0 = no)	LE extracutaneous manifestations	CLASI-A	Medications at time of biopsy*
1	38	F	DLE	ANA, anti-chromatin	1	arthritis, proteinuria	7	-
2	51	M	DLE	ANA, anti-SSA/Ro, anti-chromatin	0	proteinuria	7	-
3	55	M	DLE	-	0	-	6	-
4	55	F	DLE	anti-chromatin	0	arthritis	4	-
5	62	F	DLE	anti-sp100	0	-	6	montelukast
6	70	F	DLE	anti-chromatin	0	arthritis	10	-
7	24	F	DLE	-	0	-	10	-
8	36	F	DLE	ANA, anti-dsDNA,	1	-	1	-

				anti-histone, anti-nucleosome , anti-CL, anti-β2-GPI				
9	56	F	DLE	ANA, ENA, anti-SSA/Ro, anti-dsDNA, anti-Scl-70, anti-chromatin	1	-	2	-
10	59	F	DLE	ANA, anti-chromatin, anti-cytoplasm	0	-	3	-
11	72	F	DLE	-	0	HC	5	sulfasalazine, metformin
12	68	F	DLE	ANA, anti-SSA/Ro, anti-dsDNA, anti-RNP/Sm, RF, anti-chromatin, anti-cytoplasm, anti-β2-GPI	1	leukopenia, arthritis	11	-
13	58	F	DLE	ANA	0	-	6	-
14	47	F	DLE	ANA	1	arthritis, leukopenia	6	-
15	41	M	DLE	-	0	-	14	-
16	53	M	DLE	ANA	0	-	6	-
17	75	F	DLE	ANA	0	-	11	-
18	39	F	DLE	anti-SSA/Ro	0	-	9	-
19	28	F	DLE	-	0	-	4	-
20	78	F	DLE	-	0	-	3	-
21	57	M	DLE	-	0	-	3	-
22	66	F	DLE	anti-SSA/Ro, anti-Scl-70	0	-	5	-
23	77	M	DLE	ANA, ENA, anti-SSA/Ro, anti-cytoplasm	0	-	3	-
24	55	F	DLE	ANA	0	-	4	-
25	77	F	DLE	ENA, anti-SSB	0	HC	4	-
26	86	F	SCLE	ANA, anti-SSA/Ro, anti-SSB, RF	0	-	10	-
27	80	F	SCLE	ANA, anti-SSA/Ro, anti-SSB	0	leukopenia	19	-
28	69	F	SCLE	ANA, anti-chromatin	0	-	17	-

29	90	M	SCLE	ANA, anti-chromatin, anti-cytoplasm	0	leukopenia	7	-
30	55	M	SCLE	ANA, anti-chromatin, anti-cytoplasm	0	-	9	-
31	80	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB, RF, anti-chromatin, anti-cytoplasm	1	leukopenia, HC	9	-
32	49	F	SCLE	ANA, anti-SSA/Ro, anti-dsDNA, anti-RNP/Sm, RF, anti-chromatin	1	fever, leukopenia, arthritis, HC	22	-
33	82	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB, anti-dsDNA, anti-nucleosome , anti-chromatin, anti-cytoplasm, anti-CL, anti-β2-GPI	1	-	21	rosuvastatin
34	87	F	SCLE	-	0	-	4	metformin, atorvastatin
35	58	M	SCLE	ANA, anti-chromatin	0	-	6	-
36	86	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB	0	-	4	-
37	96	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB, RF	1	leukopenia, HC	12	atorvastatin
38	86	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-cytoplasm	0	leukopenia	20	-
39	72	F	SCLE	ANA, anti-chromatin	0	HC	4	-
40	64	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB	0	-	1	-
41	78	F	SCLE	ANA, anti-SSA/Ro,	0	-	4	-

				anti-SSB, anti-β2-GPI				
42	78	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB, anti-chromatin	0	-	5	-
43	82	F	SCLE	ENA, anti-SSA/Ro, anti-cytoplasm	0	leukopenia	19	-
44	88	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB, anti-dsDNA	1	-	21	atorvastatin
45	78	F	SCLE	ANA, anti-SSA/Ro	0	-	4	simvastatin
46	47	M	SCLE	-	0	-	13	-
47	88	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-Scl-70, anti-chromatin, anti-cytoplasm	0	-	6	-
48	72	M	SCLE	-	0	-	6	-
49	46	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB	0	-	2	-
50	84	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB, anti-chromatin	0	leukopenia	10	-
51	82	F	SCLE	ANA, ENA, anti-SSA/Ro, anti-SSB	0	-	2	atorvastatin

* This table only list medications with potential immunomodulatory or immunometabolism-modulating properties and it does not represent a comprehensive medication record.

Abbreviations: CLE = cutaneous lupus erythematosus, DLE = discoid lupus erythematosus, SCLE = subacute cutaneous lupus erythematosus, SLE = systemic lupus erythematosus, LE = lupus erythematosus, CLASI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index, ANA = antinuclear antibody, ENA = extractable nuclear antigen antibodies, anti-SSA/Ro = anti-Sjögren's syndrome-related antigen A, anti-SSB = anti-Sjögren's syndrome-related antigen B, anti-dsDNA = anti-double-stranded DNA, RF = rheumatoid factor, anti-CL = anti-Cardiolipin, anti-β2-GPI = anti-β2-glycoprotein I, HC = hypocomplementaemia

8.1.2. GLUT1 and MxA expression in lesional CLE skin

To characterize glucose metabolism and IFN-I activation in CLE lesional skin, immunohistochemical analysis of GLUT1 and MxA was performed on skin biopsies from 51 CLE patients (26 SCLE, 25 DLE) and 8 healthy controls (Figure 3).

Significantly elevated keratinocyte GLUT1 expression was found in both SCLE and DLE samples compared to healthy controls (SCLE: $p = 0.0344$; DLE: $p = 0.0356$; Figure 3A-D). There were no significant differences in epidermal GLUT1 expression between the two subtypes ($p = 0.998$). We next assessed MxA expression, a well-established surrogate marker of IFN-I pathway activation. MxA expression was significantly higher in both keratinocytes ($p = 0.0031$) and dermal infiltrating lymphocytes ($p = 0.0059$; Figure 3E-L) in all CLE samples compared to healthy controls. We also observed a significant positive correlation between keratinocyte and lymphocyte MxA expression within individual biopsies ($r = 0.602$, $p < 0.001$). Interestingly, MxA expression in either keratinocytes ($p = 0.6844$) or lymphocytes ($p = 0.9493$) did not differ significantly between SCLE and DLE samples. The expression profiles of keratinocyte GLUT1, alongside keratinocyte and lymphocyte MxA across all samples, are summarized in Figure 4A.

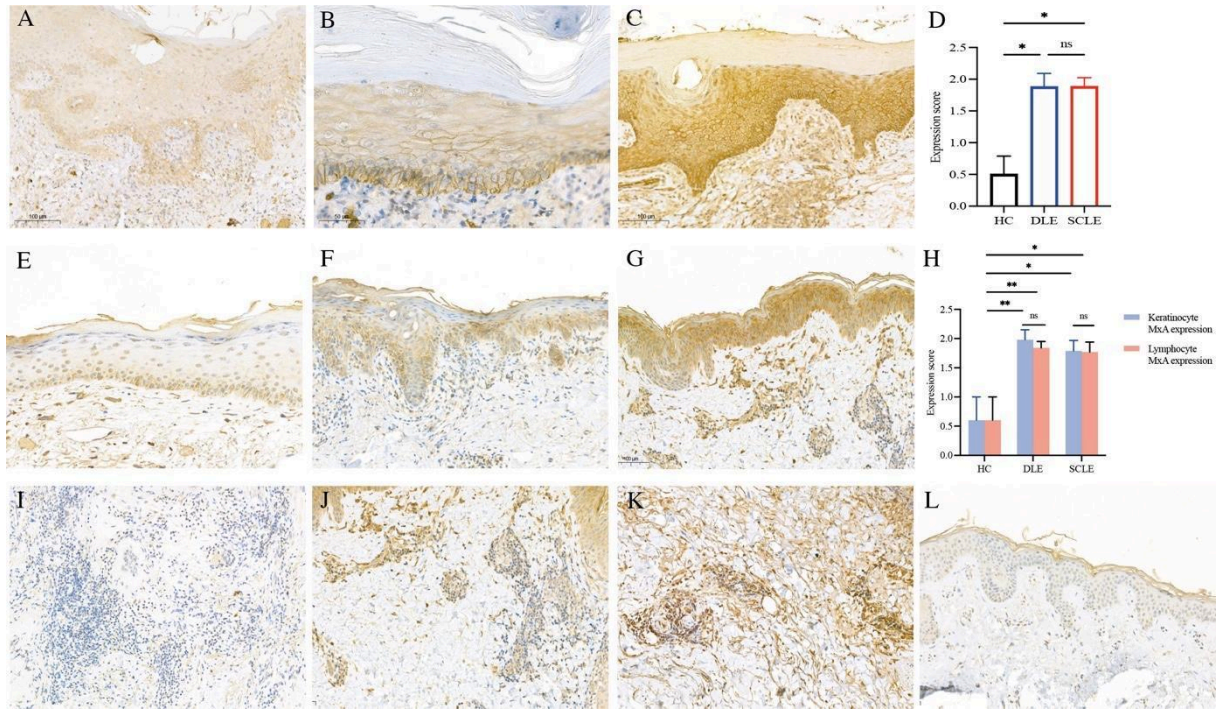


Figure 3. Immunohistochemical analysis of GLUT1 and MxA expression in lesional CLE skin

(A–C) Representative images of GLUT1 immunohistochemistry in CLE skin lesions, showing mild (A; +), moderate (B; ++), and strong (C; +++) expression. (D) Keratinocyte GLUT1 expression scores stratified by study group. (E–G) Representative images of MxA immunohistochemistry in keratinocytes in CLE skin lesions, showing mild (E; +), moderate (F; ++), and strong (G; +++) expression. (H) Keratinocyte and lymphocyte MxA expression scores stratified by study group. (I–K) Representative images of MxA immunohistochemistry in dermal infiltrating lymphocytes in CLE skin lesions, showing mild (I; +), moderate (J; ++), and strong (K; +++) expression. (L) Healthy control. Magnification: 20× for all images, except panel B (40×). Statistical analysis: ordinary one-way ANOVA with Dunnett's multiple comparisons test. Significance levels: *ns* $p > 0.05$, * $p < 0.05$, ** $p < 0.01$.

Abbreviations: HC = healthy control; DLE = discoid lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus; ns = non-significant.

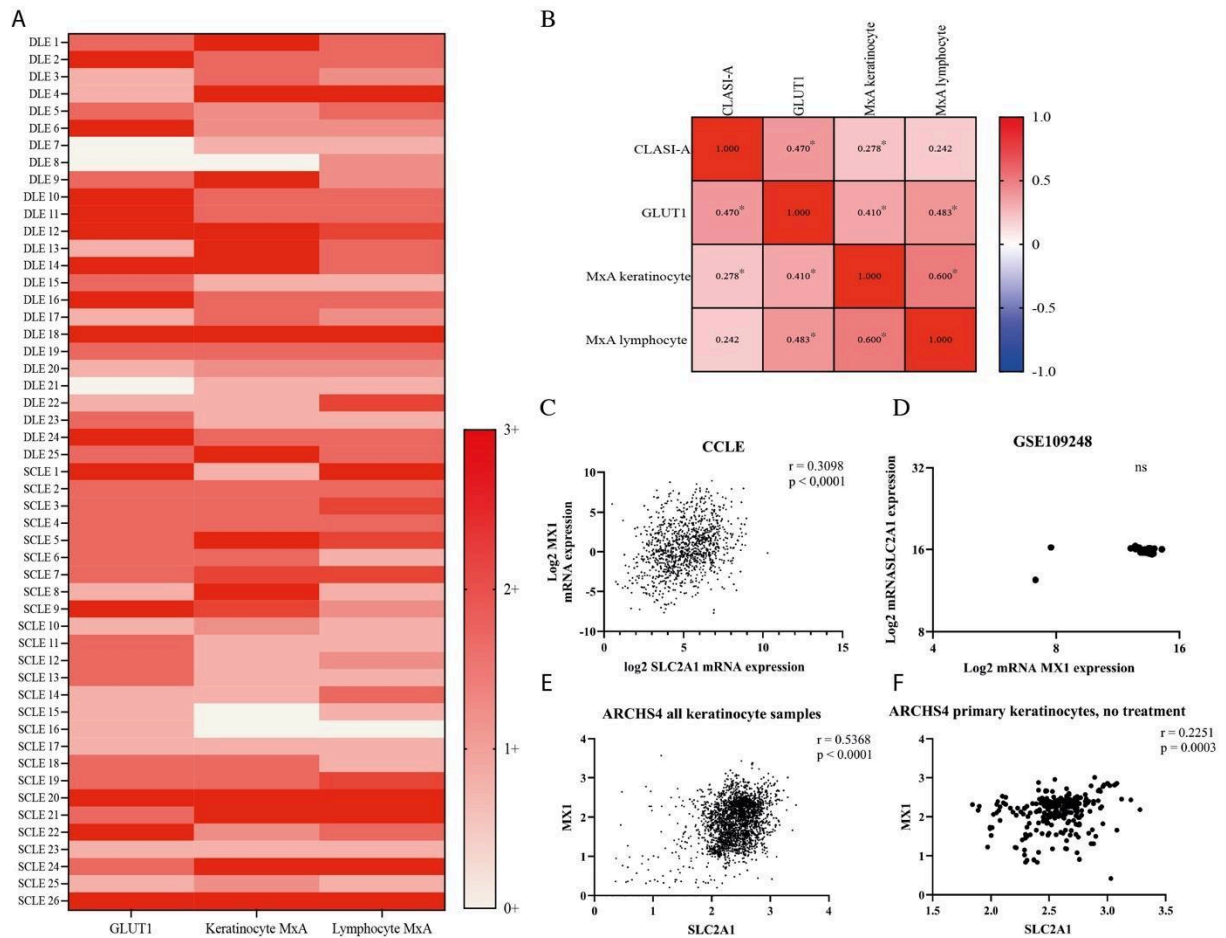


Figure 4. Expression profiles and correlations of GLUT1 and MxA across our patient cohort and public transcriptomic datasets

(A) Heatmap of GLUT1 and MxA expression levels across all CLE samples. (B) Correlation matrix of Spearman's correlation coefficients (r) among keratinocyte GLUT1, keratinocyte and lymphocyte MxA expression, and CLASI-A scores ($*p < 0.05$). (C–F) Scatter plots of SLC2A1 and MX1 mRNA co-expression across publicly available transcriptomic datasets: (C) Cancer Cell Line Encyclopedia (CCLE) dataset, 877 cell lines; (D) GSE109248 dataset with gene expression profiles of ACLE, SCLE, DLE, and healthy controls ($n = 23$, $p > 0.05$); (E) ARCHS4 database, keratinocyte-specific bulk RNA-sequencing data from over 2,900 samples; and (F) ARCHS4 database, restricted to primary untreated keratinocytes.

Abbreviations: ACLE = acute cutaneous lupus erythematosus; CLASI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index — Activity domain; CCLE =

Cancer Cell Line Encyclopedia; DLE = discoid lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus; ns = non-significant.

8.1.3. Correlations of GLUT1 expression, IFN-I activity, and disease activity

The observed upregulation of GLUT1 in lesional CLE skin prompted us to investigate whether enhanced glucose uptake is mechanistically linked to the hallmark IFN-I pathway overactivation of the disease, measured by keratinocyte and dermal infiltrating lymphocyte MxA expression. Keratinocyte GLUT1 expression showed a significant positive correlation with both keratinocyte MxA ($r = 0.41$, $p = 0.003$) and lymphocyte MxA expression ($r = 0.483$, $p < 0.001$). We then performed a subtype-specific analysis. Keratinocyte GLUT1 positively correlated with keratinocyte MxA ($r = 0.4426$, $p = 0.0236$) and lymphocyte MxA ($r = 0.6529$, $p < 0.001$) in SCLE samples. In DLE, both correlations were also significant (keratinocyte MxA: $r = 0.4073$, $p = 0.0433$; lymphocyte MxA: $r = 0.433$, $p = 0.0306$).

We next asked whether GLUT1 upregulation also affects the overall activity of the disease. Keratinocyte GLUT1 expression correlated significantly with CLASI-A scores ($r = 0.47$, $p < 0.001$), as did keratinocyte MxA expression, albeit more modestly ($r = 0.278$, $p = 0.048$). Lymphocyte MxA expression, however, did not reach statistical significance in this regard ($r = 0.242$, $p = 0.087$). The complete correlation matrix is presented in Figure 4B.

8.1.4. *In silico* validation of *SLC2A1* and *MX1* co-expression across independent transcriptomic datasets

Having established a significant correlation between keratinocyte GLUT1 and MxA expression, we sought to determine whether this relationship is reflected at the transcriptomic level across independent datasets. Spearman correlation analysis of *SLC2A1* and *MX1* mRNA expression across 877 cancer cell lines from the CCLE dataset revealed a significant positive correlation ($r = 0.3098$, $p < 0.001$; Figure 4C). When applied to the GSE109248 dataset, comprising bulk RNA sequencing data from skin biopsy samples of ACLE, SCLE, DLE, and healthy controls ($n = 23$), the correlation did not reach statistical significance (Figure 4D).

We next examined the ARCHS4 database of publicly available keratinocyte RNA-sequencing data to interrogate this relationship in a keratinocyte-specific context. In over 2,900 keratinocyte samples, *SLC2A1* expression significantly correlated with *MX1* expression ($r = 0.5368$, $p < 0.0001$; Figure 4E). When we restricted the analysis to

primary, untreated human keratinocytes, the correlation remained significant ($r = 0.2251$, $p = 0.0003$; Figure 4F).

8.2. Study II

8.2.1. Search results, study selection, and study characteristics

The systematic database search retrieved a total of 18,280 records. Following the removal of duplicate records, title and abstract screening were performed on the remaining 12,522 articles. Of these, 53 publications met the predefined selection criteria and were included in the final analysis (111-116, 123-125, 127-136, 169-202). The 53 included articles represented a diverse distribution of study designs: 18 randomized controlled trials (RCTs) (111-116, 123-125, 127-133, 135, 136), 24 observational studies, case series, or case reports (134, 169-191), 4 post-hoc analyses (199-202), 3 errata or formal corrections (192-194), 2 secondary subgroup analyses of primary trials (195, 198), and 2 long-term trial extensions (196, 197). Because 3 of the included articles each reported data from two distinct clinical trials (115, 127, 133), the total number of individual RCTs available for assessment increased to 21. These 21 trials were subsequently allocated to either quantitative synthesis or descriptive review: 15 RCTs were included in the NMA (111-115, 124, 125, 128, 130, 131, 133, 136), whereas the remaining 6 were evaluated via qualitative synthesis within the systematic review (123, 127, 129, 132, 135).

A parallel evaluation strategy was applied to the non-randomized literature. Of the 24 observational studies, case series, and case reports, 23 provided sufficient data for pooling in the conventional pairwise meta-analysis (134, 169-187, 189-191), while 1 (188) was included in the qualitative assessment only. The complete study selection process is illustrated in the PRISMA flowchart (Figure 5).

Detailed characteristics of the included studies and the baseline clinical and demographic characteristics of the patient populations are fully documented in the original published article (Table 1) and its accompanying Supplementary Material (Supplementary Tables S2 and S3) (146).

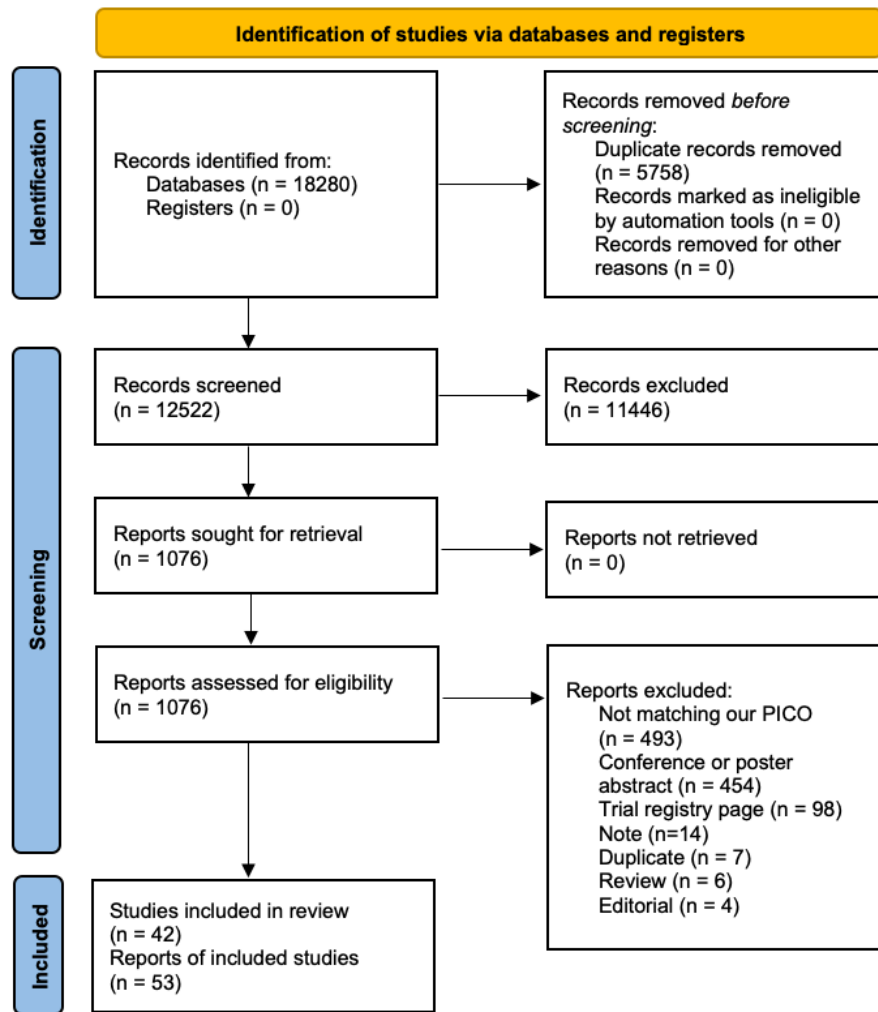


Figure 5. PRISMA 2020 flow diagram of the systematic literature search and study selection workflow

8.2.2. Efficacy of novel therapeutic interventions in CLE

In all included RCTs, novel therapeutic agents were uniformly compared against a placebo. The network of direct and indirect treatment comparisons included in the efficacy analysis is mapped in Figure 4 of the original publication (146).

Deucravacitinib was the most effective therapy for reducing CLE disease activity. Patients receiving deucravacitinib were eight times more likely to achieve a 50% reduction in disease activity compared to placebo (OR: 8.28, 95% CI: 2.22–30.91). Litifilimab and anifrolumab also outperformed placebo. The odds of achieving CLASI50 were more than 2.5 times higher with litifilimab than with placebo (OR: 2.54, 95% CI: 1.20–5.40). Anifrolumab was associated with a more than two-fold higher odds of reaching the CLASI50 (OR: 2.25, 95% CI: 1.23–4.14).

In head-to-head indirect comparisons, deucravacitinib, litifilimab, and anifrolumab each demonstrated significantly superior efficacy compared to ustekinumab (OR: 10.72, 95% CI: 2.42–47.6; OR: 3.29, 95% CI: 1.18–9.19; OR: 2.92, 95% CI: 1.16–7.36, respectively). Conversely, baricitinib was significantly less effective when compared to deucravacitinib (OR: 0.11, 95% CI: 0.03–0.49) and litifilimab (OR: 0.37, 95% CI: 0.14–0.99). Complete results of the network meta-analysis, including all pairwise comparisons, are presented in the league tables available in the Supplementary Material of the original publication (Table S4) (146). Treatment effect estimates and the probability rankings for each intervention are presented in Figures 6a and 6b, respectively.

Dose-stratified analyses, in which individual dosing regimens were examined separately rather than pooled, yielded results consistent with those of the primary analysis. These findings are presented in the Supplementary Material of the original publication (Figure S1) (146).

A traditional pairwise meta-analysis was performed to pool data from observational studies, case series, and case reports. Among the evaluated therapies, anifrolumab demonstrated the most pronounced reduction in CLASI-A scores (MD: 14.83, 95% CI: 9.67–19.99). Consistent with this finding, the highest proportion of patients achieving a CLASI50 response was also observed in the anifrolumab group (P: 0.98, 95% CI: 0.86–1.00).

Tofacitinib also demonstrated statistically significant efficacy in reducing CLE disease activity (MD: 13.61, 95% CI: 3.13–24.08). Additionally, treatment with belimumab was associated with a statistically significant, though more modest, reduction in disease activity scores (MD: 3.94, 95% CI: 1.90–5.97). The comprehensive results and corresponding forest plots are provided in the Supplementary Material of the original publication (Figure S2) (146).

(a)

(b)

Figure 6. Efficacy of novel therapies in CLE

(a) Forest plot of the odds of achieving a CLASI50 response when treated with a novel therapeutic agent compared to placebo. (b) P-score plot representing the probability of each therapy ranking as the most effective across the network.

Abbreviations: OR = odds ratio, CI = confidence interval, CLASI50 = Cutaneous Lupus Erythematosus Disease Area and Severity Index-50

8.2.3. Qualitative synthesis of non-pooled efficacy data

Six RCTs (123, 127, 129, 132, 135) and one observational study (188) did not provide sufficient data for quantitative pooling and were assessed qualitatively.

Several of these studies indicated positive therapeutic trends. Baricitinib at 2 mg/day was associated with a significant reduction in CLASI-A scores in SLE patients with cutaneous involvement compared to placebo, whereas the 4 mg/day dose did not yield a statistically significant change (129). In another trial, patients treated with iberdomide showed a trend toward improvement in CLASI-A scores from baseline at week 12, while only minimal changes were observed in the placebo group (135). Dapirolizumab pegol similarly demonstrated a significantly greater improvement in disease activity from baseline at week 48 compared to placebo (123).

Data from the non-randomized studies closely mirrored these positive clinical outcomes. In a single qualitatively assessed observational study, all three patients receiving anifrolumab achieved a clinically meaningful reduction in CLASI-A scores (188). In contrast, certain targeted therapies failed to demonstrate superior efficacy over control arms. Two publications reporting the outcomes of three RCTs found no statistically significant differences in CLASI-A scores between intervention and placebo groups for either tofacitinib or sirukumab (127, 132).

8.2.4. Analysis of adverse events

Across all included RCTs, the most frequently documented complications were urinary tract infections, mild upper respiratory tract infections, and nasopharyngitis.

The network meta-analysis revealed no statistically significant differences in the odds of experiencing an AE between the novel therapies and placebo. Treatment effect estimates and the corresponding p-score plots ranking therapies by AE probability are presented in Figures 7a and 7b, with all pairwise comparisons available in the league tables in the Supplementary Material of the original publication (Tables S5 and S6) (146). Dose-stratified safety analyses yielded results consistent with those of the primary analysis (Figure S4 of the original publication).

Pooled data from observational studies, case series, and case reports revealed considerable heterogeneity in reporting rates of AEs across the different studies and therapeutic agents. Although proportions of AEs were numerically higher for

belimumab and anifrolumab, these differences did not reach statistical significance, indicating a broadly comparable safety profile across the evaluated therapies (original article Figure S5) (146).

8.2.5. Analysis of serious adverse events

The most frequently reported serious adverse events across the included studies were serious infections, major cardiovascular events, malignancies, and venous thromboembolism. Our network meta-analysis revealed no statistically significant differences between the majority of novel interventions and placebo, with the notable exception of baricitinib, which was associated with a significantly higher odds of SAEs compared to placebo (OR: 5.26, 95% CI: 1.11–24.94). The forest plot and the corresponding P-score plot, which depict the probability that each therapy has the highest SAE rate, are presented in Figures 7c and 7d.

Dose-stratified analyses validated these findings. Patients receiving baricitinib at both doses of 2 mg and 4 mg exhibited the highest SAE rates across all treatment groups (Figure S6 of the original publication) (146). In the pairwise meta-analysis of observational study data, the pooled proportion of SAEs was numerically higher among patients treated with anifrolumab than among those treated with other therapeutic agents (Figure S7 of the original publication).

The network of direct and indirect treatment comparisons for AEs and SAEs is shown in Figure 4 of the original publication (146).

8.2.6. Qualitative synthesis of non-pooled safety data

Qualitative synthesis of the non-pooled safety data revealed no significant differences in the incidence of AEs or SAEs between tofacitinib-treated patients and those receiving placebo (132). In contrast, an increased incidence of both AEs and SAEs was linked to sirukumab treatment (127).



Figure 7. Adverse events and serious adverse events of novel therapies in CLE

(a) Forest plot illustrating the odds of experiencing any adverse event for each investigated therapeutic agent compared to placebo. (b) P-score plot depicting the probability of each treatment ranking as the safest regarding any adverse event. (c) Forest plot showing the odds of experiencing a serious adverse event for each novel intervention compared to placebo. (d) P-score plot representing the probability of each treatment ranking as the safest regarding serious adverse events.

Abbreviations: OR = odds ratio, CI = confidence interval, CLASI50 = Cutaneous Lupus Erythematosus Disease Area and Severity Index-50, AE = adverse event

8.2.7. Quality assessment

Most included RCTs were classified as having a low risk of bias, and the remaining trials demonstrated a moderate risk. Non-randomized studies, case series, and case reports were all rated as low to moderate risk. A comprehensive study-by-study breakdown of the risk of bias assessments is detailed in the Supplementary Material of the original publication (Tables S7–S13) (146).

Across all treatment comparisons, the certainty of evidence ranged from low to high. Downgrading was primarily driven by imprecision and incoherence within the evidence network. The detailed evaluation of certainty of evidence for therapeutic efficacy (CLASI50) and safety (AE and SAE) endpoints is presented in the Supplementary Material of the original publication (Tables S14–S16) (146).

9. DISCUSSION

9.1. Summary of findings, international comparisons

9.1.1. Study I

Dysregulated immunometabolism – particularly the rewiring of glucose metabolism toward a highly glycolytic state – has been increasingly implicated in the pathogenesis of a broad spectrum of conditions. In autoimmune diseases, this has been characterized in rheumatoid arthritis (203), multiple sclerosis (204), inflammatory bowel disease (205), and SLE (206), where glycolytic reprogramming of immune cells has been shown to drive and sustain chronic inflammation. A similar glycolytic shift has been described in metabolic disorders, including obesity (207), type 2 diabetes mellitus (208), and non-alcoholic fatty liver disease (209), as well as in malignancy (210). In the context of inflammatory skin diseases, GLUT1 upregulation and enhanced glycolytic activity have been most extensively characterized in psoriasis, where GLUT1 expression has been shown to positively correlate with disease activity (97). Our study addressed the analogous but previously unexplored question of whether a similar metabolic reprogramming occurs in CLE lesional skin.

We observed a statistically significant increase in GLUT1 expression in lesional keratinocytes from CLE patients compared to healthy controls. The upregulation of glucose transporters was consistent across both SCLE and DLE subtypes. These observations suggest that enhanced keratinocyte glucose uptake might represent a shared metabolic trait of active CLE, irrespective of subtype. An earlier study also documented elevated GLUT1 expression in CLE lesional skin, although the cohort consisted predominantly of ChLE cases. The analysis of a rare clinical presentation limits the generalizability of these findings to more prevalent subtypes of CLE (211).

To characterize the activation of the IFN-I pathway in CLE lesional skin, we next assessed MxA expression in both keratinocytes and dermal infiltrating lymphocytes. MxA was significantly elevated in both cell populations compared to healthy controls. These results align with previously published data of elevated MxA expression in CLE skin (60). Notably, we did not observe a significant difference in MxA expression between SCLE and DLE samples in either cell population, which is consistent with the subtype-independent pattern observed for GLUT1. We also identified a significant

positive correlation between GLUT1 expression and MxA expression in both keratinocytes and infiltrating lymphocytes. This correlation suggests that enhanced glucose uptake is mechanistically linked to the hallmark inflammatory cascade of CLE. We validated these findings through correlational analyses of publicly available transcriptional databases. SLC2A1 and MX1 mRNA expression correlated significantly across cancer cell lines and keratinocyte datasets, which suggests a possible co-regulation of the two genes. The absence of a statistically significant correlation in the GSE109248 dataset of different CLE subtypes and healthy controls is likely due to the restricted sample size paired with the limitations inherent to bulk RNA sequencing. Bulk transcriptomic profiling of skin biopsies captures an averaged signal across heterogeneous cell populations. Cell-specific associations may therefore be masked, unlike in cell line datasets or immunohistochemical analyses.

The significant positive correlation between keratinocyte GLUT1 expression and disease activity, measured by the CLASI-A score, further supports the clinical relevance of our findings. The association between enhanced glucose uptake and disease activity suggests that glycolytic reprogramming might be an active contributor to cutaneous inflammation in CLE. A previous study has shown that pharmacological GLUT1 inhibition suppresses inflammatory gene expression in psoriatic skin and reduces inflammatory cell infiltration in murine models (92). These preclinical findings raise the possibility that targeting GLUT1 could be beneficial in CLE.

Keratinocyte MxA expression also correlated with disease activity, albeit more modestly. Lymphocyte MxA expression did not correlate significantly with the CLASI-A scores. The lack of positive correlation between the activation of the IFN-I pathway in dermal infiltrating lymphocytes and disease activity may reflect the predominant role of keratinocytes as major drivers of the local inflammatory microenvironment in CLE lesional skin. This is consistent with the emerging recognition of these cells as active contributors to cutaneous inflammation rather than passive targets of cytotoxic injury (62, 63). Activated keratinocytes and immune cells have been shown to share common metabolic programs, including an elevated glycolytic state and increased expression of key metabolic regulators such as mechanistic target of rapamycin (mTOR) and HIF-1 α (212). Our findings suggest that a similar metabolic reprogramming may also occur in CLE lesional skin.

9.1.2. Study II

The clinical management of CLE remains a profound challenge. There have been recent advances in the understanding of the different molecular mechanisms driving cutaneous inflammation, yet the precise pathomechanism of the disease has not been fully characterized. A substantial proportion of patients remain resistant to available therapies, and this is further complicated by the several subtypes of CLE that respond differently to treatment (1, 2). The FDA has yet to approve a therapy with a specific indication for CLE, and clinical practice relies largely on guidelines that have not been updated in recent years. A growing number of novel targeted therapies have been investigated in CLE and SLE with mucocutaneous involvement, however, direct comparative efficacy and safety data are scarce. Consensus on the integration of these novel therapies into treatment guidelines for CLE remains limited.

The present systematic review and meta-analysis provides the first comprehensive head-to-head comparison of novel therapeutic agents in CLE. By synthesizing data from 53 publications, including 21 RCTs, alongside observational studies, case series, and case reports, this study provides an extensive comparative analysis of the efficacy and safety of novel therapies in CLE.

Deucravacitinib, an allosteric TYK2 inhibitor, was the most effective of all investigated novel therapies. Patients receiving deucravacitinib were more than eight times more likely to achieve a CLASI50 response than those on placebo. TYK2 inhibition suppresses multiple cytokine signaling pathways, including IFN-I, IL-6, IL-12, IL-17, IL-22, and IL-23. All of these are implicated in SLE and CLE pathogenesis, which may explain the superior efficacy of deucravacitinib (213-216). Beyond its inhibitory effects on cytokine signaling, TYK2 inhibition has been shown to restore the T_{fh}/T_{reg} imbalance observed in SLE, while modulating Th1, Th17, B cell, and myeloid cell function (217, 218). Additionally, deucravacitinib has been reported to suppress the expression of a broad range of pro-inflammatory genes in T cells isolated from CLE skin biopsies and in ex vivo CLE skin samples (219). Crucially, this superior efficacy of deucravacitinib was accompanied by a favorable safety profile, since there were no significant differences in the odds of AEs or SAEs compared to placebo. Although pan-JAK inhibitors have been recently associated with an elevated risk of major cardiovascular

events, venous thromboembolism, and malignancies, TYK2 inhibition does not modulate hematopoietic or thrombopoietic signaling pathways (220, 221). This selectivity may explain the favorable safety profile of deucravacitinib compared to broader JAK inhibition.

Besides deucravacitinib, litifilimab and anifrolumab also demonstrated significant superiority over placebo. Both agents target the IFN-I pathway, the most extensively characterized driver of inflammation in CLE and SLE. Anifrolumab directly blocks IFN-I signaling through IFNAR1 inhibition, while litifilimab suppresses IFN-I, IL-6, and TNF- α release by targeting BDCA2 on pDCs (222-224).

Among the therapies investigated in this analysis, belimumab and anifrolumab are the only two that have been incorporated into current SLE treatment guidelines. The 2023 updated EULAR recommendations for SLE suggest the use of both agents in patients with extrarenal disease, non-major organ involvement, and significant mucocutaneous manifestations (107). The 2025 ACR guidelines for the management of SLE recommend belimumab and anifrolumab in moderate-to-severe mucocutaneous involvement refractory to first-line therapy. A preference for anifrolumab is noted based on the more extensive clinical experience on its use, the rapid onset of its effect, and superior response rates (108). Despite the encouraging evidence on anifrolumab, it is not yet incorporated into any CLE guidelines. Litifilimab and deucravacitinib are not included in any available treatment recommendations for SLE or CLE.

The inferior performance of baricitinib compared to deucravacitinib and litifilimab warrants careful consideration. Patients treated with baricitinib had significantly lower odds of achieving the CLASI50. The highest SAE rate was observed in patients treated with baricitinib. These results are consistent with the class-wide pharmacovigilance concerns that have emerged for JAK inhibitors, suggesting that the risk-benefit profile of baricitinib may be less favorable compared to other available novel agents in CLE (225, 226).

9.2. Strengths

9.2.1. Study I

To the best of our knowledge, this study is the first to characterize the relationship between upregulated glucose uptake, the activation of the IFN-I system, and clinical

disease activity in CLE. A large, well-documented patient cohort supports the validity of these findings. Our results from the immunohistochemical analysis are further supported by consistent results across multiple independent transcriptomic datasets. The restriction of all samples to active, untreated lesional skin from patients free of systemic immunosuppressive therapy at the time of biopsy minimizes potential pharmacological confounding factors and enhances the interpretability of the results.

9.2.2. Study II

This systematic review and meta-analysis carries several strengths. To the best of our knowledge, this is the first head-to-head comparison of novel therapeutic agents in CLE. The application of a network meta-analysis enables a multi-treatment comparison of novel biologics and small molecules, generating an evidence-based ranking of efficacy and safety across the investigated interventions. The inclusion of a large and diverse patient population enhances the generalizability of our findings to everyday clinical practice.

9.3. Limitations

9.3.1. Study I

Our main limitation is that immunohistochemistry provides a semi-quantitative assessment of protein expression and does not capture the dynamic nature of the metabolome within lesional tissue. Less prevalent CLE subtypes were not included in the analysis, which limits the generalizability of our findings across the full clinical spectrum of the disease. Another of our limitations is that sun exposure history, smoking status, and disease duration were not adjusted for in the analyses. All of these factors may independently influence GLUT1 expression and disease activity.

9.3.2. Study II

One of the main limitations of this study is that the evidence base relies predominantly on indirect comparisons. Comparative trials of novel therapies in CLE are currently absent, which limits the certainty of our comparative efficacy outcomes. We also observed significant variations in the reporting of the CLASI outcome, which restricted the data available for quantitative pooling. This might introduce inconsistency across the findings. Another limitation is that the majority of included studies did not report data stratified by CLE subtype. The lack of this data prevented subgroup analyses based on different clinical presentations of the disease. Finally, it should be noted that the evidence base for deucravacitinib currently consists of a single phase 2 trial. Larger phase 3 studies are needed to confirm these findings.

10. CONCLUSION

10.1. Study I

To our knowledge, this is the first study to establish a link between upregulated glucose metabolism, IFN-I pathway overactivation, and clinical disease activity in CLE. Our results may advance our understanding of cutaneous immunometabolism and CLE pathogenesis. These findings might also highlight novel therapeutic targets and anti-inflammatory strategies that modulate metabolic pathways.

10.2. Study II

Deucravacitinib, anifrolumab, and litifilimab were the most effective novel therapies in reducing CLE disease activity. This robust efficacy was achieved with a favourable safety profile. Deucravacitinib may therefore represent a valuable option for patients with treatment-resistant CLE. Given the extensive clinical experience with anifrolumab and the robust efficacy demonstrated by deucravacitinib, both therapies might warrant inclusion into future CLE-specific treatment guidelines.

11. IMPLEMENTATION FOR PRACTICE

11.1. Study I

Our study expands the knowledge of immunometabolism in CLE. While the role of immunometabolism in this disease had not been characterized before, several studies are already investigating the efficacy of targeting metabolic pathways as an anti-inflammatory strategy in other conditions (167). Novel interventions that modify the metabolic state of immune cells or keratinocytes might therefore prove effective in CLE. The significant upregulation of GLUT1 in CLE lesional skin also raises the possibility that GLUT1 expression could serve as a biomarker of disease activity and response to specific therapies. The identification of reliable biomarkers for treatment response could contribute to a personalized therapeutic approach in CLE.

11.2. Study II

The early incorporation of emerging clinical evidence into updated treatment guidelines is essential to ensure that patients with CLE have access to the most effective and safe therapeutic options (227, 228). Deucravacitinib showed superior efficacy in our analysis. It is not yet approved for SLE or CLE and is absent from both the 2023 EULAR and 2025 ACR guidelines for SLE, as well as from existing CLE treatment guidelines. Should these findings be validated in larger, dedicated CLE trials, deucravacitinib and TYK2 inhibition as a broader therapeutic strategy may represent a significant advancement in the management of LE with mucocutaneous involvement.

The continued use of anifrolumab in clinical practice is supported by its significant efficacy and a favorable safety profile. Anifrolumab should be considered for inclusion in future CLE guidelines.

12. IMPLEMENTATION FOR RESEARCH

12.1. Study I

Further investigation of other metabolic pathways in CLE lesional skin would be valuable, including amino acid and fatty acid metabolism. Such analyses would comprehensively map the interplay between the metabolome and the immune system and explore their contribution to CLE disease activity. Single-cell sequencing and precision metabolomics approaches, such as liquid chromatography-mass spectrometry, could uncover these relationships at the cellular level. Including less prevalent CLE subtypes in future studies would provide a more comprehensive insight into the alterations of immunometabolism across the full clinical spectrum of the disease. Finally, the comparison of glucose metabolism between lesional and non-lesional skin from CLE patients would be of particular interest to clarify whether aberrant glucose metabolism drives the development of cutaneous lesions, sustains active inflammation, or both.

12.2. Study II

Skin-specific outcomes, such as the CLASI, are currently used as secondary endpoints in most SLE trials. Their adoption as primary endpoints in future RCTs would enable direct assessment of cutaneous efficacy and could support approval of novel therapies for CLE-specific indications. Unified, validated outcome measures across trials would also improve the comparability of results and allow for a more robust quantitative synthesis in future meta-analyses. Future trials should uniformly report the CLE subtypes of included patients. This would make subtype-specific analyses possible and help determine whether the response to treatment differs across clinical presentations.

Beyond trial design, several additional research implications emerge from the present analysis. Given that deucravacitinib demonstrated the most robust efficacy in this analysis based on a single phase 2 trial, confirmation from dedicated phase 3 trials in CLE is urgently needed. Finally, long-term follow-up data on both efficacy and safety are needed for the majority of the investigated novel therapies. Most of the available evidence is derived from trials with relatively short follow-up, limiting the assessment of sustained treatment response and long-term safety.

13. IMPLEMENTATION FOR POLICYMAKERS

CLE imposes a significant burden on both patients and healthcare systems. The relapsing course of the disease, permanent scarring, and treatment resistance significantly decrease the quality of life of affected individuals. Policymakers should therefore make the effective management of CLE a priority.

Some patients with isolated CLE will develop SLE over time, and this risk is not always adequately recognized. Standardized screening for systemic involvement is needed to prevent delayed diagnosis and organ damage. Although follow-up protocols exist in most healthcare settings, the interdisciplinary management of CLE is inconsistent. The management of patients with refractory disease or concurrent systemic involvement requires close collaboration among dermatology, rheumatology, and other relevant specialties to ensure that patients receive adequate and personalized treatment.

Updated, CLE-specific treatment guidelines that reflect the growing evidence on novel targeted therapies are urgently needed. Professional societies play a key role in the synthesis of emerging clinical evidence and its translation into clear, regularly updated recommendations. Regular guideline updates would standardize clinical practice and ensure that patients have access to the most effective therapeutic options.

14. FUTURE PERSPECTIVES

Advanced research technologies are rapidly developing. These advances may uncover the precise cellular and molecular drivers of cutaneous inflammation in CLE and lead to the identification of novel therapeutic targets. The recognition of immunometabolism as a driver of autoimmune pathogenesis opens a previously unexplored avenue for therapeutic intervention that may complement or enhance existing targeted strategies.

15. REFERENCES

1. Chasset F, Bouaziz JD, Costedoat-Chalumeau N, Frances C, Arnaud L. Efficacy and comparison of antimalarials in cutaneous lupus erythematosus subtypes: a systematic review and meta-analysis. *Br J Dermatol*. 2017;177(1):188-96.
2. Lu Q, Long H, Chow S, Hidayat S, Danarti R, Listiawan Y, Deng D, Guo Q, Fang H, Tao J, Zhao M, Xiang L, Che N, Li F, Zhao H, Lau CS, Ip FC, Ho KM, Paliza AC, Vicheth C, Godse K, Cho S, Seow CS, Miyachi Y, Khang TH, Ungpakorn R, Galadari H, Shah R, Yang K, Zhou Y, Selmi C, Sawalha AH, Zhang X, Chen Y, Lin CS. Guideline for the diagnosis, treatment and long-term management of cutaneous lupus erythematosus. *J Autoimmun*. 2021;123:102707.
3. Gronhagen CM, Fored CM, Granath F, Nyberg F. Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden. *Br J Dermatol*. 2011;164(6):1335-41.
4. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965-2005: a population-based study. *Arch Dermatol*. 2009;145(3):249-53.
5. Drenkard C, Parker S, Aspey LD, Gordon C, Helmick CG, Bao G, Lim SS. Racial Disparities in the Incidence of Primary Chronic Cutaneous Lupus Erythematosus in the Southeastern US: The Georgia Lupus Registry. *Arthritis Care Res (Hoboken)*. 2019;71(1):95-103.
6. Jarukitsopa S, Hoganson DD, Crowson CS, Sokumbi O, Davis MD, Michet CJ, Jr., Matteson EL, Maradit Kremers H, Chowdhary VR. Epidemiology of systemic lupus erythematosus and cutaneous lupus erythematosus in a predominantly white population in the United States. *Arthritis Care Res (Hoboken)*. 2015;67(6):817-28.
7. Kuhn A, Ruzicka T. Classification of Cutaneous Lupus Erythematosus. In: Kuhn A, Lehmann P, Ruzicka T, editors. *Cutaneous Lupus Erythematosus*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2005. p. 53-7.
8. Kuhn A, Landmann A. The classification and diagnosis of cutaneous lupus erythematosus. *J Autoimmun*. 2014;48-49:14-9.
9. Kuhn A, Wenzel J, Bijl M. Lupus erythematosus revisited. *Semin Immunopathol*. 2016;38(1):97-112.

10. Sontheimer RD. Subacute cutaneous lupus erythematosus: 25-year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological, and genetic findings. *Autoimmun Rev.* 2005;4(5):253-63.
11. Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S, Kantor J, Kim E, Militello G, McGinnis K, Richardson S, Treat J, Vittorio C, Van Voorhees A, Werth VP. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol.* 2005;125(5):889-94.
12. Chakka S, Krain RL, Concha JSS, 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(5):431.
13. Klein R, Moghadam-Kia S, Taylor L, Coley C, Okawa J, LoMonico J, Chren MM, Werth VP. Quality of life in cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2011;64(5):849-58.
14. Cepica TB, Lu G, Xie L, Faden DF, Stone CJ, Chambers S, Feng R, Werth VP, Chong BF. Cutaneous lupus damage is negatively predicted by disease subtype and systemic involvement and is associated with worse outcomes in body image: A prospective cohort study. *J Am Acad Dermatol.* 2026;94(5):1532-4.
15. Chang AY, Ghazi E, Okawa J, Werth VP. Quality of life differences between responders and nonresponders in the treatment of cutaneous lupus erythematosus. *JAMA Dermatol.* 2013;149(1):104-6.
16. Fetter T, Wenzel J. Cutaneous lupus erythematosus: The impact of self-amplifying innate and adaptive immune responses and future prospects of targeted therapies. *Exp Dermatol.* 2020;29(11):1123-32.
17. Kunz M, König IR, Schillert A, Kruppa J, Ziegler A, Grallert H, Müller-Nurasyid M, Lieb W, Franke A, Ranki A, Panelius J, Koskenmies S, Hasan T, Kere J, Rönn AC, Simon JC, Schmidt E, Wenzel J, Tuting T, Landsberg J, Zeller T, Blankenberg S, Glaser R, Patsinakidis N, Kuhn A, Ibrahim SM. Genome-wide association study identifies new susceptibility loci for cutaneous lupus erythematosus. *Exp Dermatol.* 2015;24(7):510-5.

18. Werth VP, Zhang W, Dortzbach K, Sullivan K. Association of a promoter polymorphism of tumor necrosis factor-alpha with subacute cutaneous lupus erythematosus and distinct photoregulation of transcription. *J Invest Dermatol.* 2000;115(4):726-30.
19. Jarvinen TM, Hellquist A, Koskenmies S, Einarsdottir E, Koskinen LL, Jeskanen L, Berglind L, Panelius J, Hasan T, Ranki A, Kere J, Saarialho-Kere U. Tyrosine kinase 2 and interferon regulatory factor 5 polymorphisms are associated with discoid and subacute cutaneous lupus erythematosus. *Exp Dermatol.* 2010;19(2):123-31.
20. Jarvinen TM, Hellquist A, Koskenmies S, Einarsdottir E, Panelius J, Hasan T, Julkunen H, Padyukov L, Kvarnstrom M, Wahren-Herlenius M, Nyberg F, D'Amato M, Kere J, Saarialho-Kere U. Polymorphisms of the ITGAM gene confer higher risk of discoid cutaneous than of systemic lupus erythematosus. *PLoS One.* 2010;5(12):e14212.
21. Hersh AO, Arkin LM, Prahalad S. Immunogenetics of cutaneous lupus erythematosus. *Curr Opin Pediatr.* 2016;28(4):470-5.
22. Peschke K, Friebe F, Zimmermann N, Wahlicht T, Schumann T, Achleitner M, Berndt N, Luksch H, Behrendt R, Lee-Kirsch MA, Roers A, Gunther C. Deregulated type I IFN response in TREX1-associated familial chilblain lupus. *J Invest Dermatol.* 2014;134(5):1456-9.
23. Renauer P, Coit P, Jeffries MA, Merrill JT, McCune WJ, Maksimowicz-McKinnon K, Sawalha AH. DNA methylation patterns in naive CD4+ T cells identify epigenetic susceptibility loci for malar rash and discoid rash in systemic lupus erythematosus. *Lupus Sci Med.* 2015;2(1):e000101.
24. Biazar C, Sigges J, Patsinakidis N, Ruland V, Amler S, Bonsmann G, Kuhn A, co-authors E. Cutaneous lupus erythematosus: first multicenter database analysis of 1002 patients from the European Society of Cutaneous Lupus Erythematosus (EUSCLE). *Autoimmun Rev.* 2013;12(3):444-54.
25. Foering K, Chang AY, Piette EW, Cucchiara A, Okawa J, Werth VP. Characterization of clinical photosensitivity in cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2013;69(2):205-13.

26. Lin JH, Dutz JP, Sontheimer RD, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Clin Rev Allergy Immunol*. 2007;33(1-2):85-106.
27. Katayama S, Panelius J, Koskenmies S, Skoog T, Mahonen K, Kisand K, Bondet V, Duffy D, Krjutskov K, Kere J, Ranki A. Delineating the Healthy Human Skin UV Response and Early Induction of Interferon Pathway in Cutaneous Lupus Erythematosus. *J Invest Dermatol*. 2019;139(9):2058-61 e4.
28. Piette EW, Foering KP, Chang AY, Okawa J, Ten Have TR, Feng R, Werth VP. Impact of smoking in cutaneous lupus erythematosus. *Arch Dermatol*. 2012;148(3):317-22.
29. Rahman P, Gladman DD, Urowitz MB. Smoking interferes with efficacy of antimalarial therapy in cutaneous lupus. *J Rheumatol*. 1998;25(9):1716-9.
30. White PC, Hirschfeld J, Milward MR, Cooper PR, Wright HJ, Matthews JB, Chapple ILC. Cigarette smoke modifies neutrophil chemotaxis, neutrophil extracellular trap formation and inflammatory response-related gene expression. *J Periodontal Res*. 2018;53(4):525-35.
31. Vaglio A, Grayson PC, Fenaroli P, Gianfreda D, Boccaletti V, Ghiggeri GM, Moroni G. Drug-induced lupus: Traditional and new concepts. *Autoimmun Rev*. 2018;17(9):912-8.
32. Lowe GC, Henderson CL, Grau RH, Hansen CB, Sontheimer RD. A systematic review of drug-induced subacute cutaneous lupus erythematosus. *Br J Dermatol*. 2011;164(3):465-72.
33. Bolton C, Chen Y, Hawthorne R, Schepel IRM, Harriss E, Hofmann SC, Ellis S, Clarke A, Wace H, Martin B, Smith J. Systematic Review: Monoclonal Antibody-Induced Subacute Cutaneous Lupus Erythematosus. *Drugs R D*. 2020;20(4):319-30.
34. Kuhn A, Herrmann M, Kleber S, Beckmann-Welle M, Fehsel K, Martin-Villalba A, Lehmann P, Ruzicka T, Krammer PH, Kolb-Bachofen V. Accumulation of apoptotic cells in the epidermis of patients with cutaneous lupus erythematosus after ultraviolet irradiation. *Arthritis Rheum*. 2006;54(3):939-50.
35. Biermann MH, Veissi S, Maueroeder C, Chaurio R, Berens C, Herrmann M, Munoz LE. The role of dead cell clearance in the etiology and pathogenesis of systemic

lupus erythematosus: dendritic cells as potential targets. *Expert Rev Clin Immunol*. 2014;10(9):1151-64.

36. Kuhn A, Wenzel J, Weyd H. Photosensitivity, apoptosis, and cytokines in the pathogenesis of lupus erythematosus: a critical review. *Clin Rev Allergy Immunol*. 2014;47(2):148-62.

37. Scholtissek B, Zahn S, Maier J, Klaeschen S, Braegelmann C, Hoelzel M, Bieber T, Barchet W, Wenzel J. Immunostimulatory Endogenous Nucleic Acids Drive the Lesional Inflammation in Cutaneous Lupus Erythematosus. *J Invest Dermatol*. 2017;137(7):1484-92.

38. Guiducci C, Tripodo C, Gong M, Sangaletti S, Colombo MP, Coffman RL, Barrat FJ. Autoimmune skin inflammation is dependent on plasmacytoid dendritic cell activation by nucleic acids via TLR7 and TLR9. *J Exp Med*. 2010;207(13):2931-42.

39. Kalali BN, Kollisch G, Mages J, Muller T, Bauer S, Wagner H, Ring J, Lang R, Mempel M, Ollert M. Double-stranded RNA induces an antiviral defense status in epidermal keratinocytes through TLR3-, PKR-, and MDA5/RIG-I-mediated differential signaling. *J Immunol*. 2008;181(4):2694-704.

40. Li C, Liu W, Wang F, Hayashi T, Mizuno K, Hattori S, Fujisaki H, Ikejima T. DNA damage-triggered activation of cGAS-STING pathway induces apoptosis in human keratinocyte HaCaT cells. *Mol Immunol*. 2021;131:180-90.

41. Kopfnagel V, Wittmann M, Werfel T. Human keratinocytes express AIM2 and respond to dsDNA with IL-1beta secretion. *Exp Dermatol*. 2011;20(12):1027-9.

42. Sarkar MK, Hile GA, Tsoi LC, Xing X, Liu J, Liang Y, Berthier CC, Swindell WR, Patrick MT, Shao S, Tsou PS, Uppala R, Beamer MA, Srivastava A, Bielas SL, Harms PW, Getsios S, Elder JT, Voorhees JJ, Gudjonsson JE, Kahlenberg JM. Photosensitivity and type I IFN responses in cutaneous lupus are driven by epidermal-derived interferon kappa. *Ann Rheum Dis*. 2018;77(11):1653-64.

43. Zahn S, Rehkemper C, Kummerer BM, Ferring-Schmidt S, Bieber T, Tuting T, Wenzel J. Evidence for a pathophysiological role of keratinocyte-derived type III interferon (IFNlambda) in cutaneous lupus erythematosus. *J Invest Dermatol*. 2011;131(1):133-40.

44. Lazear HM, Schoggins JW, Diamond MS. Shared and Distinct Functions of Type I and Type III Interferons. *Immunity*. 2019;50(4):907-23.

45. Barrat FJ, Crow MK, Ivashkiv LB. Interferon target-gene expression and epigenomic signatures in health and disease. *Nat Immunol.* 2019;20(12):1574-83.
46. Lambers WM, Diercks GFH, Homan FM, Doornbos-van Meer B, Bootsma H, Westra J, de Leeuw K. Myxovirus Resistance Protein A Is a Useful Additional Histological Marker in Suspected Cutaneous Lupus Erythematosus. *Acta Derm Venereol.* 2020;100(15):adv00234.
47. Fah J, Pavlovic J, Burg G. Expression of MxA protein in inflammatory dermatoses. *J Histochem Cytochem.* 1995;43(1):47-52.
48. Meller S, Winterberg F, Gilliet M, Muller A, Lauceviciute I, Rieker J, Neumann NJ, Kubitza R, Gombert M, Bunemann E, Wiesner U, Franken-Kunkel P, Kanzler H, Dieu-Nosjean MC, Amara A, Ruzicka T, Lehmann P, Zlotnik A, Homey B. Ultraviolet radiation-induced injury, chemokines, and leukocyte recruitment: An amplification cycle triggering cutaneous lupus erythematosus. *Arthritis Rheum.* 2005;52(5):1504-16.
49. Wenzel J, Worenkamper E, Freutel S, Henze S, Haller O, Bieber T, Tuting T. Enhanced type I interferon signalling promotes Th1-biased inflammation in cutaneous lupus erythematosus. *J Pathol.* 2005;205(4):435-42.
50. Braegelmann C, Fetter T, Niebel D, Dietz L, Bieber T, Wenzel J. Immunostimulatory Endogenous Nucleic Acids Perpetuate Interface Dermatitis-Translation of Pathogenic Fundamentals Into an In Vitro Model. *Front Immunol.* 2020;11:622511.
51. Grassi M, Capello F, Bertolino L, Seia Z, Pippione M. Identification of granzyme B-expressing CD-8-positive T cells in lymphocytic inflammatory infiltrate in cutaneous lupus erythematosus and in dermatomyositis. *Clin Exp Dermatol.* 2009;34(8):910-4.
52. Wenzel J, Uerlich M, Worenkamper E, Freutel S, Bieber T, Tuting 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(5):1011-5.
53. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat Immunol.* 2010;11(10):889-96.
54. Achtman JC, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Arthritis Res Ther.* 2015;17(1):182.

55. Lauffer F, Jargosch M, Krause L, Garzorz-Stark N, Franz R, Roenneberg S, Bohner A, Mueller NS, Theis FJ, Schmidt-Weber CB, Biedermann T, Eyerich S, Eyerich K. Type I Immune Response Induces Keratinocyte Necroptosis and Is Associated with Interface Dermatitis. *J Invest Dermatol.* 2018;138(8):1785-94.
56. Sontheimer RD. Lichenoid tissue reaction/interface dermatitis: clinical and histological perspectives. *J Invest Dermatol.* 2009;129(5):1088-99.
57. Fetter T, Niebel D, Braegelman C, Wenzel J. Skin-Associated B Cells in the Pathogenesis of Cutaneous Autoimmune Diseases-Implications for Therapeutic Approaches. *Cells.* 2020;9(12).
58. Debes GF, McGettigan SE. Skin-Associated B Cells in Health and Inflammation. *J Immunol.* 2019;202(6):1659-66.
59. Abernathy-Close L, Lazar S, Stannard J, Tsoi LC, Eddy S, Rizvi SM, Yee CM, Myers EM, Namas R, Lowe L, Reed TJ, Wen F, Gudjonsson JE, Kahlenberg JM, Berthier CC. B Cell Signatures Distinguish Cutaneous Lupus Erythematosus Subtypes and the Presence of Systemic Disease Activity. *Front Immunol.* 2021;12:775353.
60. de Vos L, Guel T, Niebel D, Bald S, Ter Steege A, Bieber T, Wenzel J. Characterization of B cells in lupus erythematosus skin biopsies in the context of different immune cell infiltration patterns. *Front Med (Lausanne).* 2022;9:1037408.
61. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. *Nat Rev Rheumatol.* 2019;15(9):519-32.
62. Zheng M, Hu Z, Mei X, Ouyang L, Song Y, Zhou W, Kong Y, Wu R, Rao S, Long H, Shi W, Jing H, Lu S, Wu H, Jia S, Lu Q, Zhao M. Single-cell sequencing shows cellular heterogeneity of cutaneous lesions in lupus erythematosus. *Nat Commun.* 2022;13(1):7489.
63. Wang Y, Afshari K, Haddadi NS, Lopes CS, Eng CL, Whiteman LM, Martinez N, Kyawe PP, Anufrieva KS, Wei K, Frieda K, Rosenbach M, Vleugels RA, Gallucci S, Harris JE, Rashighi M, Garber M. A spatially coordinated keratinocyte-fibroblast circuit recruits MMP9(+) myeloid cells to drive type I interferon-driven inflammation in photosensitive autoimmunity. *Nat Immunol.* 2026.
64. Hu T, Liu CH, Lei M, Zeng Q, Li L, Tang H, Zhang N. Metabolic regulation of the immune system in health and diseases: mechanisms and interventions. *Signal Transduct Target Ther.* 2024;9(1):268.

65. O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat Rev Immunol*. 2016;16(9):553-65.
66. Thorens B, Mueckler M. Glucose transporters in the 21st Century. *Am J Physiol Endocrinol Metab*. 2010;298(2):E141-5.
67. Cura AJ, Carruthers A. Role of monosaccharide transport proteins in carbohydrate assimilation, distribution, metabolism, and homeostasis. *Compr Physiol*. 2012;2(2):863-914.
68. Shi LZ, Wang R, Huang G, Vogel P, Neale G, Green DR, Chi H. HIF1 α -dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. *J Exp Med*. 2011;208(7):1367-76.
69. Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, Sullivan SA, Nichols AG, Rathmell JC. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4⁺ T cell subsets. *J Immunol*. 2011;186(6):3299-303.
70. Frauwirth KA, Riley JL, Harris MH, Parry RV, Rathmell JC, Plas DR, Elstrom RL, June CH, Thompson CB. The CD28 signaling pathway regulates glucose metabolism. *Immunity*. 2002;16(6):769-77.
71. Macintyre AN, Gerriets VA, Nichols AG, Michalek RD, Rudolph MC, Deoliveira D, Anderson SM, Abel ED, Chen BJ, Hale LP, Rathmell JC. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell Metab*. 2014;20(1):61-72.
72. Choi SC, Titov AA, Abboud G, Seay HR, Brusko TM, Roopenian DC, Salek-Ardakani S, Morel L. Inhibition of glucose metabolism selectively targets autoreactive follicular helper T cells. *Nat Commun*. 2018;9(1):4369.
73. Pearce EL, Walsh MC, Cejas PJ, Harms GM, Shen H, Wang LS, Jones RG, Choi Y. Enhancing CD8 T-cell memory by modulating fatty acid metabolism. *Nature*. 2009;460(7251):103-7.
74. Menk AV, Scharping NE, Moreci RS, Zeng X, Guy C, Salvatore S, Bae H, Xie J, Young HA, Wendell SG, Delgoffe GM. Early TCR Signaling Induces Rapid Aerobic Glycolysis Enabling Distinct Acute T Cell Effector Functions. *Cell Rep*. 2018;22(6):1509-21.

75. Doughty CA, Bleiman BF, Wagner DJ, Dufort FJ, Mataraza JM, Roberts MF, Chiles TC. Antigen receptor-mediated changes in glucose metabolism in B lymphocytes: role of phosphatidylinositol 3-kinase signaling in the glycolytic control of growth. *Blood*. 2006;107(11):4458-65.
76. Freemerman AJ, Zhao L, Pingili AK, Teng B, Cozzo AJ, Fuller AM, Johnson AR, Milner JJ, Lim MF, Galanko JA, Beck MA, Bear JE, Rotty JD, Bezavada L, Smallwood HS, Puchowicz MA, Liu J, Locasale JW, Lee DP, Bennett BJ, Abel ED, Rathmell JC, Makowski L. Myeloid Slc2a1-Deficient Murine Model Revealed Macrophage Activation and Metabolic Phenotype Are Fueled by GLUT1. *J Immunol*. 2019;202(4):1265-86.
77. Thwe PM, Pelgrom LR, Cooper R, Beauchamp S, Reisz JA, D'Alessandro A, Everts B, Amiel E. Cell-Intrinsic Glycogen Metabolism Supports Early Glycolytic Reprogramming Required for Dendritic Cell Immune Responses. *Cell Metab*. 2017;26(3):558-67 e5.
78. Krawczyk CM, Holowka T, Sun J, Blagih J, Amiel E, DeBerardinis RJ, Cross JR, Jung E, Thompson CB, Jones RG, Pearce EJ. Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. *Blood*. 2010;115(23):4742-9.
79. Palsson-McDermott EM, Curtis AM, Goel G, Lauterbach MA, Sheedy FJ, Gleeson LE, van den Bosch MW, Quinn SR, Domingo-Fernandez R, Johnston DG, Jiang JK, Israelsen WJ, Keane J, Thomas C, Clish C, Vander Heiden M, Xavier RJ, O'Neill LA. Pyruvate kinase M2 regulates Hif-1alpha activity and IL-1beta induction and is a critical determinant of the warburg effect in LPS-activated macrophages. *Cell Metab*. 2015;21(1):65-80.
80. Carr EL, Kelman A, Wu GS, Gopaul R, Senkevitch E, Aghvanyan A, Turay AM, Frauwirth KA. Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation. *J Immunol*. 2010;185(2):1037-44.
81. Angela M, Endo Y, Asou HK, Yamamoto T, Tumes DJ, Tokuyama H, Yokote K, Nakayama T. Fatty acid metabolic reprogramming via mTOR-mediated inductions of PPARgamma directs early activation of T cells. *Nat Commun*. 2016;7:13683.
82. Lee J, Walsh MC, Hoehn KL, James DE, Wherry EJ, Choi Y. Regulator of fatty acid metabolism, acetyl coenzyme a carboxylase 1, controls T cell immunity. *J Immunol*. 2014;192(7):3190-9.

83. Dufort FJ, Gumina MR, Ta NL, Tao Y, Heyse SA, Scott DA, Richardson AD, Seyfried TN, Chiles TC. Glucose-dependent de novo lipogenesis in B lymphocytes: a requirement for atp-citrate lyase in lipopolysaccharide-induced differentiation. *J Biol Chem.* 2014;289(10):7011-24.
84. Haschemi A, Kosma P, Gille L, Evans CR, Burant CF, Starkl P, Knapp B, Haas R, Schmid JA, Jandl C, Amir S, Lubec G, Park J, Esterbauer H, Bilban M, Brizuela L, Pospisilik JA, Otterbein LE, Wagner O. The sedoheptulose kinase CARKL directs macrophage polarization through control of glucose metabolism. *Cell Metab.* 2012;15(6):813-26.
85. Rath M, Muller I, Kropf P, Closs EI, Munder M. Metabolism via Arginase or Nitric Oxide Synthase: Two Competing Arginine Pathways in Macrophages. *Front Immunol.* 2014;5:532.
86. Ecker J, Liebisch G, Englmaier M, Grandl M, Robenek H, Schmitz G. Induction of fatty acid synthesis is a key requirement for phagocytic differentiation of human monocytes. *Proc Natl Acad Sci U S A.* 2010;107(17):7817-22.
87. Everts B, Amiel E, Huang SC, Smith AM, Chang CH, Lam WY, Redmann V, Freitas TC, Blagih J, van der Windt GJ, Artyomov MN, Jones RG, Pearce EL, Pearce EJ. TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKvarepsilon supports the anabolic demands of dendritic cell activation. *Nat Immunol.* 2014;15(4):323-32.
88. Beier UH, Angelin A, Akimova T, Wang L, Liu Y, Xiao H, Koike MA, Hancock SA, Bhatti TR, Han R, Jiao J, Veasey SC, Sims CA, Baur JA, Wallace DC, Hancock WW. Essential role of mitochondrial energy metabolism in Foxp3(+) T-regulatory cell function and allograft survival. *FASEB J.* 2015;29(6):2315-26.
89. van der Windt GJ, Pearce EL. Metabolic switching and fuel choice during T-cell differentiation and memory development. *Immunol Rev.* 2012;249(1):27-42.
90. Jha AK, Huang SC, Sergushichev A, Lampropoulou V, Ivanova Y, Loginicheva E, Chmielewski K, Stewart KM, Ashall J, Everts B, Pearce EJ, Driggers EM, Artyomov MN. Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. *Immunity.* 2015;42(3):419-30.

91. Vats D, Mukundan L, Odegaard JI, Zhang L, Smith KL, Morel CR, Wagner RA, Greaves DR, Murray PJ, Chawla A. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. *Cell Metab.* 2006;4(1):13-24.
92. Zhang Z, Zi Z, Lee EE, Zhao J, Contreras DC, South AP, Abel ED, Chong BF, Vandergriff T, Hosler GA, Scherer PE, Mettlen M, Rathmell JC, DeBerardinis RJ, Wang RC. Differential glucose requirement in skin homeostasis and injury identifies a therapeutic target for psoriasis. *Nat Med.* 2018;24(5):617-27.
93. Elson DA, Ryan HE, Snow JW, Johnson R, Arbeit JM. Coordinate up-regulation of hypoxia inducible factor (HIF)-1alpha and HIF-1 target genes during multi-stage epidermal carcinogenesis and wound healing. *Cancer Res.* 2000;60(21):6189-95.
94. Tochio T, Tanaka H, Nakata S. Glucose transporter member 1 is involved in UVB-induced epidermal hyperplasia by enhancing proliferation in epidermal keratinocytes. *Int J Dermatol.* 2013;52(3):300-8.
95. Tao J, Yang J, Wang L, Li Y, Liu YQ, Dong J, Li L, Wen X, Shen GX, Tu YT. Expression of GLUT-1 in psoriasis and the relationship between GLUT-1 upregulation induced by hypoxia and proliferation of keratinocyte growth. *J Dermatol Sci.* 2008;51(3):203-7.
96. Abdou AG, Maraee AH, Eltahmoudy M, El-Aziz RA. Immunohistochemical expression of GLUT-1 and Ki-67 in chronic plaque psoriasis. *Am J Dermatopathol.* 2013;35(7):731-7.
97. Hodeib AA, Neinaa YME, Zakaria SS, Alshenawy HA. Glucose transporter-1 (GLUT-1) expression in psoriasis: correlation with disease severity. *Int J Dermatol.* 2018;57(8):943-51.
98. Ali M, Kemal D, Salih Levent Ç I, Hatice K, Olgun K. The Use of GLUT-1, Ki-67 and PCNA Antibodies as Immunohistochemical Markers in Histopathological Differential Diagnosis of Psoriasis and Chronic Spongiotic Dermatitis. *Dokuz Eylül Üniversitesi Tıp Fakültesi Dergisi.* 2021;35(2):169-78.
99. Emam AAM, Eyada MMK, Gomaa AHA, Abd El-Fadeal NM, Ibrahim GH, El-Kherbetawy MK, Tawfik NZ. Glucose transporter-1 (GLUT-1) upregulation in vitiligo: A possible link to skin depigmentation. *Gene.* 2025;950:149383.

100. Wang XX, Sun HY, Yang QZ, Guo B, Sai Y, Zhang J. Hypoxia-inducible factor-1alpha and glucose transporter 1 in the malignant transformation of oral lichen planus. *Int J Clin Exp Pathol*. 2017;10(8):8369-76.
101. Choi SY, Heo MJ, Lee C, Choi YM, An IS, Bae S, An S, Jung JH. 2-deoxy-d-glucose Ameliorates Animal Models of Dermatitis. *Biomedicines*. 2020;8(2).
102. Su H, Zhang L, Zhang Q, Liu L, Zhai L, Chen X, Yang C, An N, Liu HF. Glucose metabolic reprogramming in systemic lupus erythematosus and lupus nephritis: theoretical foundations and therapeutic implications. *Front Immunol*. 2026;17:1799232.
103. Yin Y, Choi SC, Xu Z, Perry DJ, Seay H, Croker BP, Sobel ES, Brusko TM, Morel L. Normalization of CD4+ T cell metabolism reverses lupus. *Sci Transl Med*. 2015;7(274):274ra18.
104. Li W, Qu G, Choi SC, Cornaby C, Titov A, Kanda N, Teng X, Wang H, Morel L. Targeting T Cell Activation and Lupus Autoimmune Phenotypes by Inhibiting Glucose Transporters. *Front Immunol*. 2019;10:833.
105. Worm M, Zidane M, Eisert L, Fischer-Betz R, Foeldvari I, Gunther C, Iking-Konert C, Kreuter A, Muller-Ladner U, Nast A, Ochsendorf F, Schneider M, Sticherling M, Tenbrock K, Wenzel J, Kuhn A. S2k guideline: Diagnosis and management of cutaneous lupus erythematosus - Part 2: Therapy, risk factors and other special topics. *J Dtsch Dermatol Ges*. 2021;19(9):1371-95.
106. O'Kane D, McCourt C, Meggitt S, D'Cruz DP, Orteu CH, Benton E, Wahie S, Utton S, Hashme M, Mohd Mustapa MF, Exton LS, British Association of Dermatologists' Clinical Standards U. British Association of Dermatologists guidelines for the management of people with cutaneous lupus erythematosus 2021. *Br J Dermatol*. 2021;185(6):1112-23.
107. Fanouriakis A, Kostopoulou M, Andersen J, Aringer M, Arnaud L, Bae SC, Boletis J, Bruce IN, Cervera R, Doria A, Dorner T, Furie RA, Gladman DD, Houssiau FA, Ines LS, Jayne D, Kouloumas M, Kovacs L, Mok CC, Morand EF, Moroni G, Mosca M, Mucke J, Mukhtyar CB, Nagy G, Navarra S, Parodis I, Pego-Reigosa JM, Petri M, Pons-Estel BA, Schneider M, Smolen JS, Svenungsson E, Tanaka Y, Tektonidou MG, Teng YO, Tincani A, Vital EM, van Vollenhoven RF, Wincup C, Bertsias G, Boumpas DT. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis*. 2024;83(1):15-29.

108. Sammaritano LR, Askanase A, Bermas BL, Dall'Era M, Duarte-Garcia A, Hiraki LT, Son MBF, Werth VP, Aranow C, Barnado A, Broder A, Brunner HI, Chong BF, Chowdhary VR, Hersh AO, Izmirly PM, Jules M, Kalunian K, Kamen D, Rubinstein TB, Smith BJ, Smith NM, Thomas A, Timlin H, Wallace DJ, Azzam M, Bartels CM, Cunha JS, DeQuattro K, Fava A, Figueroa-Parra G, Garg S, Gomes LLA, Cuellar-Gutierrez MC, Iyer P, Johannemann AS, Jorge A, Kasturi S, Kawtharany H, Khawandi J, Legge A, Liang KP, Lockwood MM, Sanchez-Rodriguez A, Turgunbaev M, Williams JN, Turner AS, Mustafa RA. 2025 American College of Rheumatology (ACR) Guideline for the Treatment of Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)*. 2025.
109. Amoura Z, Bader-Meunier B, Antignac M, Bardin N, Belizna C, Belot A, Bonnotte B, Bouaziz JD, Chasset F, Chiche L, Cohen F, Costedoat-Chalumeau N, Daugas E, Devilliers H, Diot E, Elefant E, Faguer S, Ferreira N, Hachulla E, Hanslik T, Hie M, Jourde-Chiche N, Le Guern V, Martin T, Mathian A, Michel M, Miyara M, Papo T, Richez C, Scherlinger M, Sibilia J, Uzunhan Y, Wahl D, Wojtasik G, Yelnik C, Collaborators, Collaborators. French protocol for the diagnosis and management of systemic lupus erythematosus. *Rev Med Interne*. 2024;45(9):559-99.
110. Wei E, Lopes Almeida Gomes L, Jun S, Saksena S, Werth VP. Therapeutic Approaches for Cutaneous Lupus Erythematosus: a Changing Landscape of Clinical Trials. *J Inflamm Res*. 2026;19:547944.
111. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S, Investigators CDS. Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2017;69(2):376-86.
112. Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KC, Vital EM, Lawrence Ford T, Gupta R, Hiepe F, Santiago M, Brohawn PZ, Berglind A, Tummala R, investigators T-s. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *Lancet Rheumatol*. 2019;1(4):e208-e19.
113. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, Bae SC, Brohawn PZ, Pineda L, Berglind A, Tummala R, Investigators T-T. Trial of

Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med*. 2020;382(3):211-21.

114. Furie R, Werth VP, Merola JF, Stevenson L, Reynolds TL, Naik H, Wang W, Christmann R, Gardet A, Pellerin A, Hamann S, Auluck P, Barbey C, Gulati P, Rabah D, Franchimont N. Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. *J Clin Invest*. 2019;129(3):1359-71.

115. Werth VP, Furie RA, Romero-Diaz J, Navarra S, Kalunian K, van Vollenhoven RF, Nyberg F, Kaffenberger BH, Sheikh SZ, Radunovic G, Huang X, Clark G, Carroll H, Naik H, Gaudreault F, Meyers A, Barbey C, Musselli C, Franchimont N, Investigators LT. Trial of Anti-BDCA2 Antibody Litifilimab for Cutaneous Lupus Erythematosus. *N Engl J Med*. 2022;387(4):321-31.

116. Furie RA, van Vollenhoven RF, Kalunian K, Navarra S, Romero-Diaz J, Werth VP, Huang X, Clark G, Carroll H, Meyers A, Musselli C, Barbey C, Franchimont N, Investigators LT. Trial of Anti-BDCA2 Antibody Litifilimab for Systemic Lupus Erythematosus. *N Engl J Med*. 2022;387(10):894-904.

117. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, Sanchez-Guerrero J, Schwarting A, Merrill JT, Chatham WW, Stohl W, Ginzler EM, Hough DR, Zhong ZJ, Freimuth W, van Vollenhoven RF, Group B-S. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2011;63(12):3918-30.

118. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, Thomas M, Kim HY, Leon MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA, Group B-S. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9767):721-31.

119. Stohl W, Schwarting A, Okada M, Scheinberg M, Doria A, Hammer AE, Kleoudis C, Groark J, Bass D, Fox NL, Roth D, Gordon D. Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study. *Arthritis Rheumatol*. 2017;69(5):1016-27.

120. Zhang F, Bae SC, Bass D, Chu M, Egginton S, Gordon D, Roth DA, Zheng J, Tanaka Y. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. *Ann Rheum Dis*. 2018;77(3):355-63.
121. Ginzler E, Guedes Barbosa LS, D'Cruz D, Furie R, Maksimowicz-McKinnon K, Oates J, Santiago MB, Saxena A, Sheikh S, Bass DL, Burriss SW, Gilbride JA, Groark JG, Miller M, Pierce A, Roth DA, Ji B. Phase III/IV, Randomized, Fifty-Two-Week Study of the Efficacy and Safety of Belimumab in Patients of Black African Ancestry With Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2022;74(1):112-23.
122. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, Utset TO, Gordon C, Isenberg DA, Hsieh HJ, Zhang D, Brunetta PG. 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(1):222-33.
123. Furie RA, Bruce IN, Dorner T, Leon MG, Leszczynski P, Urowitz M, Haier B, Jimenez T, Brittain C, Liu J, Barbey C, Stach C. Phase 2, randomized, placebo-controlled trial of dapirolizumab pegol in patients with moderate-to-severe active systemic lupus erythematosus. *Rheumatology (Oxford)*. 2021;60(11):5397-407.
124. van Vollenhoven RF, Hahn BH, Tsokos GC, Wagner CL, Lipsky P, Touma Z, Werth VP, Gordon RM, Zhou B, Hsu B, Chevrier M, Triebel M, Jordan JL, Rose S. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet*. 2018;392(10155):1330-9.
125. van Vollenhoven RF, Kalunian KC, Dorner T, Hahn BH, Tanaka Y, Gordon RM, Shu C, Fei K, Gao S, Seridi L, Gallagher P, Lo KH, Berry P, Zuraw QC. 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(11):1556-63.
126. Md Yusof MY, Wittmann M, Fernandez C, Wilson D, Edward S, Abignano G, Alase A, Sharples L, Laws P, Goodfield MJ, Vital EM, Emery P. FRI0328 Targeted therapy using intradermal injection of etanercept for remission induction in discoid

lupus erythematosus (TARGET-DLE): first results from a proof-of-concept phase 2 trial. *Annals of the Rheumatic Diseases*. 2018;77(Suppl 2):700.

127. Szepietowski JC, Nilganuwong S, Wozniacka A, Kuhn A, Nyberg F, van Vollenhoven RF, Bengtsson AA, Reich A, de Vries DE, van Hartingsveldt B, Robinson DW, Jr., Gordon R, Hsu B. Phase I, randomized, double-blind, placebo-controlled, multiple intravenous, dose-ascending study of sirukumab in cutaneous or systemic lupus erythematosus. *Arthritis Rheum*. 2013;65(10):2661-71.

128. Morand E, Pike M, Merrill JT, van Vollenhoven R, Werth VP, Hobar C, Delev N, Shah V, Sharkey B, Wegman T, Catlett I, Banerjee S, Singhal S. Deucravacitinib, a Tyrosine Kinase 2 Inhibitor, in Systemic Lupus Erythematosus: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Rheumatol*. 2023;75(2):242-52.

129. Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, Dorner T, Cardiel MH, Bruce IN, Gomez E, Carmack T, DeLozier AM, Janes JM, Linnik MD, de Bono S, Silk ME, Hoffman RW. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018;392(10143):222-31.

130. Petri M, Bruce IN, Dorner T, Tanaka Y, Morand EF, Kalunian KC, Cardiel MH, Silk ME, Dickson CL, Meszaros G, Zhang L, Jia B, Zhao Y, McVeigh CJ, Mosca M. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *Lancet*. 2023;401(10381):1011-9.

131. Morand EF, Vital EM, Petri M, van Vollenhoven R, Wallace DJ, Mosca M, Furie RA, Silk ME, Dickson CL, Meszaros G, Jia B, Crowe B, de la Torre I, Dorner T. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I). *Lancet*. 2023;401(10381):1001-10.

132. Hasni SA, Gupta S, Davis M, Poncio E, Temesgen-Oyelakin Y, Carlucci PM, Wang X, Naqi M, Playford MP, Goel RR, Li X, Biehl AJ, Ochoa-Navas I, Manna Z, Shi Y, Thomas D, Chen J, Biancotto A, Apps R, Cheung F, Kotliarov Y, Babyak AL, Zhou H, Shi R, Stagliano K, Tsai WL, Vian L, Gazaniga N, Giudice V, Lu S, Brooks SR, MacKay M, Gregersen P, Mehta NN, Remaley AT, Diamond B, O'Shea JJ, Gadina M, Kaplan MJ. Phase 1 double-blind randomized safety trial of the Janus kinase inhibitor tofacitinib in systemic lupus erythematosus. *Nat Commun*. 2021;12(1):3391.

133. Werth VP, Fleischmann R, Robern M, Touma Z, Tiamiyu I, Gurtovaya O, Pechonkina A, Mozaffarian A, Downie B, Matzkies F, Wallace D. Filgotinib or lanraplenib in moderate to severe cutaneous lupus erythematosus: a phase 2, randomized, double-blind, placebo-controlled study. *Rheumatology (Oxford)*. 2022;61(6):2413-23.
134. Hu W, Zhang S, Lian C. Treatment of Discoid Lupus Erythematosus with Upadacitinib: A Case Report. *Clin Cosmet Investig Dermatol*. 2023;16:2793-800.
135. Furie RA, Hough DR, Gaudy A, Ye Y, Korish S, Delev N, Weiswasser M, Zhan X, Schafer PH, Werth VP. Iberdomide in patients with systemic lupus erythematosus: a randomised, double-blind, placebo-controlled, ascending-dose, phase 2a study. *Lupus Sci Med*. 2022;9(1).
136. Merrill JT, Werth VP, Furie R, van Vollenhoven R, Dorner T, Petronijevic M, Velasco J, Majdan M, Irazoque-Palazuelos F, Weiswasser M, Korish S, Ye Y, Gaudy A, Schafer PH, Liu Z, Agafonova N, Delev N. Phase 2 Trial of Iberdomide in Systemic Lupus Erythematosus. *N Engl J Med*. 2022;386(11):1034-45.
137. Morand EF, Dall'Era M, Sanchez-Guerrero J, Pearson DR, Werth VP, Wenzel J, Roy S, Kleinmond C, Guhring H, Sgouroudi E, Klopp-Schulze L, Moreau F, Fernandez-Ruiz R, Furie R. Enpatoran, a Toll-like receptor 7/8 inhibitor, in moderate-to-severe systemic lupus erythematosus: findings from Cohort B of a multicentre, international, double-blind, placebo-controlled dose-finding phase 2 trial. *Lancet*. 2026;407(10541):1809-24.
138. Morand EF, Werth VP, Wenzel J, Furie R, Dall'Era M, Sanchez-Guerrero J, Roy S, Goodson SG, Moreau F, Guhring H, Sgouroudi E, Klopp-Schulze L, Pearson DR. Efficacy and safety of enpatoran, a Toll-like receptor 7/8 inhibitor, in patients with skin manifestations of cutaneous lupus erythematosus or systemic lupus erythematosus: findings from Cohort A of a multicentre, international, double-blind, placebo-controlled, dose-finding phase 2 trial. *Lancet Rheumatol*. 2026.
139. Barretina J, Caponigro G, Stransky N, Venkatesan K, Margolin AA, Kim S, Wilson CJ, Lehar J, Kryukov GV, Sonkin D, Reddy A, Liu M, Murray L, Berger MF, Monahan JE, Morais P, Meltzer J, Korejwa A, Jane-Valbuena J, Mapa FA, Thibault J, Bric-Furlong E, Raman P, Shipway A, Engels IH, Cheng J, Yu GK, Yu J, Aspesi P, Jr., de Silva M, Jagtap K, Jones MD, Wang L, Hatton C, Palescandolo E, Gupta S, Mahan

- S, Sougnez C, Onofrio RC, Liefeld T, MacConaill L, Winckler W, Reich M, Li N, Mesirov JP, Gabriel SB, Getz G, Ardlie K, Chan V, Myer VE, Weber BL, Porter J, Warmuth M, Finan P, Harris JL, Meyerson M, Golub TR, Morrissey MP, Sellers WR, Schlegel R, Garraway LA. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature*. 2012;483(7391):603-7.
140. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov*. 2012;2(5):401-4.
141. de Bruijn I, Kundra R, Mastrogiacomio B, Tran TN, Sikina L, Mazor T, Li X, Ochoa A, Zhao G, Lai B, Abeshouse A, Baiceanu D, Ciftci E, Dogrusoz U, Dufilie A, Erkoc Z, Garcia Lara E, Fu Z, Gross B, Haynes C, Heath A, Higgins D, Jagannathan P, Kalletla K, Kumari P, Lindsay J, Lisman A, Leenknecht B, Lukasse P, Madela D, Madupuri R, van Nierop P, Plantalech O, Quach J, Resnick AC, Rodenburg SYA, Satravada BA, Schaeffer F, Sheridan R, Singh J, Sirohi R, Sumer SO, van Hagen S, Wang A, Wilson M, Zhang H, Zhu K, Rusk N, Brown S, Lavery JA, Panageas KS, Rudolph JE, LeNoue-Newton ML, Warner JL, Guo X, Hunter-Zinck H, Yu TV, Pilai S, Nichols C, Gardos SM, Philip J, Aacr Project Genie Bpc Core Team APGC, Kehl KL, Riely GJ, Schrag D, Lee J, Fiandalo MV, Sweeney SM, Pugh TJ, Sander C, Cerami E, Gao J, Schultz N. Analysis and Visualization of Longitudinal Genomic and Clinical Data from the AACR Project GENIE Biopharma Collaborative in cBioPortal. *Cancer Res*. 2023;83(23):3861-7.
142. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, Cerami E, Sander C, Schultz N. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal*. 2013;6(269):p11.
143. Mande P, Zirak B, Ko WC, Taravati K, Bride KL, Brodeur TY, Deng A, Dresser K, Jiang Z, Ettinger R, Fitzgerald KA, Rosenblum MD, Harris JE, Marshak-Rothstein A. Fas ligand promotes an inducible TLR-dependent model of cutaneous lupus-like inflammation. *J Clin Invest*. 2018;128(7):2966-78.
144. Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, Marshall KA, Phillippy KH, Sherman PM, Holko M, Yefanov A, Lee H, Zhang N,

- Robertson CL, Serova N, Davis S, Soboleva A. NCBI GEO: archive for functional genomics data sets--update. *Nucleic Acids Res.* 2013;41(Database issue):D991-5.
145. Lachmann A, Torre D, Keenan AB, Jagodnik KM, Lee HJ, Wang L, Silverstein MC, Ma'ayan A. Massive mining of publicly available RNA-seq data from human and mouse. *Nat Commun.* 2018;9(1):1366.
146. Bokor LA, Martyin K, Krebs M, Galajda NA, Meznerics FA, Szabo B, Hegyi P, Lorincz K, Kiss N, Banvolgyi A, Hidvegi B. Deucravacitinib shows superior efficacy and safety in cutaneous lupus erythematosus compared to various biologics and small molecules - A systematic review and meta-analysis. *Autoimmun Rev.* 2025;24(3):103723.
147. The EndNote Team. EndNote. EndNote 20.6 ed. Philadelphia, PA: Clarivate; 2013.
148. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5(1):210.
149. Rohatgi A. WebPlotDigitizer. WebPlotDigitizer; 2020, <https://automeris.io>.
150. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
151. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg.* 2003;73(9):712-6.
152. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, Stephenson M, Aromataris E. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBIC Evid Synth.* 2020;18(10):2127-33.
153. Moola S, Tufanaru C, Aromataris E, Sears K, Sfetc R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P-F. Chapter 7: Systematic Reviews of Etiology and Risk. 2020.

154. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, Salanti G. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med.* 2020;17(4):e1003082.
155. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Syst Rev.* 2020;16(1):e1080.
156. Salanti G, Kavvoura FK, Ioannidis JP. Exploring the geometry of treatment networks. *Ann Intern Med.* 2008;148(7):544-53.
157. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. *Doing Meta-Analysis With R: A Hands-On Guide.* 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021 2021.
158. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, Kuss O, Higgins JP, Langan D, Salanti G. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods.* 2016;7(1):55-79.
159. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rucker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods.* 2019;10(3):476-83.
160. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med.* 2010;29(29):3046-67.
161. Clopper CJ, Pearson ES. THE USE OF CONFIDENCE OR FIDUCIAL LIMITS ILLUSTRATED IN THE CASE OF THE BINOMIAL. *Biometrika.* 1934;26(4):404-13.
162. Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, Schwarzer G. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. *Journal of Statistical Software.* 2023;106(2):1 - 40.
163. Beliveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. *BMC Med Res Methodol.* 2019;19(1):196.
164. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, Smolen JS, Wofsy D, Boumpas DT, Kamen DL, Jayne D, Cervera R, Costedoat-Chalumeau N, Diamond B, Gladman DD, Hahn B, Hiepe F, Jacobsen S,

- Khanna D, Lerstrom K, Massarotti E, McCune J, Ruiz-Irastorza G, Sanchez-Guerrero J, Schneider M, Urowitz M, Bertsias G, Hoyer BF, Leuchten N, Tani C, Tedeschi SK, Touma Z, Schmajuk G, Anic B, Assan F, Chan TM, Clarke AE, Crow MK, Czirjak L, Doria A, Graninger W, Halda-Kiss B, Hasni S, Izmirly PM, Jung M, Kumanovics G, Mariette X, Padjen I, Pego-Reigosa JM, Romero-Diaz J, Rua-Figueroa Fernandez I, Seror R, Stummvoll GH, Tanaka Y, Tektonidou MG, Vasconcelos C, Vital EM, Wallace DJ, Yavuz S, Meroni PL, Fritzler MJ, Naden R, Dorner T, Johnson SR. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2019;71(9):1400-12.
165. Li R, Huang X, Yang L, Liang X, Huang W, Lai KP, Zhou L. Integrated Analysis Reveals the Targets and Mechanisms in Immunosuppressive Effect of Mesalazine on Ulcerative Colitis. *Front Nutr*. 2022;9:867692.
166. Dong H, Liu F, Ma F, Xu L, Pang L, Li X, Liu B, Wang L. Montelukast inhibits inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. *Int Immunopharmacol*. 2018;61:215-21.
167. Palsson-McDermott EM, O'Neill LAJ. Targeting immunometabolism as an anti-inflammatory strategy. *Cell Res*. 2020;30(4):300-14.
168. Blanco-Colio LM, Tunon J, Martin-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. *Kidney Int*. 2003;63(1):12-23.
169. 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(4):425-7.
170. Bonnardeaux E, Dutz JP. Oral tofacitinib citrate for recalcitrant cutaneous lupus. *JAAD Case Rep*. 2022;20:61-4.
171. Bosch-Amate X, Morgado-Carrasco D, Combalia A, Giavedoni P, Espinosa G, Mascaro JM, Jr. Successful treatment of two cases of refractory cutaneous lupus erythematosus with belimumab. *Indian J Dermatol Venereol Leprol*. 2021;87(3):421-4.
172. Breillat P, Mathian A, Rozenberg F, Dutheil A, Barbaud A, Amoura Z, Chasset F. Is there an increased risk of severe COVID-19 among patients with systemic lupus erythematosus treated with anifrolumab? *Lupus*. 2023;32(3):453-5.
173. 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(2):210-8.

174. Chasset F, Jaume L, Mathian A, Abisror N, Dutheil A, Barbaud A, Kottler D, Girard C, Jousse-Joulin S, Tauber M, Livideanu CB, Avettand-Fenoel V, Lhote R, Pha M, Amoura Z, group Es. Rapid efficacy of anifrolumab in refractory cutaneous lupus erythematosus. *J Am Acad Dermatol*. 2023;89(1):171-3.

175. Dahl C, Johansen C, Kragballe K, Olesen AB. Ustekinumab in the treatment of refractory chronic cutaneous lupus erythematosus: a case report. *Acta Derm Venereol*. 2013;93(3):368-9.

176. Dresco F, Puzenat E, Delobbeau M, Salard D, Lihoreau T, Pelletier F, Aubin F. [Resistant and progressive cutaneous lupus erythematosus treated with belimumab: A retrospective monocentric study]. *Rev Med Interne*. 2020;41(3):152-9.

177. Fushida N, Horii M, Oishi K, Matsushita T. Anifrolumab for systemic lupus erythematosus: A clinical study of Japanese patients in Kanazawa University Hospital. *J Dermatol*. 2024;51(4):607-11.

178. Gatto M, Saccon F, Zen M, Regola F, Fredi M, Andreoli L, Tincani A, Urban ML, Emmi G, Ceccarelli F, Conti F, Bortoluzzi A, Govoni M, Tani C, Mosca M, Ubiali T, Gerosa M, Bozzolo E, Canti V, Cardinaletti P, Gabrielli A, Tanti G, Gremese E, De Marchi G, De Vita S, Fasano S, Ciccia F, Pazzola G, Salvarani C, Negrini S, Puppo F, Di Matteo A, De Angelis R, Orsolini G, Rossini M, Faggioli P, Laria A, Piga M, Mathieu A, Scarpato S, Rossi FW, de Paulis A, Brunetta E, Ceribelli A, Selmi C, Prete M, Racanelli V, Vacca A, Bartoloni E, Gerli R, Larosa M, Iaccarino L, Doria A. Early Disease and Low Baseline Damage as Predictors of Response to Belimumab in Patients With Systemic Lupus Erythematosus in a Real-Life Setting. *Arthritis Rheumatol*. 2020;72(8):1314-24.

179. Gunther C, Wolf C, Fennen L, Rosing S, Beissert S, Aringer M, Lee-Kirsch MA. 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.

180. Heide M, von Figura A, Rademacher JG, Wincup C, Tampe B, Korsten P. Steroid-free flare management of a severe cutaneous lupus flare with anifrolumab. *Lupus*. 2023;32(13):1585-7.

181. Iaccarino L, Andreoli L, Bocci EB, Bortoluzzi A, Ceccarelli F, Conti F, De Angelis R, De Marchi G, De Vita S, Di Matteo A, Emmi G, Emmi L, Gatto M, Gerli R, Gerosa M, Govoni M, Larosa M, Meroni PL, Mosca M, Pazzola G, Reggia R, Saccon F, Salvarani C, Tani C, Zen M, Frigo AC, Tincani A, Doria A. Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. *J Autoimmun.* 2018;86:1-8.
182. Iaccarino L, Bettio S, Reggia R, Zen M, Frassi M, Andreoli L, Gatto M, Piantoni S, Nalotto L, Franceschini F, Larosa M, Fredi M, Punzi L, Tincani A, Doria A. Effects of Belimumab on Flare Rate and Expected Damage Progression in Patients With Active Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken).* 2017;69(1):115-23.
183. Joos L, Vetterli F, Jaeger T, Cozzio A, von Kempis J, Rubbert-Roth A. Treatment of refractory subacute cutaneous lupus erythematosus with baricitinib. *Clin Exp Dermatol.* 2022;47(4):748-50.
184. Parodis I, Gomez A, Frodlund M, Jonsen A, Zickert A, Sjowall C, Bengtsson AA, Gunnarsson I. Smoking reduces the efficacy of belimumab in mucocutaneous lupus. *Expert Opin Biol Ther.* 2018;18(8):911-20.
185. Pluss 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(12).
186. Salle R, Chasset F, Kottler D, Picard-Dahan C, Jannic A, Mekki N, De Risi-Pugliese T, Monfort JB, Barbaud A, Frances C, Descamps V. Belimumab for refractory manifestations of cutaneous lupus: A multicenter, retrospective observational study of 16 patients. *J Am Acad Dermatol.* 2020;83(6):1816-9.
187. Shaw K, Sanchez-Melendez S, Taylor D, Barker J, LaChance A, Shahriari N, Vleugels RA. Assessment of Clinical Response to Anifrolumab in Patients With Refractory Discoid Lupus Erythematosus. *JAMA Dermatol.* 2023;159(5):560-3.
188. Tanaka Y, Takeuchi T, Okada M, Ishii T, Nakajima H, Kawai S, Nagashima T, Hayashi N, Wang L, Tummala R. Safety and tolerability of anifrolumab, a monoclonal antibody targeting type I interferon receptor, in Japanese patients with systemic lupus

erythematosus: A multicenter, phase 2, open-label study. *Mod Rheumatol*. 2020;30(1):101-8.

189. Torrente-Segarra V, Peramiquel L, Bonet M. Belimumab in subacute cutaneous lupus erythematosus. *Lupus*. 2021;30(12):2017-8.

190. Trentin F, Tani C, Elefante E, Stagnaro C, Zucchi D, Mosca M. Treatment With Anifrolumab for Discoid Lupus Erythematosus. *JAMA Dermatol*. 2023;159(2):224-6.

191. Vashisht P, Borghoff K, O'Dell JR, Heath-Holmes M. Belimumab for the treatment of recalcitrant cutaneous lupus. *Lupus*. 2017;26(8):857-64.

192. Department of Error. *Lancet*. 2018;392(10146):476.

193. Correction to: Phase 2, randomized, placebo-controlled trial of dapirolizumab pegol in patients with moderate-to-severe active systemic lupus erythematosus. *Rheumatology (Oxford)*. 2022;62(1):486.

194. Correction to *Lancet Rheumatol* 2022; 4: e282–92. *The Lancet Rheumatology*. 2022;4(9):e588.

195. Zen M, Gatto M, Depascale R, Regola F, Fredi M, Andreoli L, Franceschini F, Urban ML, Emmi G, Ceccarelli F, Conti F, Bortoluzzi A, Govoni M, Tani C, Mosca M, Ubiali T, Gerosa M, Bozzolo EP, Canti V, Cardinaletti P, Gabrielli A, Tanti G, Gremese E, De Marchi G, De Vita S, Fasano S, Ciccia F, Pazzola G, Salvarani C, Negrini S, Di Matteo A, De Angelis R, Orsolini G, Rossini M, Faggioli P, Laria A, Piga M, Cauli A, Scarpato S, Rossi FW, De Paulis A, Brunetta E, Ceribelli A, Selmi C, Prete M, Racanelli V, Vacca A, Bartoloni E, Gerli R, Zanatta E, Larosa M, Saccon F, Doria A, Iaccarino L. 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(4).

196. van Vollenhoven RF, Hahn BH, Tsokos GC, Lipsky P, Fei K, Gordon RM, Gregan I, Lo KH, Chevrier M, Rose S. Maintenance of Efficacy and Safety of Ustekinumab Through One Year in a Phase II Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Crossover Trial of Patients With Active Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2020;72(5):761-8.

197. van Vollenhoven RF, Hahn BH, Tsokos GC, Lipsky P, Gordon RM, Fei K, Lo KH, Chevrier M, Rose S, Berry P, Yao Z, Karyekar CS, Zuraw Q. Efficacy and Safety

- of Ustekinumab in Patients With Active Systemic Lupus Erythematosus: Results of a Phase II Open-label Extension Study. *J Rheumatol*. 2022;49(4):380-7.
198. Tanaka Y, Atsumi T, Okada M, Miyamura T, Ishii T, Nishiyama S, Matsumura R, Hayashi N, Abreu G, Tummala R, Morand EF, Takeuchi T. The efficacy and safety of anifrolumab in Japanese patients with systemic lupus erythematosus: TULIP-2 subanalysis. *Mod Rheumatol*. 2023;33(1):134-44.
199. Morand EF, Furie RA, Bruce IN, Vital EM, Dall'Era M, Maho E, Pineda L, Tummala R. Efficacy of anifrolumab across organ domains in patients with moderate-to-severe systemic lupus erythematosus: a post-hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials. *Lancet Rheumatol*. 2022;4(4):e282-e92.
200. Merrill JT, Furie R, Werth VP, Khamashta M, Drappa J, Wang L, Illei G, Tummala R. 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(1):e000284.
201. Furie R, Morand EF, Askanase AD, Vital EM, Merrill JT, Kalyani RN, Abreu G, Pineda L, Tummala R. Anifrolumab reduces flare rates in patients with moderate to severe systemic lupus erythematosus. *Lupus*. 2021;30(8):1254-63.
202. Bruce IN, van Vollenhoven RF, Psachoulia K, Lindholm C, Maho E, Tummala R. Time to onset of clinical response to anifrolumab in patients with SLE: pooled data from the phase III TULIP-1 and TULIP-2 trials. *Lupus Sci Med*. 2023;10(1).
203. Gan PR, Wu H, Zhu YL, Shu Y, Wei Y. Glycolysis, a driving force of rheumatoid arthritis. *Int Immunopharmacol*. 2024;132:111913.
204. Kunkl M, Sambucci M, Ruggieri S, Amormino C, Tortorella C, Gasperini C, Battistini L, Tuosto L. CD28 Autonomous Signaling Up-Regulates C-Myc Expression and Promotes Glycolysis Enabling Inflammatory T Cell Responses in Multiple Sclerosis. *Cells*. 2019;8(6).
205. Adolph TE, Meyer M, Schwarzler J, Mayr L, Grabherr F, Tilg H. The metabolic nature of inflammatory bowel diseases. *Nat Rev Gastroenterol Hepatol*. 2022;19(12):753-67.
206. Takeshima Y, Iwasaki Y, Fujio K, Yamamoto K. Metabolism as a key regulator in the pathogenesis of systemic lupus erythematosus. *Semin Arthritis Rheum*. 2019;48(6):1142-5.

207. Sharma M, Boytard L, Hadi T, Koelwyn G, Simon R, Ouimet M, Seifert L, Spiro W, Yan B, Hutchison S, Fisher EA, Ramasamy R, Ramkhelawon B, Moore KJ. Enhanced glycolysis and HIF-1 α activation in adipose tissue macrophages sustains local and systemic interleukin-1 β production in obesity. *Sci Rep*. 2020;10(1):5555.
208. Witcoski Junior L, de Lima JD, Somensi AG, de Souza Santos LB, Paschoal GL, Uada TS, Bastos TSB, de Paula AGP, Dos Santos Luz RB, Czaikowski AP, Davanzo MR, Braga TT. Metabolic reprogramming of macrophages in the context of type 2 diabetes. *Eur J Med Res*. 2024;29(1):497.
209. Fan N, Zhang X, Zhao W, Zhao J, Luo D, Sun Y, Li D, Zhao C, Wang Y, Zhang H, Rong J. Covalent Inhibition of Pyruvate Kinase M2 Reprograms Metabolic and Inflammatory Pathways in Hepatic Macrophages against Non-alcoholic Fatty Liver Disease. *Int J Biol Sci*. 2022;18(14):5260-75.
210. Hay N. Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? *Nat Rev Cancer*. 2016;16(10):635-49.
211. Ivanova I, Svilenska T, Maisch T, Karrer S, Niebel D, Berneburg M, Kurz B. The role of UV-induced cutaneous matrix metalloproteinases and mi-RNAs in the pathogenesis of lupus erythematosus. *J Transl Autoimmun*. 2025;10:100265.
212. Cibrian D, de la Fuente H, Sanchez-Madrid F. Metabolic Pathways That Control Skin Homeostasis and Inflammation. *Trends Mol Med*. 2020;26(11):975-86.
213. Jensen LT, Attfield KE, Feldmann M, Fugger L. Allosteric TYK2 inhibition: redefining autoimmune disease therapy beyond JAK1-3 inhibitors. *EBioMedicine*. 2023;97:104840.
214. 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.
215. Tang YY, Wang DC, Chen YY, Xu WD, Huang AF. Th1-related transcription factors and cytokines in systemic lupus erythematosus. *Front Immunol*. 2023;14:1305590.
216. 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(3):903-10.
217. Satoh-Kanda Y, Nakayamada S, Kubo S, Yamagata K, Nawata A, Tanaka H, Kosaka S, Kanda R, Yu S, Fujita Y, Sonomoto K, Tanaka Y. Modifying T cell

phenotypes using TYK2 inhibitor and its implications for the treatment of systemic lupus erythematosus. *RMD Open*. 2024;10(2).

218. Burke JR, Cheng L, Gillooly KM, Strnad J, Zupa-Fernandez A, Catlett IM, Zhang Y, Heimrich EM, McIntyre KW, Cunningham MD, Carman JA, Zhou X, Banas D, Chaudhry C, Li S, D'Arienzo C, Chimalakonda A, Yang X, Xie JH, Pang J, Zhao Q, Rose SM, Huang J, Moslin RM, Wroblewski ST, Weinstein DS, Salter-Cid LM. Autoimmune pathways in mice and humans are blocked by pharmacological stabilization of the TYK2 pseudokinase domain. *Sci Transl Med*. 2019;11(502).

219. Wasserer S, Seiringer P, Kurzen N, Jargosch M, Eigemann J, Aydin G, Raunegger T, Schmidt-Weber CB, Eyerich S, Biedermann T, Eyerich K, Lauffer F. Tyrosine kinase 2 inhibition improves clinical and molecular hallmarks in subtypes of cutaneous lupus. *Br J Dermatol*. 2025;193(6):1192-203.

220. Morand E, Merola JF, Tanaka Y, Gladman D, Fleischmann R. TYK2: an emerging therapeutic target in rheumatic disease. *Nat Rev Rheumatol*. 2024;20(4):232-40.

221. Wlassits R, Muller M, Fenzl KH, Lamprecht T, Erlacher L. JAK-Inhibitors - A Story of Success and Adverse Events. *Open Access Rheumatol*. 2024;16:43-53.

222. Riggs JM, Hanna RN, Rajan B, Zerrouki K, Karnell JL, Sagar D, Vainshtein I, Farmer E, Rosenthal K, Morehouse C, de Los Reyes M, Schifferli K, Liang M, Sanjuan MA, Sims GP, Kolbeck R. Characterisation of anifrolumab, a fully human anti-interferon receptor antagonist antibody for the treatment of systemic lupus erythematosus. *Lupus Sci Med*. 2018;5(1):e000261.

223. Pellerin A, Otero K, Czerkowiec JM, Kerns HM, Shapiro RI, Ranger AM, Otipoby KL, Taylor FR, Cameron TO, Viney JL, Rabah D. Anti-BDCA2 monoclonal antibody inhibits plasmacytoid dendritic cell activation through Fc-dependent and Fc-independent mechanisms. *EMBO Mol Med*. 2015;7(4):464-76.

224. Kim JM, Park SH, Kim HY, Kwok SK. A Plasmacytoid Dendritic Cells-Type I Interferon Axis Is Critically Implicated in the Pathogenesis of Systemic Lupus Erythematosus. *Int J Mol Sci*. 2015;16(6):14158-70.

225. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, Germino R, Menon S, Sun Y, Wang C, Shapiro AB, Kanik KS, Connell CA,

Investigators OS. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med*. 2022;386(4):316-26.

226. Administration USFaD. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions 2021 [Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death>].

227. Hegyi P, Petersen OH, Holgate S, Eross B, Garami A, Szakacs Z, Dobszai D, Balasko M, Kemeny L, Peng S, Monteiro J, Varro A, Lamont T, Laurence J, Gray Z, Pickles A, FitzGerald GA, Griffiths CEM, Jassem J, Rusakov DA, Verkhatsky A, Szentesi A. Academia Europaea Position Paper on Translational Medicine: The Cycle Model for Translating Scientific Results into Community Benefits. *J Clin Med*. 2020;9(5).

228. Hegyi P, Eross B, Izbeki F, Parniczky A, Szentesi A. Accelerating the translational medicine cycle: the Academia Europaea pilot. *Nat Med*. 2021;27(8):1317-9.

16. BIBLIOGRAPHY

16.1. Publications related to the thesis

Bokor LA, Szabolcs BL, Király Z, Mohos A, Szepesi Á, Varga V, Sebestyén A, Kemény LV, Holló P, Hidvégi B. *Upregulated GLUT1 expression correlates with type I interferon activity and disease severity in cutaneous lupus erythematosus*. J Transl Autoimmun. 2026 May 29;12:100375. doi: 10.1016/j.jtauto.2026.100375.

IF: 3.8

Bokor LA, Martyin K, Krebs M, Galajda NÁ, Meznerics FA, Szabó B, Hegyi P, Lőrincz K, Kiss N, Bánvölgyi A, Hidvégi B. *Deucravacitinib shows superior efficacy and safety in cutaneous lupus erythematosus compared to various biologics and small molecules - A systematic review and meta-analysis*. Autoimmun Rev. 2025 Feb 28;24(3):103723. doi: 10.1016/j.autrev.2024.103723.

IF: 9.8

16.2. Publications not related to the thesis

Tang J, Pernes G, Nakagaki B, Tran N, **Bokor L**, Prenen F, Yi M, Robertson AE, Cronin R, Sarmini M, Pierscianowski J, Roberts V, Ryback BA, Novina CD, Auclair K, Xiao H, Mills EL. *Macrophage-derived itaconate is a negative regulator of adipose tissue thermogenesis*. Nat Metab. 2026 Jul 14. doi: 10.1038/s42255-026-01572-2.

IF: 27.5

Martyin K, Meznerics FA, **Bokor LA**, Szabó B, Hegyi P, Kiss N, Bánvölgyi A. *Diagnostic accuracy of teledermatology for skin diseases: a systematic review and meta-analysis*. Front Med (Lausanne). 2026 Mar 2;13:1739592. doi: 10.3389/fmed.2026.1739592.

IF: 3.6

17. ACKNOWLEDGEMENTS

The completion of this dissertation would not have been possible without the support and guidance of many individuals, to whom I owe my deepest gratitude.

First and foremost, I would like to express my sincere gratitude to my supervisor, Bernadett Hidvégi, M.D., Ph.D. She has supported me throughout my research career since I was a medical student. She introduced me to the world of immunometabolism, which has remained my primary research interest ever since. I have learned immensely from her about immunology and autoimmune skin diseases, which has become the field of dermatology I wish to pursue during my upcoming clinical years. Without her continued guidance and unwavering support, this work would not have been possible.

I am also deeply grateful to my co-supervisor, András Bánvölgyi, M.D., Ph.D. His positivity and enthusiasm carried me through the more challenging periods of my doctoral studies, and his critical thinking and broad knowledge were invaluable to the completion of this work.

I'm sincerely grateful to Prof. Péter Holló, M.D., Ph.D., the head of the Department of Dermatology, Venereology and Dermatoooncology, Semmelweis University, for his continuous support of our research and for facilitating my academic studies abroad.

I would also like to thank Prof. Péter Hegyi, M.D., Ph.D., D.Sc., director of the Centre for Translational Medicine (CTM), for welcoming me into the PhD program and fostering such a motivating research community.

My heartfelt thanks go to my methodological supervisor, Fanni Meznerics, M.D., Ph.D., for her continuous assistance, insightful comments, and encouragement throughout this journey.

I also owe a special thanks to Zsófia Király, M.D., Ph.D., who guided my very first steps in research during my years as a medical student. The countless hours spent on immunohistochemistry together remain a fond memory.

I am exceptionally grateful to Prof. Anna Sebestyén, M.D., Ph.D. and her entire team at the Tumor Biology – Tumor Metabolism Research Group in the Department of Pathology and Experimental Cancer Research, Semmelweis University. Their generosity, expertise, and support were indispensable to this work.

I would also like to thank Anita Mohos, M.D., Ph.D., and Ágota Szepesi, M.D., Ph.D., for their immense investment of time and meticulous execution of the immunohistochemical analyses.

I'm incredibly thankful to Lajos Vince Kemény, M.D., Ph.D. and Botond Szabolcs, M.D., whose brilliance and dedication to the *in silico* analyses contributed significantly to the depth of our findings.

I could not have completed this thesis without the collaborative spirit and hard work of my co-authors: Katalin Martyn, M.D., Máté Krebs, M.D., Noémi Ágnes Vámosi-Galajda, M.D., Ph.D., Kende Lőrincz, M.D., Ph.D., Norbert Kiss, M.D., Ph.D., and Viktória Varga, M.D.

Finally, I am profoundly grateful to my family. Their unconditional love, patience, and steadfast support carried me through the most difficult moments of this journey and kept me motivated throughout my doctoral studies. I could not have done this without them.