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Tyrosine kinase 2 inhibition improves clinical and molecular hallmarks in subtypes of cutaneous lupus

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Abstract

Background Cutaneous lupus erythematosus (CLE) is a chronic inflammatory skin disease with various clinical subtypes. Although its pathogenesis is not yet fully understood, T-cell-mediated autoimmunity and elevated levels of type I interferons (IFNs) are two major factors that contribute to the development of cutaneous lesions. Type I IFNs transduce their signal via tyrosine kinase 2 (TYK2).

Objectives To investigate the impact of TYK2 signalling in preclinical models of CLE.

Methods CLE skin biopsies were investigated by RNA sequencing (RNAseq) and immunohistochemistry. T cells isolated from CLE skin biopsies (lesional T cells) were restimulated with anti-CD3/anti-CD28 and cytokine release was quantified by enzyme-linked immunosorbent assay and Luminex®. Primary human keratinocytes and three-dimensional skin models were stimulated with IFN-α or lesional T-cell supernatant in the presence or absence of the TYK2 inhibitor deucravacitinib, followed by RNAseq. Skin biopsies from patients with different CLE subtypes were treated *ex vivo* with deucravacitinib followed by real-time quantitative polymerase chain reaction.

Results Bulk RNAseq revealed a strong correlation between TYK2 and interface dermatitis, a histological hallmark of CLE. Immunohistochemistry confirmed a high abundance of TYK2 in different CLE subtypes. Inhibiting TYK2 reduced inflammation and normalized epidermal impairments in primary human keratinocytes, reconstructed human epidermis and CLE T cells. *Ex vivo* TYK2 inhibition in CLE skin biopsies reduced IFN response and necroptosis-related gene expression. Finally, four patients with different therapy-refractory subtypes of CLE (acute, subacute, chronic discoid, chilblain CLE) were successfully treated with deucravacitinib.

Conclusions IFN-α and T-cell-derived cytokines both contribute to skin inflammation in CLE. TYK2 inhibition is a promising approach for different subtypes of CLE as it controls inflammation in various preclinical models and patients with CLE who are refractory to treatment.

Lay summary

Cutaneous lupus erythematosus (CLE) is an autoimmune disease. In this condition, the body's immune system mistakenly attacks the skin. How CLE develops is not fully understood. However, it is known that certain immune cells in the body such as 'T cells' can be involved. High levels of proteins called interferons can contribute to the development of skin symptoms. Interferons interact with another protein called TYK2. This is why TYK2 might be a potential new target for treating CLE.

In this study, we investigated the role of TYK2 in CLE. We did this by taking skin samples from patients with the disease and doing other laboratory tests. Four patients with the disease who were not responding to the usual treatment were given a drug called 'deucravacitinib'. This medicine works to inhibit the TYK2 protein. As a result, interferon signalling is weakened and skin symptoms may improve. We found there were higher levels of TYK2 in skin samples from patients with different types of CLE. By blocking the TYK2 protein, inflammation was reduced. In the lab, we did some tests using models that are similar to human skin. Interferons and other proteins produced by T cells weakened the structure of the skin model. This was prevented when the skin model was treated with deucravacitinib. Additionally, lower levels of TYK2 resulted in less inflammation in skin cells treated with deucravacitinib. In the four patients whose cutaneous lupus disease wasn't responding to the usual treatment, deucravacitinib quickly improved their skin and quality of life.

Our results highlight the potential role of inhibiting TYK2 as a new approach to treating CLE.

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What is already known about this topic?

- Type I interferons (IFNs) and B-cell-mediated immunity drive the pathophysiology of systemic lupus erythematosus (SLE).
- In cutaneous lupus (CLE), T-cell-mediated immune responses and type I IFNs are the predominant drivers of the disease.
- Inhibiting tyrosine 2 (TYK2) blocks IFN-α signalling and leads to improvement in SLE.

What does this study add?

- TYK2 inhibition exhibits a dual mode of action in CLE by simultaneously inhibiting type I IFN and T-cell-mediated pathogenic effects.
- Different subtypes of CLE, including poorly investigated CLE subtypes like chilblain lupus, showed rapid clinical improvement upon TYK2 inhibition.

What is the translational message?

- We provide a mechanistic and clinical rationale for the further development of TYK2 inhibition for the treatment of CLE.

Lupus erythematosus is a chronic autoimmune disease that has a severe impact on patients' quality of life.[1,2] While systemic lupus erythematosus (SLE) involves multiple organs, cutaneous lupus erythematosus (CLE) predominantly affects the skin. There are three major clinical subtypes of CLE: acute (ACLE), subacute (SCLE) and chronic discoid (CDLE).[3] ACLE and SCLE carry a 4–25% risk of progressing to SLE.[4] Managing SLE and CLE is a challenging task for clinicians due to the high heterogeneity; it often requires a multidisciplinary approach. A dysregulated immune response, encompassing type I interferons (IFNs), as well as cytotoxic T cells and a cascade of cytokines and cellular interactions, represents the common mechanism of lupus erythematosus. Histologically, the presence of a dense subepidermal infiltration of lymphocytes in combination with keratinocyte cell death is called interface dermatitis, a histological hallmark of CLE.[5–7] While SLE is defined by the presence of antinuclear autoantibodies, a large proportion of patients with CLE do not produce autoantibodies, indicating that – in contrast to SLE – humoral immunity might be less relevant in CLE.[8–10] CLE belongs to the type I inflammatory skin diseases, also known as lichenoid diseases, and is characterized by a strong IFN-α and type I immune response causing apoptosis and necroptosis of keratinocytes.[11,12] The inflammatory cascade is initiated by various environmental factors, such as ultraviolet light. A deficiency in phagocytosis results in the inadequate elimination of damaged keratinocytes and DNA.[13] Consequently, damage-associated molecular patterns are recognized by Toll-like receptor (TLR)7, TLR8 and TLR9 on antigen-presenting cells.[13] Upon ligand binding, they release type I IFN, which triggers the expression of CXCL9 and CXCL10 by keratinocytes and the influx of effector lymphocytes into the skin.[13,14] For SLE, anifrolumab (a monoclonal antibody against IFN-α) and belimumab [a monoclonal antibody against B lymphocyte stimulator (BLyS)] are both approved as first-line therapies and improve SLE-associated organ damage; however, their efficacy for cutaneous lesions is limited,[15–19] and, despite recent advancements in the treatment of SLE, therapeutic options for CLE remain scarce.[20] This is why CLE treatment remains restricted to topical glucocorticoids and broad-acting systemic immunosuppressants.[21] Therefore, a detailed understanding of the pathophysiology of CLE is essential to the development of new therapeutic options.

In this context, tyrosine kinase 2 (TYK2) might play a pivotal role in CLE as it regulates the downstream effects of type I IFNs, as well as of interleukin (IL)-12 and IL-23, and modifies T helper cell (Th)1, Th17, B-cell and myeloid cell function.[22,23] Deucravacitinib allosterically inhibits TYK2 pseudokinase activity, locking TYK2 in an inactive state. As a result, receptor-mediated downstream effects such as phosphorylation of signal transducer and activator of transcription (STAT)1, STAT2, STAT3 and STAT5 are inhibited.[22,24,25]

Recently, deucravacitinib gained US Food and Drug Administration and European Medicines Agency approval for the treatment of psoriasis, after demonstrating high efficacy in the treatment of plaque psoriasis.[26] Interestingly, blocking TYK2 reduces inflammation in murine models of lupus erythematosus nephritis and colitis.[23] These results qualify TYK2 as a promising target for the treatment of CLE. In a phase II trial that investigated the effects of deucravacitinib in SLE, cutaneous manifestations improved significantly.[27] Nonetheless, mechanistic data evaluating the effects of deucravacitinib in the treatment of different types of CLE are currently lacking, although a phase II trial for discoid LE (DLE) and SCLE is ongoing.[28]

In this study, we aimed to investigate effects of TYK2 inhibition in primary human keratinocytes, T cells, three-dimensional (3D) skin models and CLE skin biopsies. Further, we report a case series of four patients with therapy-refractory CLE subtypes who were successfully treated off-label by TYK2 inhibition.

Materials and methods

Study cohort

Punch biopsies (6 mm) of lesional and nonlesional skin were divided into three parts. One was used for RNA sequencing (RNAseq) analysis, one for histological analysis and one for the isolation of T cells. For *ex vivo* treatment, specimens were halved and cultured with deucravacitinib (1 μmol L^{-1}) or pure medium.

Independently of the *in vitro* experiments, four patients with therapy-refractory CLE were treated off-label with deucravacitinib. Their symptoms were assessed according to the CARE case report guidelines (Figure S1; see Supporting Information). All *in vitro* and *ex vivo* experiments were performed with the nonclinical drug provided by Bristol-Myers Squibb (BMS). The BMS-provided nonclinical drug was not used for off-label patient treatment. The acquired commercial drug approved for the treatment of psoriasis was not used in *in vitro* or *ex vivo* studies. Further information about the cohort can be found in Tables S1 and S2 (see Supporting Information).

Keratinocytes and reconstructed human epidermis

Human keratinocytes were isolated via suction blister from healthy volunteers and cultivated at 37 °C in 5% CO_2 in DermaLife Basal Medium supplemented with the DermaLife K LifeFactor Kit. More information can be found in Appendix S1 (see Supporting Information).[29]

Quantitative real-time polymerase chain reaction

Sequences for quantitative real-time polymerase chain reaction (qRT-PCR), RNA isolation and the qRT-PCR protocol are provided in Table S3 (see Supporting Information). 18S was used as the housekeeping gene. Gene expression levels were quantified using the $2^{-\Delta\Delta CT}$ method.

Lesional T cells

T cells were isolated from lesional skin biopsies taken from patients with CLE ($n=3$) and other interface dermatitis diseases ($n=6$) by migrating towards an IL-2 gradient, as described previously.[11] T cells were stimulated with anti-CD3/anti-CD28 and with IFN-α (50 ng mL^{-1}), in the presence or absence of deucravacitinib (1 μmol L^{-1}), and the supernatant (T-cell supernatant; TCSN) was collected. A detailed description can be found in Appendix S1.

RNA sequencing

A detailed description of the RNAseq protocol can be found in Appendix S1. An adjusted *P*-value threshold of <0.05 was applied throughout the analysis (gene set enrichment analysis)[30] to determine statistical significance.

Immunohistochemistry

Immunohistochemistry of TYK2 on 38 formalin-fixed paraffin-embedded slides of type I inflammatory skin diseases [25 μg mL^{-1} in citrate buffer; ab39550 (Abcam, Cambridge, UK)] on a Bond-III Fully Automated IHC and ISH Staining System (21.2201; Leica Biosystems, Nussloch, Germany) was performed according to the manufacturer's protocol. Standardized images were taken with an EVOS M3000 Imaging System (Thermo Fisher Scientific, Waltham, MA, USA). The staining intensity of the epidermis vs. the background was measured with ImageJ (version 1.54d; NIH, Bethesda, MD, USA) and the colour deconvolution plugin as described previously.[31] Visualization was done with Microsoft Excel (2010). The number of vacuolized keratinocytes in the reconstructed human epidermis (RHE) models was quantified by two dermatologists in a blinded manner at ×40 high-resolution magnification; epidermal thickness was measured across two representative images with ImageJ.

Skin biopsy culture

Skin biopsies were cultured in RPMI medium supplemented with human serum 1% (H4522-100ML; Sigma-Aldrich, St. Louis, MO, USA), 0.1 mmol L^{-1} NEAA (11140-035; Thermo Fisher Scientific), 2 mmol L^{-1} L-glutamine (25030-024; Thermo Fisher Scientific), 1 mmol L^{-1} sodium pyruvate (11360-039; Thermo Fisher Scientific) and 100 U mL^{-1} penicillin/streptomycin (15140-122; Thermo Fisher Scientific) for 4 h. RNA was isolated with a miRNeasy Kit for miRNA Purification (catalogue no. 217004; Qiagen, Hilden, Germany), in accordance with the manufacturer's protocol.

Statistical analysis

A one-way ANOVA with Tukey's multiple comparisons test was applied for gene expression between two groups and different patients. A *P*-value ≤ 0.05 was determined to denote statistical significance.

Results

Tyrosine kinase 2 expression is associated with interface dermatitis and abundant in various forms of cutaneous lupus

Firstly, we screened a previously published bulk RNAseq dataset of skin biopsies from 265 patients with different inflammatory skin diseases for TYK2 and typical type I immune response genes (*CXCL9*, *CXCL10*).[32] All patients were systematically characterized clinically and histologically. We correlated type I-related genes to the intensity of interface dermatitis. For this, the strength of interface dermatitis was ranked from 0 to 3 based on the amount of infiltrating immune cells and the number of dyskeratotic epidermal cells (level 0 = none; level 1 = low; level 2 = moderate; level 3 = severe interface dermatitis). The expression of *TYK2*, *CXCL9* and *CXCL10* correlated significantly with the intensity of interface dermatitis (Figure 1a–c). However, there was no difference in *TYK2* expression at the RNA level (Figure 1d). As TYK2 function is not based on genetic regulation, but on the rapid translocation to the receptor upon stimulation, we performed immunohistochemistry of TYK2 in different CLE subtypes (CDLE: $n=7$; SCLE: $n=5$; ACLE: $n=3$) and different type I-mediated ISDs (lichen planus: $n=6$; erythema multiforme: $n=7$; dermatomyositis: $n=4$) and healthy skin ($n=5$). TYK2 was primarily found in the keratinocyte layer (Figure 1 g). In comparison with other Th1-driven inflammatory skin diseases, the highest TYK2 staining intensity relative to background was seen in all CLE subtypes (Figure 1e), while healthy skin exhibited low TYK2 protein expression (Figure 1f, g). In summary, *TYK2* expression increased significantly with the degree of interface dermatitis. At protein level TYK2 was detected predominantly in keratinocytes of all CLE subtypes.

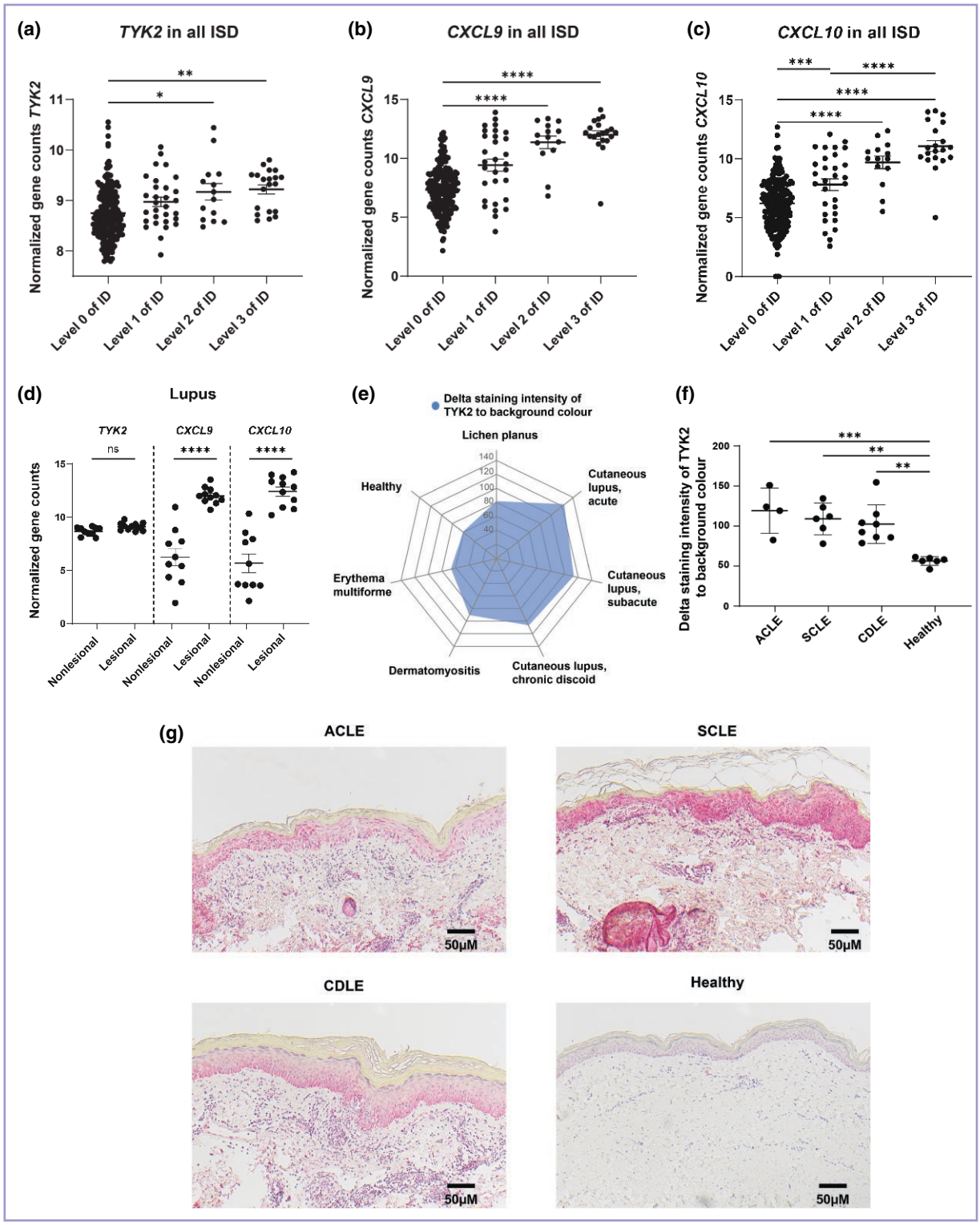

Figure 1 *TYK2* expression is associated with the degree of interface dermatitis (ID) and is abundant in various forms of cutaneous lupus. (a–c) Normalized gene counts of *TYK2*, *CXCL9* and *CXCL10* from a large RNA sequencing (RNAseq) cohort of patients with inflammatory skin disease [lichen planus (n=30), cutaneous lupus (n=10), atopic dermatitis (n=43), dishydrotic eczema (n=5), nummular eczema (n=49), hyperkeratotic-rhagadiform hand eczema (n=4), psoriasis (n=87), pustular psoriasis (n=5), guttate psoriasis (n=7), pityriasis rubra pilaris (n=7), cutaneous lymphoma (n=18)] were grouped according to the severity of ID (0=none, 1=low, 2=moderate, 3=severe). (d) Normalized gene counts of *TYK2*, *CXCL9* and *CXCL10* in lesional (L; n=11) and nonlesional (NL; n=10) lupus erythematosus skin analysed by bulk RNAseq. For statistical analysis a paired *t*-test was performed. (e–g) Immunohistochemical staining of tyrosine kinase (TYK2) in various diseases with ID. (e) Radar plot displaying the delta colour intensity of TYK2 vs. background staining. TYK2 immunohistochemistry in different lupus entities vs. healthy skin is shown in (g) representative images and (f) quantified. ACLE, acute cutaneous lupus erythematosus; CLDE, chronic discoid lupus erythematosus; ISD, inflammatory skin disease; ns, not significant (i.e. $P>0.05$); SCLE, subacute cutaneous lupus erythematosus. *$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$ (ANOVA).

Inhibiting tyrosine kinase 2 attenuates interferon-α-mediated inflammation in keratinocytes and cutaneous lupus erythematosus T cells

Given the high abundance of TYK2 in CLE, we further investigated the functional role of TYK2 in primary human keratinocytes, in T cells isolated from CLE skin biopsies and in RHE skin models that mimic key features of CLE (Figure 2a). For this, we stimulated human keratinocytes with IFN-α and measured the expression of the type I chemoattractants CXCL9 and CXCL10 after adding different concentrations (100 μmol L^{-1}, 10 μmol L^{-1}, 1 μmol L^{-1}, 100 nmol L^{-1}, 10 nmol L^{-1}) of deucravacitinib (Figure 2b, c). We found a significant dose-dependent inhibition of CXCL9 and CXCL10 with a blocking rate exceeding 95% at a concentration of 1 μmol L^{-1} (Figure 2b, c). Therefore, all subsequent keratinocyte experiments were conducted with a concentration of 1 μmol L^{-1} deucravacitinib. Next, we isolated lesional T cells from CLE skin biopsies, which were stimulated with anti-CD3/anti-CD28 and IFN-α in the absence or presence of deucravacitinib. Here, deucravacitinib reduced the release of IFN-γ in a dose-dependent manner (IFN-α: 100%; 1 μmol L^{-1} deucravacitinib: 69%; 10 μmol L^{-1} deucravacitinib: 38%) (Figure 2d). To better mimic the conditions of human disease, we generated RHE skin models from three keratinocyte donors and stimulated them with IFN-α in the presence or absence of deucravacitinib and performed RNAseq. Principal component (PC) analysis revealed that IFN-α-stimulated models and IFN-α + TYK2 inhibitor-stimulated samples clustered separately (PC1: 59%; PC2: 30% variance) (Figure 2e). Investigating the top significantly regulated pathways, we found that TYK2 inhibition enriched mitosis-related pathways in the IFN-α-stimulated samples, whereas gene sets of adaptive and innate immunity were suppressed upon TYK2 inhibition (Figure 2f). Interestingly, genes belonging to the pathways 'defence response to virus' and 'leucocyte chemotaxis', which both exhibited a negative enrichment score upon TYK2 inhibition (Table S4; see Supporting Information), include several IFN response genes (*IRF1*, *IRF2*, *IRF7*, *STAT1*, *STAT2*, *IFI27*, *IFI44L*, *MX1*, *ZBP1*) and are connected by *CXCL9*, *CXCL10*, *IL6*, *IL1B* and *IL23A* (Figure 2g). Some of these genes belong to a frequently investigated SLE gene set,[33,34] which was also downregulated by TYK2 inhibition (Figure 2h). Further, deucravacitinib led to a significant downregulation of chemoattractants that promote the influx of type I immune cells (Figure 2i). In summary, our findings indicated that TYK2 inhibition reduces IFN-α-mediated inflammation in keratinocytes, T cells and RHE skin models.

Secretome of lesional T cells contributes to cutaneous inflammation

In addition to the central role of IFN-α, skin-infiltrating T cells also play a crucial role in maintaining skin inflammation in CLE. Our previous work demonstrated that IFN-γ + tumour necrosis factor (TNF)-α-positive T cells are present in inflammatory skin diseases with interface dermatitis and mediate epidermal inflammation.[11]

To further assess the impact of TYK2 inhibition in CLE, we aimed to mimic the cutaneous inflammatory milieu of CLE as realistically as possible *in vitro*. Therefore, we isolated T cells from different skin diseases with interface dermatitis (CLE and lichen planus, $n=6$) and subsequently generated a pooled lesional TCSN that was analysed by Luminex® (Table S5; see Supporting Information). The type I T-cell secretome is dominated by TNF-α and IFN-γ; IL-13, IL-22 and IL-6 are present in lower concentrations (Table S5). In contrast to the previous experiments, IFN-α was not found in the TCSN, evaluated by enzyme-linked immunosorbent assay (Table S5). Subsequently, RHE skin models were stimulated with TCSN, mimicking the microenvironment of interface dermatitis, with and without TYK2 inhibition (Figure 3a), followed by RNAseq. Firstly, the TCSN gene response signature was defined by calculating differentially expressed genes (DEGs; false discovery rate < 0.05, log2 fold change > 1.5) between deucravacitinib-treated and untreated skin models. Comparing this signature with the IFN-α gene response signature (as shown in Figure 2e–i), TYK2 inhibition resulted in a higher number of significantly regulated genes in the type I TCSN-stimulated skin models (1854 DEGs) than in the IFN-α skin models (736 DEGs; Figure 3b). Nevertheless, 560 genes overlapped, corresponding to approximately 79% of all genes significantly regulated upon IFN-α stimulation and TYK2 inhibition. Overall, the shared gene signature exhibited a similar molecular profile to that observed in the IFN-α cohort (Table S4).

Further gene set enrichment analysis of deucravacitinib-treated and deucravacitinib-untreated TCSN-stimulated RHE skin models revealed that the top 10 suppressed gene sets were primarily associated with attenuated immune response, adaptive immune response, innate immune response, response to IFN-γ, and antigen processing and presentation (Figure 3c). To better estimate the contribution of T-cell-released cytokines, we next focused on genes that were significantly regulated by type I TCSN but not by IFN-α. An over-representation analysis of these 1294 genes revealed an enrichment of genes associated with epidermis development, keratinocyte differentiation and cornified envelope, as well as cell–cell junctions and hypoxia response (Figure 3d). Notably, genes that belong to the 'late cornified envelope' and 'keratinocyte differentiation' pathways were upregulated by the type I immune response in comparison with unstimulated cells and were normalized by TYK2 inhibition (Figure 3e). These include, for example, *LCE3D*, the genes encoding small proline-rich proteins (*SPRR2D*, *SPRR1B*, *SPRR2B*, *SPRR2G*) and *KRT6A* (Figure 3e). The whole gene set enrichment analysis of TYK2/TCSN vs. TCSN is depicted in Table S6 (see Supporting Information). Histological analysis of RHE skin models confirmed these findings. While IFN-α-stimulated 3D skin models developed a similar epidermal structure to the unstimulated control, type I TCSN induced epidermal thickness, as well as vacuolized keratinocytes, indicating cell death (Figure 3f, g). These effects were normalized upon TYK2 inhibition. In conclusion, our findings demonstrated that lesional T cells contribute to epidermal alterations in CLE – an effect that can be reversed by TYK2 inhibition.

Tyrosine kinase 2 inhibition reduces expression of proinflammatory genes in cutaneous lupus erythematosus

Next, we sought to investigate the effects of TYK2 inhibition in skin biopsies from five patients with different subtypes of CLE (Table S1). Punch biopsies from these patients were cultured *ex vivo* without any further stimulation, in the presence or absence of deucravacitinib. Gene expression of CLE marker genes (defined in Figures 2, 3) was analysed

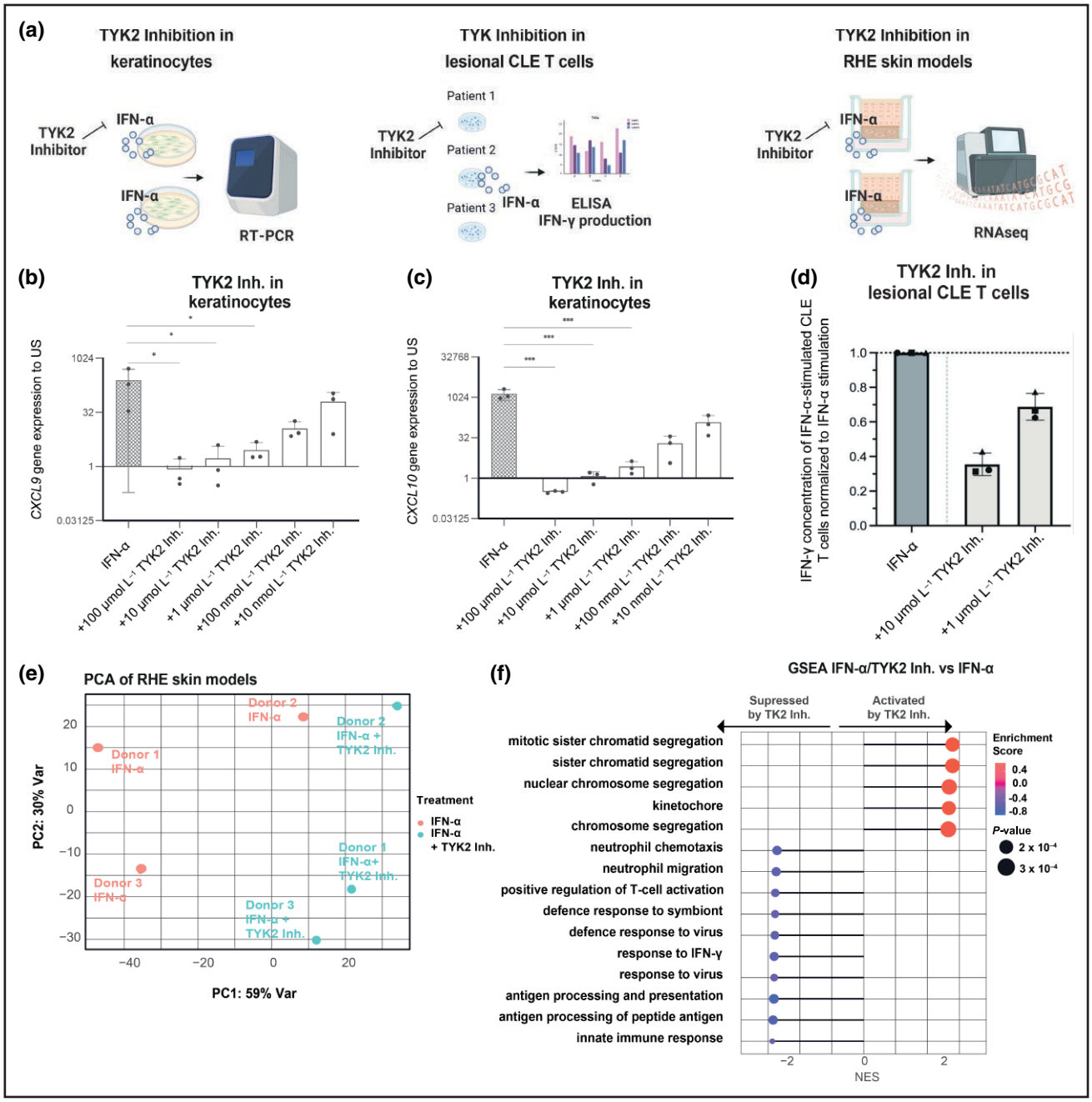

Figure 2 Inhibiting tyrosine kinase 2 (TYK2) attenuates interferon (IFN)-α-mediated inflammation in keratinocytes and lesional T cells from patients with lupus erythematosus. (a) Overview of the experimental setup. (b, c) Effects of indicated concentrations of the TYK2 inhibitor deucravacitinib on primary human keratinocytes ($n=3$) stimulated with IFN-α (50 ng mL^{-1}). Gene expression of (b) *CXCL9* and (c) *CXCL10* was measured by real-time polymerase chain reaction (RT-PCR), calculated as $2^{-\Delta\Delta CT}$ value and displayed as relative gene expression to unstimulated control. (d) IFN-γ secretion of lesional T cells isolated from skin biopsies from patients with cutaneous lupus erythematosus (CLE; $n=3$) after IFN-α stimulation and TYK2 inhibition by deucravacitinib measured by enzyme-linked immunosorbent assay (ELISA) and normalized to IFN-α stimulation. (e–i) TYK2 inhibition in reconstructed human epidermis (RHE) skin models. RHE skin models ($n=3$) were stimulated with IFN-α (50 ng mL^{-1}) alone or in the presence of 1 µmol L^{-1} TYK2 inhibitor, followed by RNAseq analysis. (e) Principal component analysis (PCA) of IFN-α alone and IFN-α+TYK2 inhibitor samples. (f) Gene set enrichment analysis (GSEA) displaying the top 10 suppressed and top 5 activated gene sets (Gene Ontology) by TYK2 inhibition in IFN-α-stimulated RHE skin models vs. IFN-α alone. The enrichment score is indicated by node colour (activated=red; suppressed=blue) and the *P*-value by node size. (g) Cnetplot of genes in TYK2-suppressed pathways related to 'defence response to virus' and 'leucocyte chemotaxis'. (h, i) Normalized gene counts of IFN-α response and chemoattractant genes. Inh, inhibitor/inhibition; NES, normalized enrichment score; TK2, TYK2; US, unstimulated; Var, variance. *$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$. (*Continued*)

by real-time PCR (Figure 4a). Here, genes related to leucocyte chemotaxis (*CXCL9*, *CXCL10*, *CCL8*) were significantly downregulated upon incubation with deucravacitinib (Figure 4b). Further, *TLR7* expression, which is a high-risk gene locus for SLE,[35] was significantly reduced upon TYK2 inhibition (Figure 4c). Furthermore, TYK2 inhibition exhibited

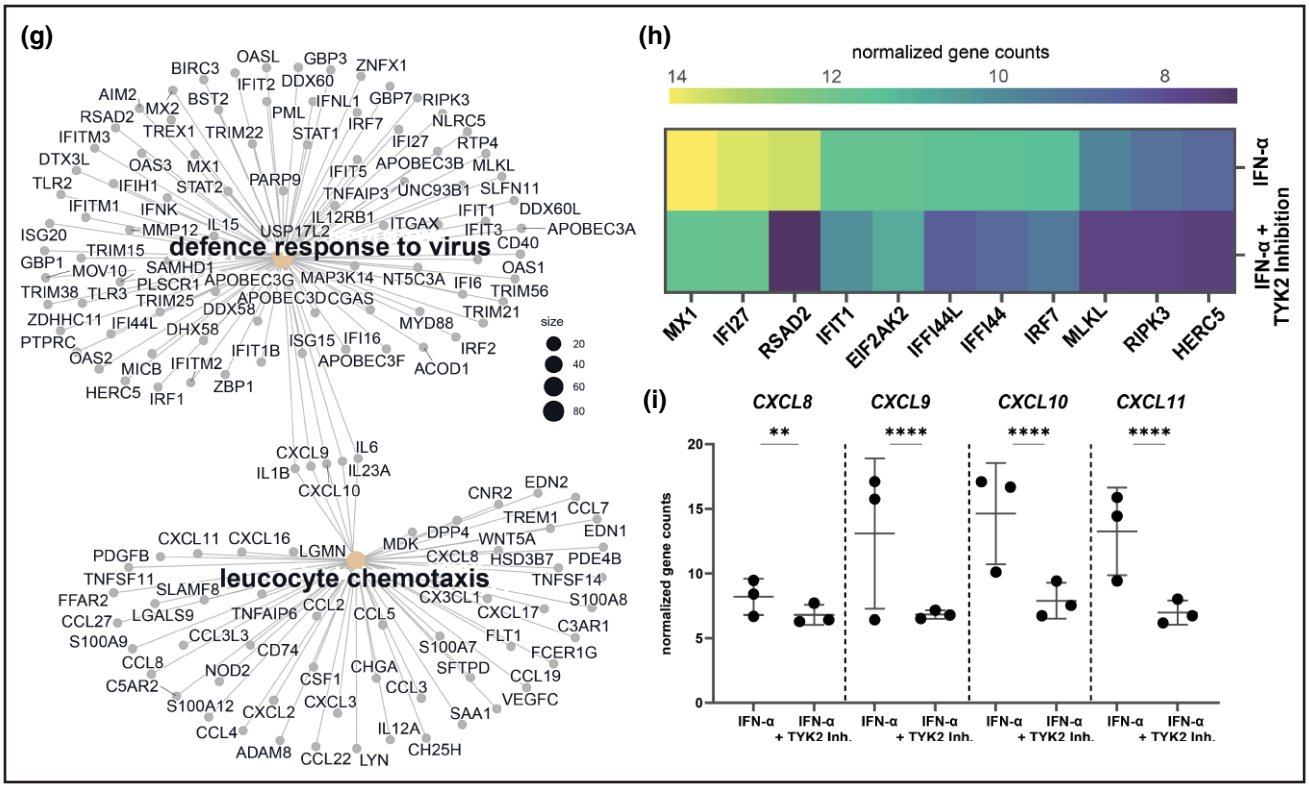

Figure 2 (*Continued*)

a significant reduction in the expression of typical type I IFN response genes (*IFI44*, *IFI44L*, *RSAD2*, *EIF2AK2*, *IFIT1*, *MX1*, *IRF7*). Of note, the expression of *MLKL* and *RIPK3*, two markers of necroptosis – which is known to be involved in interface dermatitis disease and CLE[11] – was also significantly reduced (Figure 4c). In summary, *ex vivo* TYK2 inhibition led to a profound reduction in the type I inflammatory response in human skin biopsies of CLE.

Off-label tyrosine kinase 2 inhibition shows rapid clinical improvement in different cutaneous lupus erythematosus subtypes

Independently of the *in vitro* study, four patients with different subtypes of CLE (SCLE, chilblain, ACLE and CDLE) who were refractory to treatment were treated off-label with 6 mg deucravacitinib once daily (Figure 5a). Of note, all patients were recalcitrant to multiple previous treatments, including hydroxychloroquine, anifrolumab and belimumab. Baseline medication with 200 mg hydroxychloroquine twice daily was continued in all patients, but oral prednisolone was tapered to a maximum of 5 mg once daily and other systemic agents were discontinued with a washout period of at least 4 weeks prior to starting deucravacitinib treatment. A rapid and sustained improvement in clinical symptoms was observed in all patients, at weeks 4 and 12 (Figure 5a). Median Physician Global Assessment score decreased from 3.75 at baseline to 1.33 at week 4 (Figure 5b), and mean Dermatology Life Quality Index score improved drastically within 4 weeks (from 17.8 points at baseline to 6.5 points at week 4; Figure 5c). No adverse events occurred during treatment. A detailed description of the patients' characteristics, including their individual disease courses, can be found in Table S2.

Discussion

Our study found that IFN-α and T-cell-derived cytokines play a pivotal role in CLE pathogenesis and that blocking TYK2 is a promising therapeutic strategy for various CLE subtypes.[33,36] A rapid induction of the inflammatory cascade is presumably driven by IFN-α, which promotes the release of CXCL9/CXCL10, mediating the migration of type I immune cells to the dermoepidermal junction zone via CXCR3.[37] This central inflammatory cascade was sufficiently blocked by TYK2 inhibition. Further, we demonstrated that CLE T cells produce a substantial amount of IFN-γ in response to IFN-α stimulation, which is significantly reduced upon TYK2 inhibition. This is particularly relevant as IFN-γ and TNF-α can induce the necroptosis and apoptosis of keratinocytes.[11] These findings agree with previous reports on single-cell RNAseq of CLE, which found an elevated type I IFN signature in keratinocytes both in lesional and nonlesional skin. Blocking TYK2 in RHE models resulted in a decrease in proinflammatory signals and in a normalization of gene sets associated with keratinocyte differentiation and epidermal formation.[38] Interestingly, epidermal alterations were induced by TCSN but not by IFN-α and could be normalized upon TYK2 inhibition, probably due to modulating the effects of IL-12, IL-13 and IL-22.[23] IL-13 is known to induce epidermal oedema and IL-22 is a potent stimulator of hyper- and parakeratosis in keratinocytes.[39,40] Besides the histological hallmark of interface dermatitis, para- and hyperkeratosis

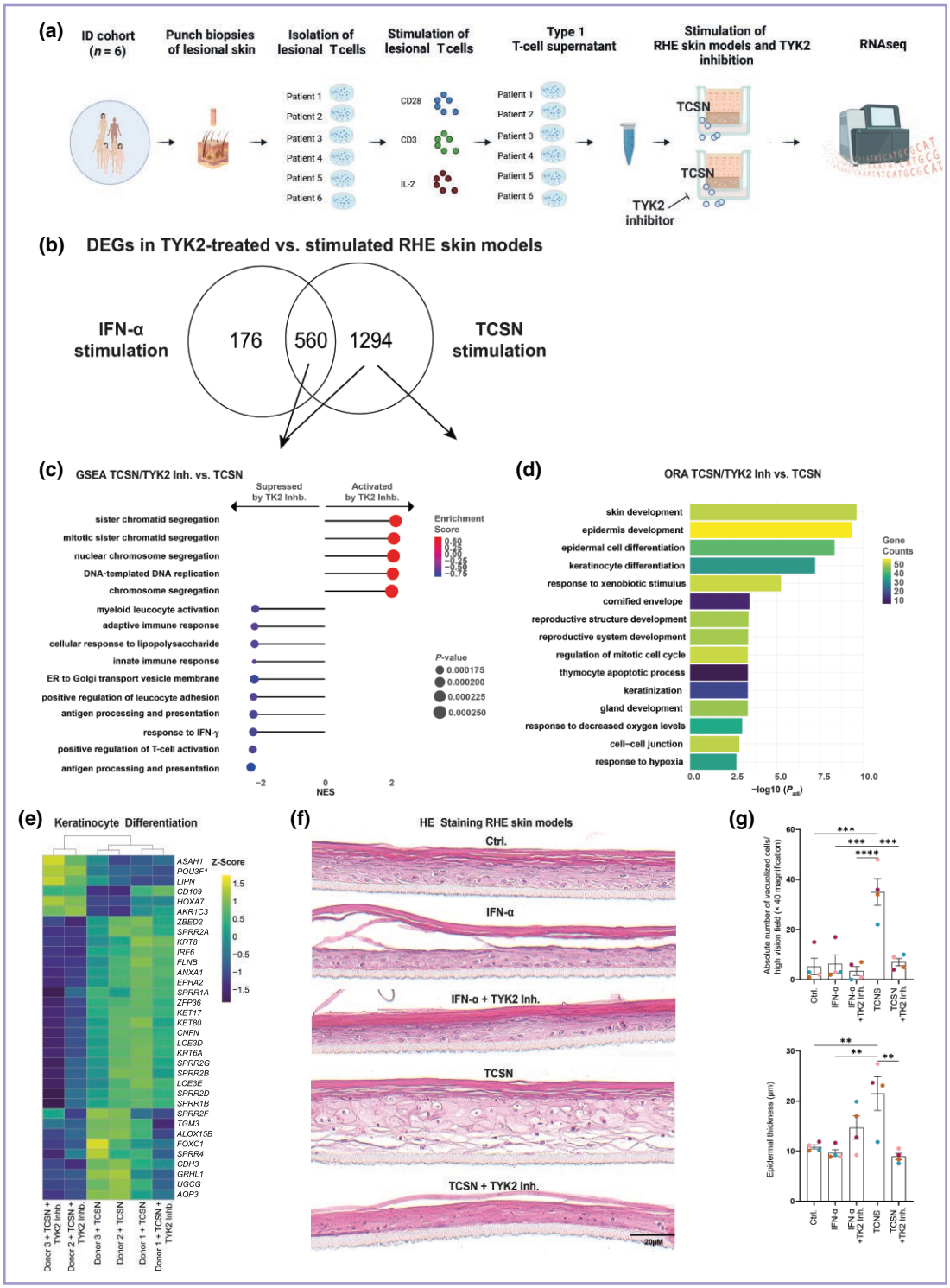

Figure 3 The secretome of lesional T cells contributes to interface dermatitis (ID) and is profoundly inhibited upon tyrosine kinase 2 (TYK2) inhibition. (a) Lesional skin biopsies (6 mm) from patients with ID disease ($n=6$) were collected. Subsequently, lesional T cells were isolated, expanded and stimulated. Lesional T-cell supernatant (TCSN) was collected and reconstructed human epidermis (RHE) skin models were subsequently stimulated with TCSN in the presence or absence of 1 µmol L^{-1} deucravacitinib and subjected to RNA sequencing (RNAseq). (b) RNAseq analysis was performed and differentially expressed genes (DEGs) were calculated (TYK2 + TCSN vs. TCSN). Gene signatures were defined for the TCSN-stimulated models (log2 fold change ≤/≥2, false discovery rate ≤0.05) and compared by Venny. (c) Top 10 downregulated and top 5 upregulated pathways of gene set enrichment analysis (GSEA) for all 1854 DEGs of TCSN/TYK2 inhibitor vs. TCSN gene signature genes. (d) Over-representation analysis (ORA) for the 1294 DEGs only affected by TCSN/TYK2 inhibitor vs. TCSN. (e) Heatmap of genes belonging to 'keratinocyte differentiation'. (f) Haematoxylin and eosin staining of RHE skin models ($n=4$) under the following conditions: control; interferon (IFN)-α (50 ng mL^{-1}); IFN-α + TYK2 inhibitor (1 µmol L^{-1}); type I stimulated TCSN (1 : 10); TCSN (1 : 10) + TYK2 inhibitor (1 µmol L^{-1}). (g) Quantification of vacuolized cells per high vision field (× 40 magnification) and epidermal thickness of the RHE skin models. Ctrl, control; ER, endoplasmic reticulum; IL, interleukin; Inh., inhibition/inhibitor; NES, normalized enrichment score. $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$ (ANOVA).

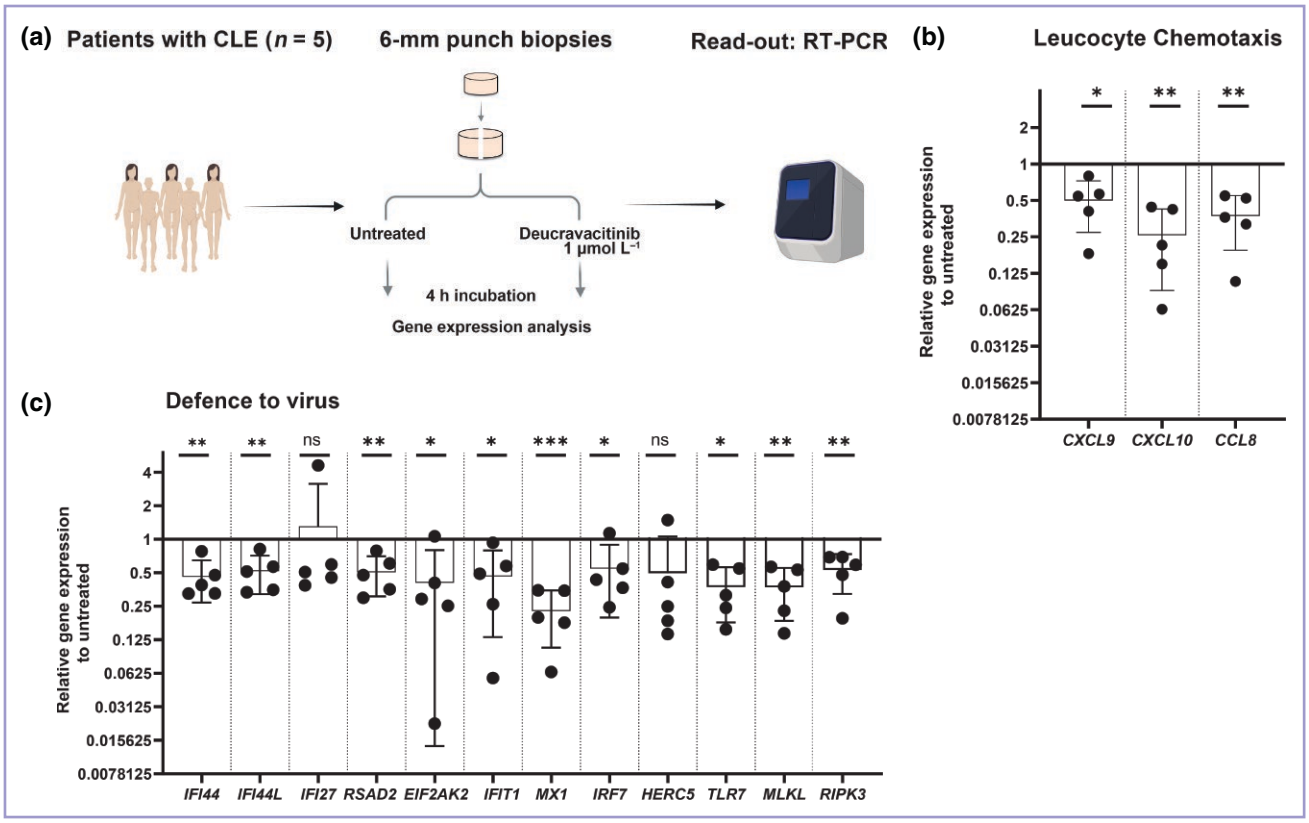

Figure 4 Blocking tyrosine kinase 2 (TYK2) in biopsies from patients with cutaneous lupus erythematosus (CLE) significantly reduces chemoattractant and inflammatory signature genes. (a) Lesional skin biopsies (6 mm) from five patients with cutaneous skin lesions were obtained and equally divided. One half was incubated with 1 µmol L^{-1} of the TYK2 inhibitor deucravacitinib for 4 h, while the other half was left untreated. Subsequently, gene expression was analysed by real-time polymerase chain reaction (RT-PCR). (b, c) Relative gene expression of genes associated with (b) leucocyte chemotaxis and (c) virus defence in deucravacitinib-treated biopsies vs. untreated skin. ns, not significant ($P > 0.05$). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

– but not oedema – represent epidermal alterations seen in CLE.[41] IL-22 exhibits an enhanced proinflammatory effect on keratinocytes, following their activation by IFN-α, and TYK2 inhibition suppresses IL-22 signalling but has limited effects on IL-13.[23,42] Further, elevated levels of IL-12 and IL-23 have been found in patients with CLE. The initial results of a phase II study with ustekinumab (anti-IL-12/23) indicated a significant reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI).[9,43] However, the subsequent phase III study failed to demonstrate superiority over placebo,[44] indicating that these cytokines do not play a central role in CLE pathogenesis. There have been reports of belimumab, a monoclonal antibody against the B-cell activator BlyS, approved for the treatment of SLE, having positive effects on CLE lesions, but the first cutaneous improvements were observed rather late, at week 20.[45]

Recently, a phase II study of deucravacitinib demonstrated an improvement of skin lesions in patients with SLE; 69.6% of patients receiving deucravacitinib (3 mg twice daily) achieved a ≥ 50% improvement in CLASI vs. 16.7% in the placebo group.[46] Further, there are positive case reports of deucravacitinib use in patients with DLE, tumid LE and SCLE.[47–50] A phase II study of CLE is currently recruiting patients.[28] In agreement with the literature, we found a rapid clinical improvement in patients with CLE treated with deucravacitinib (i.e. within a few weeks), including poorly investigated CLE subtypes such as chilblain lupus. The rapid improvement suggests that the type I IFN axis and T-cell-mediated inflammation together represent two central inflammatory pathways in the pathogenesis of CLE.

In summary, our data show that TYK2 inhibition exhibits a dual mode of action by simultaneously inhibiting the signalling of IFN-α and other relevant cytokines in the lesional T-cell infiltrate, providing a rationale for further clinical development of deucravacitinib in CLE.

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Conflicts of interest

F.L. has been an advisor for and/or received speaker's honoraria and/or received grants and/or participated in clinical trials for the following companies: AbbVie, Almirall, Amgen,

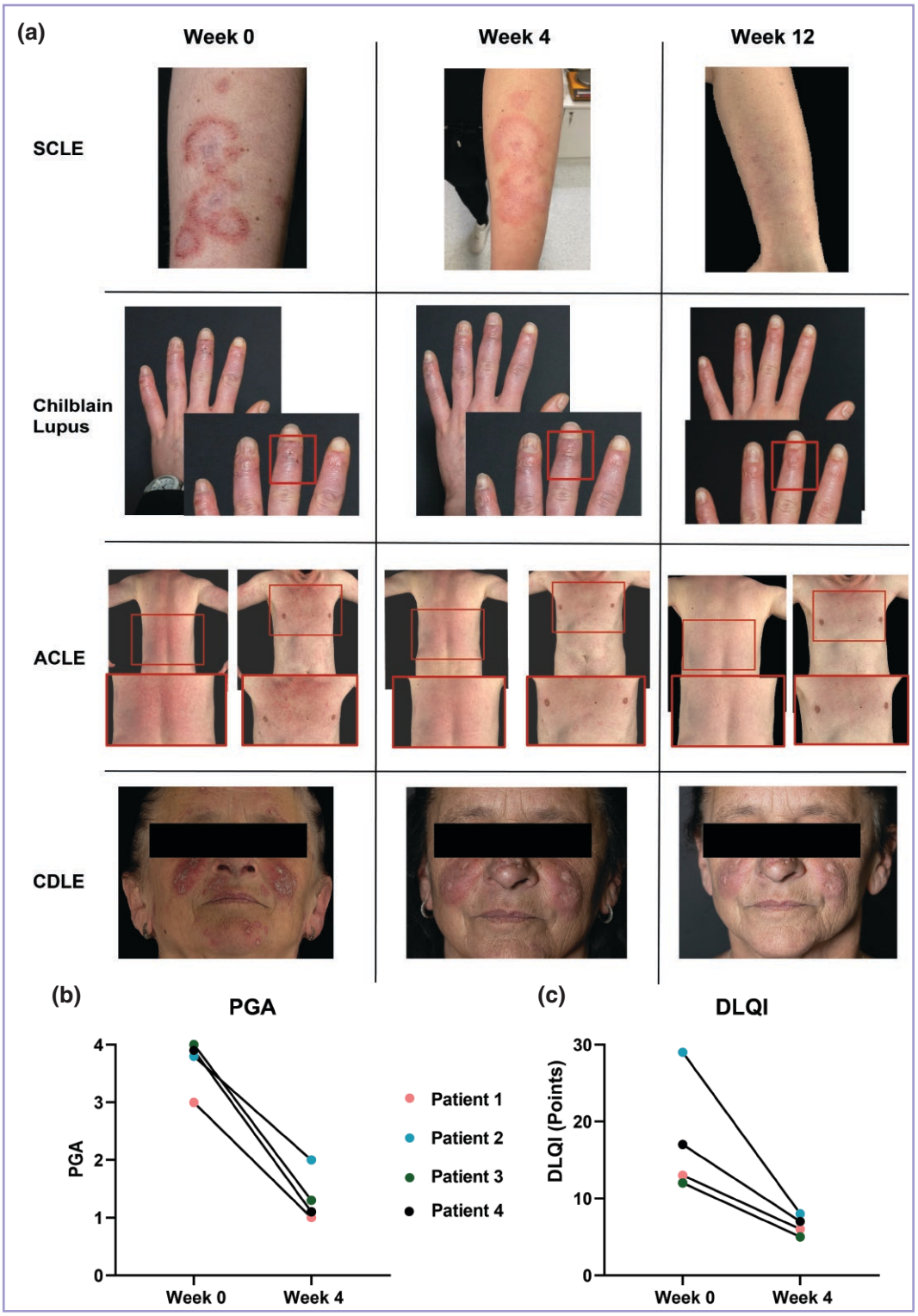

Figure 5 Off-label tyrosine kinase 2 (TYK2) inhibition shows rapid clinical improvement in different forms of cutaneous lupus erythematosus (CLE). (a–c) Four patients with treatment-resistant cutaneous forms of lupus erythematosus [subacute CLE (SCLE), chilblain, acute CLE (ACLE) and chronic discoid CLE (CDLE)] were treated with 6 mg deucravacitinib once daily. (a) Skin lesions, (b) Physician Global Assessment [PGA (0–4; 0=clear, 1=almost clear; 3=moderate; 4=severe)] and (c) Dermatology Life Quality Index [DLQI (0–30; 0=no impact, 30=severe negative impact on quality of life)] before (week 0), and 4 and 12 weeks after the start of treatment.

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Data availability

All data are available in the main text or the Supporting Information, or can be requested by contacting the corresponding author.

Ethics statement

The study design was approved by a local ethics committee (Klinikum Rechts der Isar, 44/16 S, 5590/12, 2023-21-S-SR).

Patient consent

Written informed consent was obtained from every patient for publication of anonymized clinical data and images.

AI disclosure

Text editing, language and grammar correction were assisted by DeepL and ChatGPT4. All content originally derived from the authors.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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