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LEADING ARTICLE

Targeting IL-36 in Inflammatory Skin Diseases

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Abstract
Interleukin (IL)-36 cytokines are members of the IL-1 superfamily of cytokines. IL-36 cytokines are composed of three agonists (IL-36α, IL-36β, and IL-36γ) and two antagonists (IL-36 receptor antagonist [IL36Ra] and IL-38). These work in innate and acquired immunity and are known to contribute to host defense and to the pathogenesis of autoinflammatory diseases, autoimmune diseases, and infectious diseases. In the skin, IL-36α and IL-36γ are mainly expressed by keratinocytes in the epidermis, although they are also produced by dendritic cells, macrophages, endothelial cells, and dermal fibroblasts. IL-36 cytokines participate in the first-line defense of the skin against various exogenous assaults. IL-36 cytokines play significant roles in the host defense system and in the regulation of inflammatory pathways in the skin, collaborating with other cytokines/chemokines and immune-related molecules. Thus, numerous studies have shown IL-36 cytokines to play important roles in the pathogenesis of various skin diseases. In this context, the clinical efficacy and safety profiles of anti-IL-36 agents such as spesolimab and imsidolimab have been evaluated in patients with generalized pustular psoriasis, palmoplantar pustulosis, hidradenitis suppurativa, acne/acneiform eruptions, ichthyoses, and atopic dermatitis. This article comprehensively summarizes the roles played by IL-36 cytokines in the pathogenesis and pathophysiology of various skin diseases and summarizes the current state of research on therapeutic agents that target IL-36 cytokine pathways.

Key Points

Interleukin (IL)-36 cytokines play essential roles in the skin with regard to regulation of immunity, both innate and adaptive, as well as allergic reactions, through the T-helper (Th)-1 and Th-17 inflammatory pathways.

IL-36 cytokine pathways are closely associated with the pathogeneses and pathophysiologies of various inflammatory skin diseases.

In recent years, the efficacy and safety of anti-IL-36 pathway agents have been studied for numerous skin diseases, including those mentioned above. As a result, new drugs such as spesolimab have recently been approved, which provides a positive outlook for patients affected with such diseases.

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1 Introduction

Interleukin (IL)-36 cytokines (IL-36α, β and γ; IL-36 receptor antagonist [IL36Ra]; and IL-38) are members of the IL-1 superfamily of cytokines. IL-1 family cytokines work in innate and acquired immunity and to pathogeneses of autoinflammatory diseases, autoimmune diseases, infectious diseases, and cancers [1]. IL-1 family cytokines are classified into three subfamilies—IL-1, IL-18, and IL-36—by the lengths of their propeptide precursors (approximately 270, 190, and 150 amino acids, respectively) [2, 3]. IL-36 cytokines were first recognized in silico about 20 years ago [4]. The IL-36 subfamily is made up of three agonists (IL-36α, β, and γ) and two antagonists (IL36Ra and IL-38) [4]. The N-terminal cleavage of propeptides is required for the maturation of IL-36 subfamily members. When the N-terminus of the propeptides of IL-36 subfamily members cleave, mature cytokines can bind to their receptors and work as agonists and antagonists [2].

IL-36 cytokines play important roles in the regulation of innate immunity. The excessive expression and activation of the three agonists with proinflammatory functions, IL-36α, β, and γ, lead to pathogenic inflammatory

reactions, such as those seen in pustular psoriasis [5]. IL-36 cytokines are predominantly produced by epithelial and immune cells. All IL-36 subfamily members share an identical receptor complex—the IL-36 receptor (IL-36R) [6].

As mentioned above, IL-36 cytokines are secreted as precursor proteins and need N-terminal cleavage to gain their significant proinflammatory functions [7]. Cleavage and activation are performed by a number of proteases, including cathepsin G, proteinase 3, and elastase, which are derived from neutrophils, and by cathepsin S, which is released from keratinocytes and fibroblasts [8–12]. The proteases released from neutrophils are contained in neutrophil extracellular traps (NETs) [10]. Protease inhibitors derived from keratinocytes control the IL-36-mediated inflammatory pathway. α1-antitrypsin, encoded by *SERPINA1*, and α1-antichymotrypsin, encoded by *SERPINA3*, inhibit neutrophil elastase and cathepsin G, respectively, and prevent the processing of IL-36 cytokines [13].

Recently, the upregulation of IL-36 signaling due to the increased expression of IL-36 family cytokines, IL36Ra insufficiency, and the decreased activity of SERPINA3 and myeloperoxidase (MPO) have been reported to play important roles in various inflammatory skin diseases. Naturally, there has been renewed interest in studying drugs targeting these pathways, and a recent major event was the approval of spesolimab for the treatment of generalized pustular psoriasis (GPP). This review summarizes the roles of IL-36 signaling in inflammatory skin diseases and discuss the potential of various treatments for cutaneous inflammatory disorders targeting IL-36 pathways.

2 The Function of Interleukin (IL)-36 and the Roles of IL-36 Signaling in the Skin

Among the IL-36 subfamily members, three splice variants of IL-36 (IL-36α, β, and γ) are powerful proinflammatory cytokines that are predominantly expressed at barrier sites of the body, including the skin, bronchus, and intestines [14].

In the integument, IL-36α and γ are mainly expressed by keratinocytes in the epidermis, although they are also produced by endothelial cells, dermal fibroblasts, Langerhans cells, dermal dendritic cells, and macrophages [6, 15, 16]. Furthermore, for two of the antagonists in the IL-36 subfamily (IL-36Ra and IL-38), keratinocytes are also major producers among cells that constitute the skin [5]. IL-36 cytokine production is stimulated by agonists for toll-like receptors, pro-inflammatory cytokines including TNF-α, IL-1β, and IL-17, and IL-36 cytokines themselves [17].

IL-36α, β, and γ bind to the heterodimeric receptor complex of the IL-36R and the IL-1 receptor accessory protein (IL-1RAcP), where they work as agonists triggering downstream signal transduction via an adaptor protein complex, myeloid differentiation factor 88 (MyD88), nuclear factor-κB (NF-κB), and mitogen-activated protein kinase (MAPK), thereby promoting pro-inflammatory responses in keratinocytes, macrophages, dendritic cells, diverse T-cell subsets, fibroblasts, and endothelial cells [18, 19].

IL36Ra and IL-38 also bind to the receptor complex of IL-36R and IL-1RAcP, where they conversely work as antagonists, inhibiting downstream signaling and showing anti-inflammatory effects [20].

IL-36 cytokines participate in the first-line defense of the skin against various exogenous attacks [21]. IL-36 cytokines play important roles in cross-talk between innate and adaptive immunity, interacting with various pathways, including the Th-1 and Th-17 axes [22]. Furthermore, IL-36 cytokines have been reported to participate in the regulation of allergic reactions [4].

Mature IL-36α, β, and γ promote the production of pro-inflammatory cytokines, chemokines, and related molecules including IL-1β, TNF-α, IL-6, IL-12, and IL-23 by dendritic cells and by activated $CD4^+$ T cells [23]. In addition, activated IL-36α, β, and γ induce T-cell proliferation and Th-1 and Th-17 cell differentiation. Cytokines released from skin-infiltrating Th-1 cells and Th-17 cells additionally promote the inflammatory loop in the skin by stimulating keratinocytes to produce IL-36 cytokines and other molecules with pro-inflammatory functions, including TNF-α, IL-6, and CXCL8 (IL-8) [24]. Furthermore, IL-36α, β, and γ give signals to keratinocytes in an autocrine manner, inducing the further release from keratinocytes of pro-inflammatory cytokines, neutrophil-attracting chemokines (CXCL1, CXCL2, and CXCL8 (IL-8)), and antimicrobial peptides [25, 26] (Fig. 1).

Neutrophils do not express IL-36R. However, IL-36α, β, and γ contribute indirectly to neutrophil activation. IL-36α, β, and γ show a robust potential to attract neutrophils to the skin by stimulating keratinocytes to release neutrophil chemoattractants [27]. Conversely, neutrophil-derived proteases cleave IL-36 precursor proteins, converting them to mature, highly active IL-36α, β, and γ [8]. Neutrophil infiltration is thought to be a significant factor in the acceleration of IL-36-driven skin inflammation; conversely, IL-36α, β, and γ might play significant roles in the pathogeneses of neutrophil-associated skin disorders [28].

In addition to activating epidermal keratinocytes, IL-36α, β, and γ are known to activate various immune cells expressing the IL-36R complex in the skin, i.e., Langerhans cells, dermal $CD1a^+$ dendritic cells and macrophages. Macrophages stimulated by IL-36γ release large amounts of TNF-α and IL-23, which activate endothelial cells, resulting in the accelerated adherence of monocytes [29]. Conversely, activated monocytes release high levels of IL-23, stimulating the IL-17/IL-23 pathway [29]. Furthermore, M2

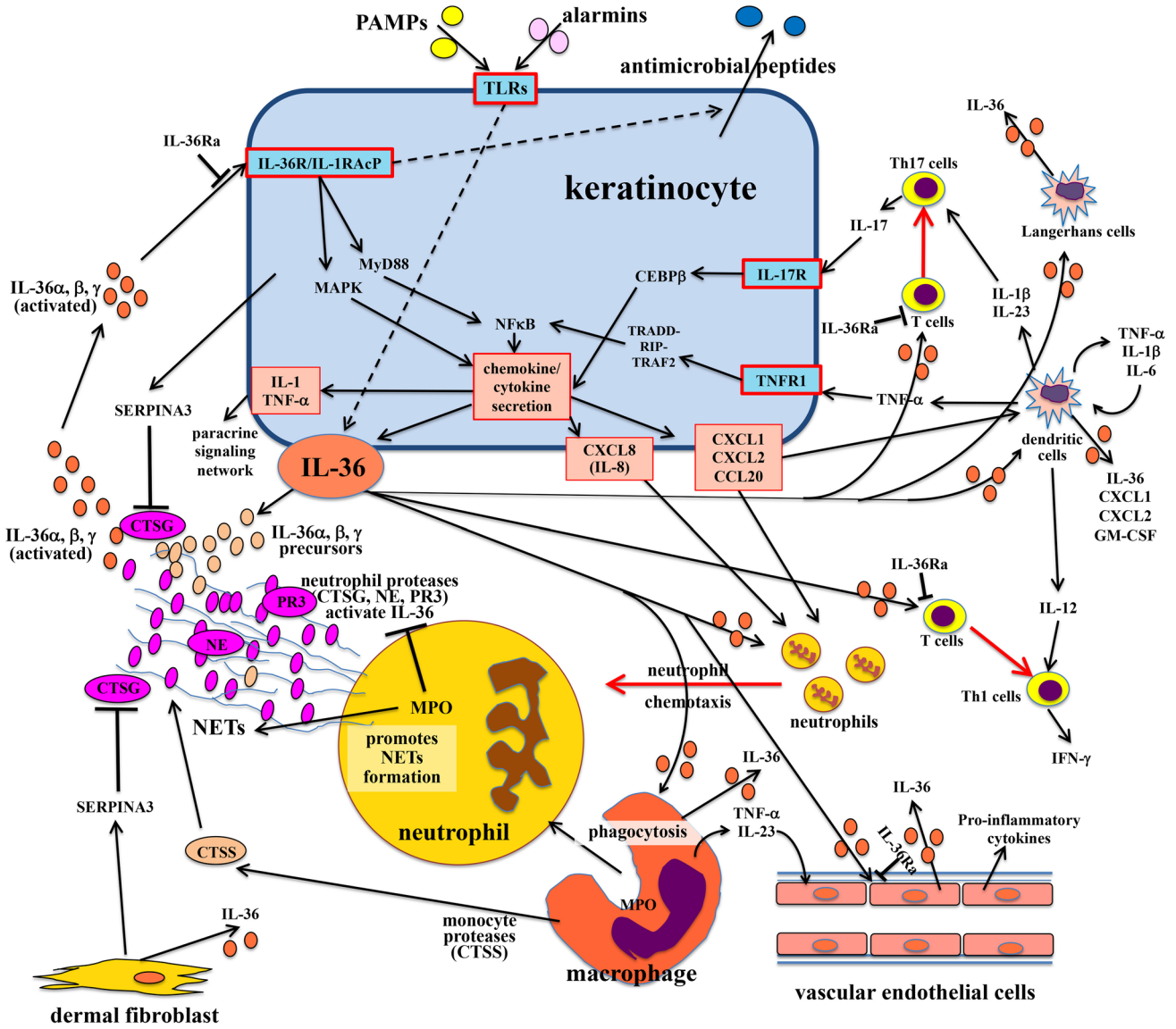

Fig. 1 Inflammatory pathways and factors involved in IL-36-associated inflammation in the skin. IL-36α and γ are predominantly produced by keratinocytes in the skin, although IL-36 cytokines are also expressed by Langerhans cells, dermal dendritic cells, macrophages endothelial cells, and dermal fibroblasts. IL-36 cytokines bind to the receptor complex of IL-36R/IL-1RAcP and induce downstream signal transduction via MyD88, NF-κB, and MAPK to provoke pro-inflammatory responses in keratinocytes, macrophages, dendritic cells, T cells, dermal fibroblasts, and endothelial cells. IL36Ra also binds to IL-36R/IL-1RAcP, but works as antagonists, inhibiting downstream signaling and exhibiting anti-inflammatory effects. IL-36 signaling accelerates the paracrine cytokine/chemokine signaling network in the epidermis and the superficial dermis, and mediates innate and adaptive immunity, as well as host defense mechanisms and allergic reactions in the skin. IL-36 signaling promotes the secretion by keratinocytes of the chemokines/cytokines IL-36, IL-8, CXCL1, CXCL2, and CCL20. These chemokines/cytokines induce the activation of dendritic cells and neutrophils in the skin. IL-36 precursors are cleaved and activated by various proteases, including CTSG, PR3, and NE, which are released from neutrophils, and by CTSS, which is secreted from keratinocytes and fibroblasts. SERPINA3 inhibits CTSG activity, resulting in the downregulation of processing of IL-36 precursors to maturation. MPO inhibits neutrophil proteases and promotes NET formation, resulting in a decrease of soluble proteases that leads to the decreased activation of IL-36 precursors. Black arrows represent secretion or activation; red arrows represent cell differentiation or chemotaxis; ⊥ represents inhibition; and dotted arrows represent indirect upregulation. *IL* interleukin, *MyD88* myeloid differentiation factor 88, *NF-κB* nuclear factor-κB, *MAPK* mitogen-activated protein kinase, *IL-36R* interleukin-36 receptor, *PAMPs* pathogen-associated molecular patterns, *TLRs* toll-like receptors, *CTSG* cathepsin G, *PR3* proteinase 3, *NE* neutrophil elastase, *CTSS* cathepsin S, *MPO* myeloperoxidase, *SERPINA3* serine protease inhibitor A3, *TNF* tumor necrosis factor, *NETs* neutrophil extracellular traps, *Th* T-helper, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *CXCL* chemokine C-X-C ligand, *CCL20* chemokine ligand 20, *CEBPβ* CCAAT/enhancer-binding protein beta, *TRADD* tumour necrosis factor receptor-associated death domain, *RIP* receptor-interacting protein, *TRAF2* tumour necrosis factor receptor-associated factor 2

macrophages are converted to M1 macrophages that produce proinflammatory cytokines [23].

As described above, IL-36 cytokines play significant roles in the host defense system and inflammatory processes in the skin [30], collaborating with other cytokines/chemokines and immune-related molecules and regulating multiple inflammatory pathways.

3 The Role of IL-36 Signaling in Inflammatory Skin Diseases

The IL-36 axis is an important component of the inflammatory process in the skin, and their roles in various inflammatory skin disorders are summarized as follows (Table 1).

3.1 Pustular Psoriasis

Pustular psoriasis, especially GPP, is considered to be a representative disorder of autoinflammatory keratinization diseases (AiKDs) [31, 32]. Pustular psoriasis is divided into generalized and localized forms [33]. The generalized forms consist of GPP and annular pustular psoriasis; the localized forms include acrodermatitis continua of Hallopeau (ACH) and palmoplantar pustular psoriasis (PPPP).

GPP is the most severe subtype of pustular psoriasis and is characterized by diffuse, widely distributed erythema and sterile pustules with high fever and general malaise. Impetigo herpetiformis (IH) is a pregnancy-induced GPP. ACH, a subtype of localized pustular psoriasis, shows pustules and erythema on the acral regions, typically on the tips of the fingers and toes.

Mutations/variants of five molecules—IL36Ra [34], caspase recruitment domain family member 14 (CARD14) [35, 36], adaptor-related protein complex 1, sigma-3 subunit (AP1S3) [37], MPO [38], and serine protease inhibitor A3 (SERPINA3) [39]—that are related to autoinflammation have been recently recognized as predisposing factors for pustular psoriasis. IL-36 cytokines are closely associated with the recently clarified pathomechanisms of pustular psoriasis due to mutations/variants of these five molecules.

Loss-of-function mutations in *IL36RN*, which encodes IL36Ra, an anti-inflammatory cytokine in the IL-36 cytokine family, are the most significant genetic defects causative of pustular psoriasis [40]. They lead to the deficiency of IL36Ra, resulting in the hyperactivation of IL-36 signals, the acceleration of downstream immune responses including innate immune reactions, and the occurrence of pustular psoriasis [33]. In the subtypes of pustular psoriasis, mutations in *IL36RN* are much more prevalent in cases of GPP (23.7%) and ACH (17.4%) than in cases of PPPP (5.1%) [41]. It is noteworthy that early-onset GPP patients without concomitant psoriasis vulgaris frequently harbor *IL36RN* mutations [41–44]. GPP patients carrying *IL36RN* mutations are thought to have a more severe autoinflammatory phenotype, showing a high risk of systemic involvement [45].

In *AP1S3*, which encodes the adaptor-related protein complex 1, sigma-3 subunit (AP1S3), variants have been detected in patients with GPP, ACH, and PPPP [37, 40, 41, 46]. It was revealed that *AP1S3* loss-of-function mutations cause defective autophagy and the excessive accumulation of p62 in keratinocytes [46]. As p62 activates NFκB, the abnormal accumulation of p62 leads to NFκB hyperactivation, resulting in the upregulated secretion of IL-36α from keratinocytes, contributing to the development of pustular psoriasis [46].

Haskamp et al. [38] revealed loss-of-function variants in *MPO* among GPP, ACH, and AGEP cases, and MPO deficiency was suggested to contribute to GPP susceptibility. Three neutrophil serine proteases—cathepsin G (CTSG), elastase (NE), and proteinase 3 (PR3)—and one monocytic protease—cathepsin S (CTSS)—cleave IL-36 precursors and activate IL-36α, β and γ. Neutrophil serine proteases have been shown to have increased activity in neutrophils with MPO deficiency due to *MPO* loss-of-function variants in pustular psoriasis patients [38]. In addition, NET formation is decreased in MPO-deficient neutrophils, leading to increases in soluble neutrophil proteases which proteolyze IL-36 precursors more efficiently than NET-bound neutrophil proteases do [38]. By these mechanisms, loss-of-function variants in *MPO* are considered to cause the hyperactivation of IL-36 and to generate pustular psoriasis [38].

SERPINA3, encoded by *SERPINA3*, inhibits various proteases, of which CTSG, a neutrophil serine protease, is most effectively inhibited. It is speculated that the loss of function of SERPINA3 might cause the insufficient inhibition of CTSG, resulting in excessive IL-36 activation [39].

In this context, IL-36 pathways are significant drivers of inflammatory responses including autoinflammation in the pathophysiology of pustular psoriasis associated with variants in the five known pathogenesis-related genes (*IL36RN*, *CARD14*, *AP1S3, MPO,* and *SERPINA3*). IL-36 cytokine hyperactivation induces neutrophil chemotaxis, neutrophil-driven inflammatory responses, and the hyperactivation of innate immunity. These processes suggest that pustular psoriasis predominantly has innate immune inflammation, including the activation of the IL-36 axis, as an AiKD [13, 47].

3.2 Plaque Psoriasis (Psoriasis Vulgaris)

The upregulated expression of the three IL-36 cytokines IL-36α, β, and γ has been reported in the serum and skin of plaque psoriasis patients, showing a positive correlation with disease severity [5, 15, 48]. In addition, IL-38 levels are

Table 1 Inflammatory skin diseases associated with IL-36 pathways

Skin inflammatory disease	Clinical manifestations	Key events or abnormalities	Involved inflammatory pathways and factors
Generalized pustular psoriasis (GPP)	Generalized diffuse erythema and sterile pustules with high fever and malaise	Neutrophilic pustules in the epidermis	IL-36, IL-8 CXCL1, CXCL2, CCL20 TNFα, IL-17
Localized pustular psoriasis	Pustules and erythema on the acral regions, mainly on the tips of the fingers and toes (ACH) or on the palms and soles (PPPP)	Neutrophilic pustules in the epidermis	IL-36, IL-8 CXCL1, CXCL2, CCL20 TNFα, IL-17
Plaque psoriasis	Hyperkeratotic erythematous plaques scattered on the whole body	Accelerated turnover of epidermal keratinocytes, mixed inflammatory infiltration in the epidermis and dermis	IL-17, IL-23, TNFα IL-36
Palmoplantar pustulosis (PPP)	Vesicles and sterile pustules on the palms and soles	Vesicular formation and neutrophil accumulation in and around the acrosyringium	IL-36, IL-17, IL-22, IL-8, LL37, IL-1α, IL-1β
Acute generalized exanthematous pustulosis (AGEP)	Drug-induced generalized diffuse erythema and sterile pustules	T-cell stimulation by causative drugs, induction of IL-18 production	IL-36, IL-8, IL-17, IL-22
Hidradenitis suppurative		Keratin plug formation, hair follicle occlusion	IL-17, IL-18, G-CSF IL-8, IL-36 various genetic autoinflammatory factors (γ-secretase complex, *MEFV, NOD2, LPIN2, NLRP3, NLRP12, PSMB8, MVK, IL1RN*)
Ichthyosis	Hyperkeratotic erythema and scales on most of the body surface	Barrier defects, thickening of the stratum corneum	IL-17, IL-36 activation of innate immunity (IL-1β, IL-8, type I IFN)
Atopic dermatitis	Widespread chronic recurrent eczema and pruritis	Acute and chronic eczematous reactions	IL-4, IL-13, IL-31, IL-36
Acne/acneiform eruption	Comedones, inflammatory papules and pustules mainly on the face, upper back, and chest	Follicular hyperkeratinization, hypersecretion of sebum, *Cutibacterium acnes* infection	IL-36, IL-8, EGFR inhibitor, MEK inhibitor, KLF4, *Cutibacterium acnes*

ACH acrodermatitis continua of Hallopeau, *PPPP* palmoplantar pustular psoriasis, *IL* interleukin, *TNF* tumor necrosis factor, *CXCL* chemokine C-X-C ligand, *CCL20* chemokine ligand 20, *EGFR* epidermal growth factor receptor, *G-CSF* granulocyte colony-stimulating factor, *IFN* interferon

low in the skin and blood of patients with plaque psoriasis, indicating the activation of the IL-36 axis [49].

In plaque psoriasis, IL-36 cytokines are known to affect the processes of epidermal keratinization by influencing keratinocytes through the induction of Th-17 and Th-1 cytokine production by dendritic cells and macrophages [6]. The IL-36 pathway also contributes to neutrophil recruitment in plaque psoriasis.

IL-36 cytokines accelerate cutaneous inflammation in psoriasis by promoting leukocyte chemotaxis and angiogenesis. IL-36γ stimulates dermal endothelial cells to release increased levels of IL-6, CXCL1, CXCL8, and CCL20 [49]. IL-36α and IL-36γ enhance the production by keratinocytes of various growth factors, including vascular endothelial growth factor (VEGF)-A and heparin-binding EGF-like growth factor (HB-EGF) [49]. These factors act on fibroblasts and vascular endothelial cells, resulting in their increased proliferation and the branching of vascular structures [29, 49].

In addition, the IL-36 pathway enhances the activation of Toll-like-receptor (TLR)-9 and the production of IFN-α, promoting systemic inflammatory reactions in psoriasis [50]. Furthermore, large numbers of NETosis cells were reported to be seen in the peripheral blood of patients with psoriasis, and the NETosis cell count was found to correlate with psoriasis disease severity [51]. The NETosis of neutrophils produces NETs, which play important roles in the activation of macrophages, which in turn secrete IL-36 cytokines in psoriasis [8, 10]. In IL36Ra-deficient psoriasis model mice, NETs were reported to be induced, which in turn led to an increase of IL-36 cytokines within psoriatic lesional areas [52].

3.3 Palmoplantar Pustulosis (PPP)

Palmoplantar pustulosis (PPP) shows multiple pustular lesions restricted to the palms and soles. PPP comprises of two subtypes [53]. In Type A PPP, vesicular eruptions appear prior to pustule formation; in Type B PPP, no vesicles are seen [53]. Type B PPP is thought to be a variant of pustular psoriasis related to PPPP [53].

Limited information exists on the roles of IL-36 cytokines in the pathogenesis of PPP. The expressions of IL-36γ mRNA and protein were reported to be upregulated significantly in skin lesions of PPP compared with control skin samples [54]. In contrast, IL-36Ra protein expression levels in PPP were similar to those in healthy skin controls, although IL-36Ra mRNA expression was obviously upregulated in PPP lesions compared with healthy skin control samples [54]. IL-8 mRNA and protein were increased in skin lesions of PPP, and the increase might have been induced by IL-36γ overexpression [54]. Furthermore, IL-36γ immunostaining was observed in keratinocytes surrounding pustular lesions of PPP and in the sweat ducts of the dermis, and IL-8 immunostaining was seen in neutrophils infiltrating the pustular lesions of PPP [54].

3.4 Acute Generalized Exanthematous Pustulosis (AGEP)

AGEP is a severe drug eruption that shows similar clinical and histopathological findings to those of GPP [55, 56]. IL-36 cytokines are thought to play a role in the pathogenesis of AGEP [55, 56]. IL-36γ levels are significantly upregulated in the epidermis in AGEP [57]. It was demonstrated that certain causative drugs, including penicillin- and macrolide-type antibiotics, antifungals, and diuretics (among others), cause drug-specific IL-36γ overexpression, which results in the production of IL-8 by macrophages and T-cells, and the subsequent neutrophil infiltration in AGEP skin lesions [57]. A case with AGEP caused by dihydrocodeine phosphate was reported to have a heterozygous *IL36RN* mutation [58]. Furthermore, biallelic *MPO* mutations were found in two AGEP cases [59].

3.5 Hidradenitis Suppurativa (HS)

In HS lesions, it is mainly the keratinocytes that secrete IL-36 cytokines [21]. IL-36 cytokines secreted from keratinocytes induce the production by dendritic cells of pro-inflammatory cytokines including IL-12 and IL-23, and these pro-inflammatory cytokines promote Th-1 and Th-17 axis responses. Activated IL-36γ was reported to induce hyperkeratosis and psoriasiform changes in a model of the human epidermis that showed pathological characteristics similar to those of early HS [60, 61].

IL-36γ activates NF-κB in keratinocytes, resulting in IL-8 secretion from keratinocytes and neutrophil recruitment in the inflammatory lesions of HS. Then, dendritic cells secrete IL-36 cytokines, forming an autocrine loop that amplifies inflammation in HS lesions [62]. Significantly increased expressions of mRNA and protein of IL-36α, β, and γ were reported in both skin lesions and serum samples in HS patients, compared with those in healthy controls [62–64]. In contrast, it was reported that IL-36Ra expression was not increased in HS lesions [64, 65]. Thus, the imbalance in expression of IL-36 cytokines and IL-36Ra might play an important role in the pathogenesis of HS.

In addition, IL-36 cytokines were reported to induce increases in G-CSF levels [66]. The upregulated G-CSF is thought to work in the recruitment and survival of neutrophils in HS lesions [66]. From these data, IL-36 cytokines are considered to play important roles in mutual interactions between keratinocytes and immune cells, contributing to the pathogenesis of HS [62].

The NCSTN/MAPK/KLF4 pathway and bacterial factors are assumed to account for the upregulation of IL-36 cytokine expression and the hyperactivation of IL-36 cytokines in HS lesions. Concerning the association between the genetic predisposing factors for HS and IL-36 cytokines, the expression level of IL-36α is upregulated in the epidermis of NCSTN knockout mice [67]. Cathepsin S is known to cleave and to activate IL-36γ [61]. Thus, the elevated expression of cathepsin S in HS lesions might also play a significant role in IL-36γ activation in the early stage of HS development [64].

3.6 Ichthyosis

Inherited ichthyoses are a group of genetic keratinization disorders showing hyperkeratosis and scales over almost the entire skin. Until recently, ichthyosis phenotypes had been considered to be caused mostly by abnormalities in the skin keratinization system and the resultant skin barrier defects. Immune profiling was performed in patients with four major ichthyotic subtypes: congenital ichthyosiform erythroderma (CIE), lamellar ichthyosis (LI), epidermolytic ichthyosis (EI), and Netherton's syndrome (NS) [68, 69].

Malik et al. [70] showed the increased expressions of mRNA and protein of IL-36 cytokines and IL-36R in these four major subtypes of ichthyosis (CIE, LI, EI and NS). The upregulated expression levels of IL-36 cytokines and IL-36R were found to significantly correlate with ichthyosis severity and increased transepidermal water loss (TEWL) as an indicator of skin barrier defects [70]. These data and other studies [71–74] further suggest the involvement of IL-36 cytokines and IL-36R in the Th-17 axis in the ichthyoses. In NS patients, those with ichthyosis linearis circumflexa and those with scaly erythroderma ichthyosis showed the activation of the IL-17 and IL-36 axes in skin lesions and peripheral blood [75].

3.7 Atopic Dermatitis

In atopic dermatitis patients, mRNA expressions of IL-36α and γ were significantly upregulated in eczematous skin regions compared with those in non-eczematous, but the IL-36α and γ protein levels were not significantly increased [76, 77]. IL-36γ is thought to work in the progression of atopic dermatitis from the acute phase to the chronic phase [78], although the exact mechanism for this remains unclear. However, one explanation for these results could be that repeated trauma from scratching, a key factor in the acute-to-chronic progression, induces upregulation of mRNA. Subsequently, protein levels gradually increase, as the lesion turns chronic. Acute lesions were studied, hence why only mRNA levels were increased; should one study chronic eczematous lesions in detail, significantly upregulated IL-36α and γ protein levels are to be expected.

Staphylococcus aureus is found in about 70% of the affected skin regions in patients with atopic dermatitis and is well known as an atopic dermatitis-associated bacterium [79]. *S. aureus*-driven immune responses are considered to be associated with the pathogenesis of atopic dermatitis.

Liu et al. [80] reported that epicutaneous *S. aureus* exposure induces IL-36α expression and promotes IL-36R/MyD88 pathway-mediated IL-17 production by T cells, resulting in skin inflammation. Furthermore, Nakagawa et al. [81] revealed that a group of virulence peptides called phenol-soluble modulins (PSMs) secreted from commensal *S. aureus* on the skin surface damage keratinocytes and induce the release of alarmins including IL-36α from keratinocytes in the epidermis, leading to skin inflammation with IL-17 production. In addition, epicutaneous *S. aureus* is reported to enhance serum IgE elevation via IL-36 production [82].

3.8 Acne/Acneiform Eruptions

The expression of IL-36 cytokines is elevated in skin lesions of acne vulgaris, suggesting that IL-36 cytokines contribute to the pathogenesis of acne vulgaris [64]. In fact, upregulated IL-36 expression and down-regulated IL-38 expression are significantly associated with the development and severity of acne vulgaris [83].

IL-36γ was reported to drive the development of acneiform eruptions due to EGF receptor (EGFR) inhibitors and MEK inhibitors [84]. EGFR inhibitors and MEK inhibitors mediate the expression of a transcription factor called Krüppel-like factor 4 (KLF4) in the epidermis. In addition, EGFR inhibitors and MEK inhibitors, in cooperation with the skin commensal *Cutibacterium acnes,* induce NF-κB activation. Subsequently, upregulated KLF4 and hyperactivated NF-κB synergistically induce IL-36γ production in keratinocytes, leading to IL-8 expression that results in inflammation with neutrophil infiltration and acneiform eruptions [84].

4 IL-36 Therapies in Skin Disease

Recently, knowledge on the genetic background and pathomechanisms of inflammatory skin conditions has expanded significantly [44, 47]. However, sufficient treatments have not been established. A number of biologics targeting pathways such as the IL-17 (e.g. secukinumab), TNF-α (e.g. infliximab), and IL-23 (e.g. guselkumab) pathways are now available for conditions such as pustular psoriasis. The complex IL-17 pathway is implicated in autoinflammatory skin conditions, with the overexpression of

IL-17A thought to be of particular relevance [85]. The IL-17 pathway interacts with the IL-36 pathway in a positive feedback system [86], which would suggest that inhibition of either pathway would create a downstream effect on the other. Furthermore, IL-36 cytokines are inducers of IL-23 and TNF-α also, cytokines that are essential in creating an inflammatory response [29, 87]. While individual antagonism of IL-23/TNF-α are effective, a more fundamental target in the IL-36 family should also provide similar, if not better, clinical outcomes. Indeed, some patients suffer from pustular psoriasis that is resistant to conventional biologics and from recurrent flares. Highly effective novel treatments are required, and in this context, the IL-36 pathway is a promising target for treatment. The recent wave of interest in the development of IL-36 pathway antagonists could be due to the ease of obtaining preliminary study results due to their specificity towards the target protein.

Concerning safety, individuals with loss-of-function mutations in *IL1RL2*, which encodes IL-36R interleukin-1 receptor-like 2 (IL1RL2), have been studied [88]. Individuals with functional loss of the IL36 receptor show no defective immune function. Thus, it was suggested that the inhibition of IL-36 signaling does not substantially compromise the host defense and can be a safe therapeutic strategy [88].

Currently, two drugs, spesolimab (BI655130) and imsidolimab (ANB019), offer the most optimistic outlooks for treatment (Table 2). Indeed, spesolimab has already been approved recently for the treatment of GPP [89], and imsidolimab has completed several trials and is awaiting approval. REGN6490 was another potential medication targeting the IL-36 pathway; however, its trials were terminated.

4.1 Spesolimab

Spesolimab is an IgG1 antibody working specifically against IL-36R, causing a blockage in the IL-36 axis [90], thereby reducing T-cell stimulation and the pro-inflammatory process. It has further been suggested that spesolimab directly downregulates various members in the IL-36 family, as well as others such as IL-17C (directly, and indirectly through the IL-17/36 interaction mentioned earlier), which contributes to inhibited Th cell activity [91].

With regard to its evidence base from a clinical perspective, a search of the NIH site ClinicalTrials.gov identified 13 clinical trials for spesolimab: seven for GPP (three completed, one recruiting, two active but not recruiting, and one not yet recruiting), three for PPP (two completed and one active but not recruiting), two for hidradenitis suppurativa (one completed and one active but not recruiting), and one for atopic dermatitis (completed). In addition, one trial for spesolimab in atopic dermatitis was identified, but this had been terminated (https://clinicaltrials.gov/ct2/results?cond=&term=spesolimab&cntry=&state=&city=&dist= Accessed 2 February 2023). Outside of dermatology, clinical trials of spesolimab have been completed or are underway for Crohn's disease and ulcerative colitis.

The results of these trials demonstrate that spesolimab seems to be significantly effective for inflammatory skin diseases, with the most evidence being provided for GPP. A phase I, open-label, proof-of-concept study on spesolimab indicated that conventional biologic-naïve adult patients with moderate GPP flares showed speedy improvement of the cutaneous manifestations after a single intravenous administration of spesolimab at 10 mg/kg [92]. 73.2 % and 79.8 % reductions in mean values for the GPP area and severity index (GPPASI) were achieved in patients 2 and 4 weeks after spesolimab administration, respectively, and the effect was maintained at week 20 [92]. No serious adverse events were observed in the study [92]. Of the seven patients, three had biallelic *IL36RN* mutations, including one with an additional heterozygous *CARD14* variant. No variant/mutation in *IL36RN*, *CARD14*, or *AP1S3* was detected in the other four patients. Spesolimab showed sufficient efficacy in GPP patients irrespective of the presence or absence of GPP-associated mutations [92]. The fact that spesolimab was effective against GPP without *IL36RN* mutations further supports the idea that the IL-36 signaling pathway may play an important role in GPP pathogenesis in GPP patients who have genetic backgrounds other than IL36Ra deficiency.

A phase II randomized double-blind placebo-controlled study of a single 900-mg intravenous administration of spesolimab was conducted [93, 94]. The primary and secondary end points were a GPP Physician Global Assessment (GPPGA) pustulation subscore of 0 (no visible pustules) and a GPPGA total score of 0 or 1 (clear or almost clear skin), respectively, at the end of week 1. A total of 53 patients with GPP flares were enrolled, with 35 patients receiving spesolimab and 18 receiving the placebo. Both the primary and the secondary end points were met; 54% and 43% of the spesolimab group had a GPPGA pustulation subscore of 0 and a total score of 0 or 1, respectively, as compared with 6% and 11% of the placebo group [93]. However, infections and systemic drug reactions were seen in patients in the spesolimab group [93].

Following on from these results, a further Phase II randomized double-blind placebo-controlled study of spesolimab in GPP was conducted [95]. Patients were treated with varying loading and maintenance doses of intravenous spesolimab. Although not yet published at the time of writing, the trial itself has been completed, and the results are projected to be available in the very near future. Furthermore, four other trials examining spesolimab efficacy in GPP are currently underway, with the newest trial being

Table 2 Clinical trials targeting IL-36 signaling for inflammatory skin diseases

Agent	Disease	Study population	Phase	Clinical trial number (reference)	Current status	Results	Estimated completion date
Spesolimab	GPP	Active GPP	I	NCT02978690	Completed	Significant improvement in GPP symptoms [92]	
	GPP	Acute flare of GPP	II	NCT03782792	Completed	Significant improvement in GPP symptoms [93, 94]	
	GPP	Acute flare of GPP	II	NCT04399837	Completed	Not available [95]	
	GPP	Active GPP	II	NCT03886246	Active, not recruiting	Not available	20 January 2028
	GPP	Acute flare of GPP	III	NCT05200247	Active, not recruiting	Not available	13 March 2023
	GPP	Acute flare of GPP	III	NCT05239039	Recruiting	Not available	30 July 2023
	GPP	Active GPP	IV	NCT05670821	Not yet recruiting	Not available	31 December 2025
	PPP	Active PPP	II	NCT03135548	Completed	Significant improvement in PPP symptoms (but endpoint not achieved) [96]	
	PPP	Active PPP	II	NCT04015518	Completed	Significant improvement in PPP symptoms [97]	
	PPP	Active PPP	II	NCT04493424	Active, not recruiting	Not available	24 March 2023
	HS	Active HS	II	NCT04762277	Completed	Not available	
	HS	Active HS	II	NCT04876391	Active, not recruiting	Not available	29 April 2024
	AD	Active AD	II	NCT03822832	Completed	Non-significant improvement in AD symptoms [99]	
Imsidolimab	None	Healthy volunteers	I	–	Completed	Good safety profile [100]	
	GPP	Active GPP	II	NCT03619902	Completed	Significant improvement in GPP symptoms	
	GPP	Active GPP	III	NCT05352893	Recruiting	Not available [101]	Dec 2023
	GPP	Active GPP	III	NCT05366855	Recruiting	Not available	Dec 2026
	PPP	Active PPP	II	NCT03633396	Completed	No significant improvement	
	Acne vulgaris	Active acne vulgaris	II	NCT04856917	Completed	Not available	
	HS	Active HS	II	NCT04856930	Not yet recruiting	Not available	30 November 2022

GPP generalized pustular psoriasis, *PPP* palmoplantar pustulosis, *HS* hidradenitis suppurativa, *AD* atopic dermatitis

registered in January 2023 (NCT03886246; NCT05200247; NCT05239039; NCT05670821).

Although fewer in number, spesolimab trials have been conducted in other skin disorders. A Phase IIa, double-blind, randomized, placebo-controlled pilot study of spesolimab (300 mg or 900 mg every 4 weeks) for PPP has been completed [96]. 31.6% of the patients with PPP in both dosage groups achieved a 50% reduction in PPP Area and Severity Index score (PPP ASI50) at week 16 [96]. The data suggest the potential of spesolimab as a treatment for PPP, but the primary endpoint of the trial (significant improvement in the rate of patients achieving PPP ASI50) was not achieved [96]. A further, Phase IIb double-blind, randomized, placebo-controlled trial investigated its therapeutic effect in

PPP [97]. This demonstrated significant objective and subjective improvements in PPP symptoms through the PPP Physician's Global Assessment, Dermatology Life Quality Index, and pain visual analog scores over a period of 1 year (the indicators were assessed once at 16 weeks and again at 52 weeks) [97]. Another clinical trial of spesolimab for PPP is currently recruiting (NCT04493424). It is hoped that further clinical trials will provide information on the efficiency and safety of spesolimab in PPP [98].

Concerning HS, one clinical trial with spesolimab (NCT04762277) has been completed (no results published) and another with spesolimab (NCT04876391) is active, but not recruiting. Results were recently published for a clinical trial investigating spesolimab use in atopic dermatitis [99]. This was a phase IIa, randomized, double-blind, placebo-controlled study, which demonstrated a statistically non-significant reduction in patients' Eczema Area and Severity Index (EASI) scores over a 16-week period (spesolimab group patients found on average a 37.9% reduction, compared to a 12.3% in the placebo group) [99]. A further clinical trial of spesolimab (NCT04086121) was initiated but was terminated due to sponsor decision. Currently, no clinical trials of anti-IL-36 agents are underway for atopic dermatitis.

4.2 Imsidolimab

Imsidolimab is another IL-36R antagonist, which has shown a satisfactory safety profile in a Phase I clinical trial for healthy individuals [100]. Phase II clinical trials of imsidolimab have been completed or are underway. A search of the NIH site ClinicalTrials.gov found six of these clinical trials: three for GPP (one completed and two recruiting), one for PPP (completed), one for acne (completed), and one for hidradenitis suppurativa (active, not recruiting). Additionally, one trial each for acne and ichthyosis had been terminated (https://clinicaltrials.gov/ct2/results?cond=&term=imsidolimab&cntry=&state=&city=&dist= Accessed 2 February 2023).

Of the trials studying imsidolimab in GPP, one completed trial has demonstrated improvements in GPP symptoms with imsidolimab across all outcomes measured (NCT03619902). Following these results, two further clinical trials have been designed and are still recruiting patients (NCT05352893; NCT05366855) [101]. It is hoped that these studies will further clarify the efficacy and safety of imsidolimab in GPP.

Regarding other skin conditions, a phase II study of imsidolimab for PPP patients has been completed (NCT03633396). However, there were no statistically significant results when compared to a placebo. One phase II, randomized, double-blind, placebo-controlled study focusing on acne has recently been completed, although the results are yet to be published (NCT04856917). A further trial regarding acne had been initiated, but was terminated (NCT04697069). One clinical trial with imsidolimab for HS is currently active (NCT04856930). One clinical trial with imsidolimab for ichthyosis has been terminated (NCT04697056), and no other trials involving IL-36 pathway inhibitors and ichthyosis are active as of yet.

4.3 Treatments in Development

Currently, two new IL-36R monoclonal antibodies are in development. HB0034 (Huaota) has recently completed a phase Ia randomized double-blinded placebo-controlled trial (NCT05064345), and recruitment is ongoing for a phase Ib (NCT05512598) and Ic trial (NCT05460455). The other drug in development, IMG008 (Inmagene Bio), is expected to commence trials in the near future, although the plan submission has been delayed [102].

Malik et al. [70] offered novel insights into the significant roles of IL-17 pathways in the formation of clinical features of ichthyosis and advocated for the therapeutic potential of IL-17, IL-36, and IL-23 inhibitors for the major ichthyosis subtypes. Barbieux et al. [75] revealed that IL-36 pathways play important roles in the pathogenesis of NS and suggested that biologics targeting IL-36 pathways might be effective against NS. Future studies building from these findings can be expected, which would provide more definitive treatment options for hard-to-treat conditions such as NS.

Other therapeutic strategies targeting IL-36 pathways are being studied [103]. An anti-IL-1RAcP antibody called mAb81.2 was created and its effects were studied in disease model systems of myeloid leukemia [104]. Clinical trials targeting IL-1RAcP have been completed or are underway on treatments for the exacerbation of chronic obstructive pulmonary disease, acute myeloid leukemia, breast cancer, and mild cognitive impairment. However, no clinical trials targeting IL-1RAcP for skin diseases were found. IL-1RAcP is not only used by IL-36, but also by other cytokines including IL-1α, IL-1β, and IL-33 [105]. Theoretically, a blanket blockade of these pathways by antagonizing IL-1RAcP could be beneficial for a wide variety of dermatological and non-dermatological conditions, and could be safe considering that there are some shared effects across the cytokines (IL-33, for example, activates the MyD88 and NF-κB pathways as well). Another agent, MAB92, has recently been developed, and mouse studies have been performed [106]. This has not been developed into a medical product as of yet. Further studies are still needed to evaluate the eligibility of IL-1RAcP as a safe target for the treatment of inflammatory skin diseases.

CAN10 (Cantargia) is another example of an anti-IL-1RAcP monoclonal antibody. No trials are currently underway to examine its efficacy in autoinflammatory keratinization diseases, but there has been a report of CAN10 being

effective in systemic sclerosis, albeit in mice rather than human subjects [107]. Should CAN10 reach a stage where clinical trials are feasible, evaluation into its effectiveness against conditions like GPP or PPP would be interesting. ALM27134 (Almirall) is an anti-IL-RAcP monoclonal antibody in the making [108]. Although no plans or dates are apparent, it is hoped that ALM27134 will be an effective new player in the market in the not-too-distant future.

A small molecule called oxypyrimidine A-552 binds to IL-36γ and blocks its interaction with IL-36R, resulting in the inhibition of IL-36 γ signaling [109]. Oxypyrimidine A-552 was reported to reduce inflammation experimentally in vitro and in vivo via the inhibition of IL-36 γ signaling [109]. No clinical trials have been planned on the molecule, but this represents an interesting future potential target for therapy.

5 Outlook and Future Directions

Novel therapies targeting IL-36 pathways are expected to be applied for various skin diseases, including GPP, PPP and HS. Studies on the specific roles of different IL-36 isoforms and their antagonists and regulators (IL-36Ra, IL-38, and protease inhibitors) in IL-36 pro-inflammatory pathways and on the pathogenesis of several diseases mentioned above are highly important [103]. Knowledge on the biological contributions of these molecules to GPP, PPP, HS, atopic dermatitis, and ichthyoses is expected to facilitate the design of promising targeted therapeutic strategies and personalized medicine that will improve the quality of life of patients with these diseases [103]. For example, mutations/variants in *IL36RN*, *CARD14, AP1S3, MPO*, and *SERPINA3* have been identified as predisposing factors for GPP. The products of these five genes are all associated with IL-36 pathways [33]. Thus, IL-36 pathways and various IL-36 pathway-related cytokines might play significant roles in the pathophysiology of GPP, and agents targeting IL-36 pathways are promising treatments for GPP. Further clinical trials are necessary to evaluate the efficacy and safety of molecular targeting agents that inhibit the IL-36 axis.

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