REVIEW ARTICLE

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Therapeutic potential of targeting interleukin-1 family cytokines in chronic inflammatory skin diseases*

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Summary

The interleukin (IL)-1 family of cytokines is a central regulator of a myriad of immunological responses. It comprises several cytokines, including those belonging to the IL-1, IL-36 and IL-18 subfamilies, as well as IL-33. The IL-1 family primarily plays a role in orchestrating innate immune responses, but is also involved in adaptive immunity. Increased interest in the IL-1 family occurred following the discovery that dysregulation of IL-1 signalling underlies the pathogenesis of several monogenic autoinflammatory diseases, characterized by sterile inflammation involving the skin and other organs. This also provided increased understanding of the role of innate immunity and the IL-1 family in polygenic autoinflammatory skin conditions, such as neutrophilic dermatoses, as well as in some of the most common chronic inflammatory skin diseases, such as psoriasis and hidradenitis suppurativa. Several therapeutic agents have been developed to inhibit the IL-1 family members and their signalling pathways. These have shown therapeutic efficacy in several chronic inflammatory skin disorders. The aim of this review is to thoroughly describe the consequences of pathological dysregulation of the IL-1, IL-33, IL-36 and IL-18 pathways in dermatological conditions and to provide a forward-looking update on therapeutic strategies targeting signalling by IL-1 family cytokines.

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Introduction

Cytokines of the interleukin-1 family

The interleukin (IL)-1 family comprises a large group of cytokines, partially sharing a conformational structure, a common receptor-binding mode, and a similar signalling pathway.[1] All members, albeit to different degrees, are key molecules involved in a myriad of immunological responses, primarily orchestrating innate immunity and bridging innate and adaptive immune responses. The IL-1 family encompasses 11 cytokines, seven with agonistic effects on their receptors and four with antagonistic effects (Table 1).[2,3] IL-1α, IL-1β, IL-36α, IL-36β, IL-36γ, IL-33 and IL-18 bind to a cognate membrane receptor to form a binary complex, and thereupon a coreceptor is recruited so as to form a signal-competent ternary complex (Figure 1).[2]

IL-1α and IL-1β[2,4] bind to a common transmembrane receptor IL-1R1, with subsequent recruitment of the coreceptor IL-1 receptor accessory protein (IL-1RAP, also named IL-1R3). Conversely, the antagonistic cytokine IL-1 receptor antagonist (IL-1Ra) engages the binding site of IL-R1 without recruiting the coreceptor IL-1R3, thus blocking signal transmission.[2]

The IL-36 subfamily comprises IL-36α, IL-36β, IL-36γ, IL-36Ra and IL-38, with the latter two exerting an antagonistic function.[5] The IL-36 receptor (IL-36R, IL-1R6) is the common receptor of all five members, which upon binding of IL-36α/β/γ recruits the coreceptor IL-1R3, forming a ternary complex.[6]

IL-33 binds to its receptor IL-33R (ST2 or IL-1R4) with subsequent recruitment of IL-1R3.[3,7] Finally, IL-18 and IL-37 belong to the IL-18 subfamily and exert pro- and anti-inflammatory effects, respectively.[8] IL-18 binds to the receptor IL-18Rα (IL-1R5, IL-1Rrp1), recognized by the coreceptor IL-18Rβ (IL-1R7), thus also forming a ternary complex.[9,10]

Receptors of the interleukin-1 family

The IL-1 receptor family includes 10 members, numbered from IL-1R1 to IL-1R10 (Table 2). IL-1R1 (IL-1RI, CD121a),

Table 1 Interleukin (IL)-1 family cytokines

Cytokine	Gene name	Other gene names	Chromosomal location	Property	Receptor (alternative names)	Coreceptors (alternative names)
IL-1α	*IL1A*	IL1F1	2q14	Proinflammatory	IL-1R1 IL-1R2 (decoy receptor)	IL1-R3 (IL-1RacP, IL1RAP)
IL-1β	*IL1B*	IL1F2	2q14	Proinflammatory	IL-1R1 IL-1R2 (decoy receptor)	IL1-R3 (IL-1RacP, IL1RAP)
IL-1Ra	*IL1RN*	IL1F3, IL1RA	2q14.2	Antagonist for IL-1α, IL-1β	IL-1R1 IL-1R2 (decoy receptor)	
IL-36α	*IL36A*	IL1F6, FIL1E, IL1E	2q12–q14.1	Proinflammatory	IL-R6 (IL-36R, IL-1Rrp2)	IL1-R3 (IL-1RacP, IL1RAP)
IL-36β	*IL36B*	IL1F8, IL1H2	2q14	Proinflammatory	IL-R6 (IL-36R, IL-1Rrp2)	IL1-R3 (IL-1RAcP, IL1RAP)
IL-36γ	*IL36G*	IL1F9, IL1E, IL1H1, IL1RP2, UNQ2456/PRO5737		Proinflammatory	IL-R6 (IL-36R, IL-1Rrp2)	IL1-R3 (IL-1RAcP, IL1RAP)
IL-36Ra	*IL36RN*	IL1F5, FIL1D, IL1HY1, IL1L1, IL1RP3, UNQ1896/PRO4342	2q14	Antagonist for IL-36α, IL-36β, IL-36γ	IL-R6 (IL-36R, IL-1Rrp2)	
IL-38	*IL1F10*	FIL1T, IL1HY2, IL38, FKSG75, UNQ6119/PRO20041	2q13	Anti-inflammatory	IL-R6, IL-36R, IL-1Rrp2 IL-R9	Unknown
IL-18	*IL18*	IL1F4, IGIF	11q22.2–q22.3	Proinflammatory	IL-1R5	IL-R7 (IL-18Rβ, IL18RacP)
IL-33	*IL33*	IL1F11, C9orf26, IL1F11, NFHEV	9p24.1	Proinflammatory and T helper 2 responses	IL-1R4 (IL-33R, ST2)	IL1-R3 (IL-1RAcP, IL1RAP)
IL-37	*IL37*	FIL1Z, IL1F7, IL1H4, IL1RP1	2q12–q14.1	Anti-inflammatory	IL-1R5 (IL-18R-1, IL-18Rα, IL-1Rp)	IL-R8 (TIR8, SIGIRR)

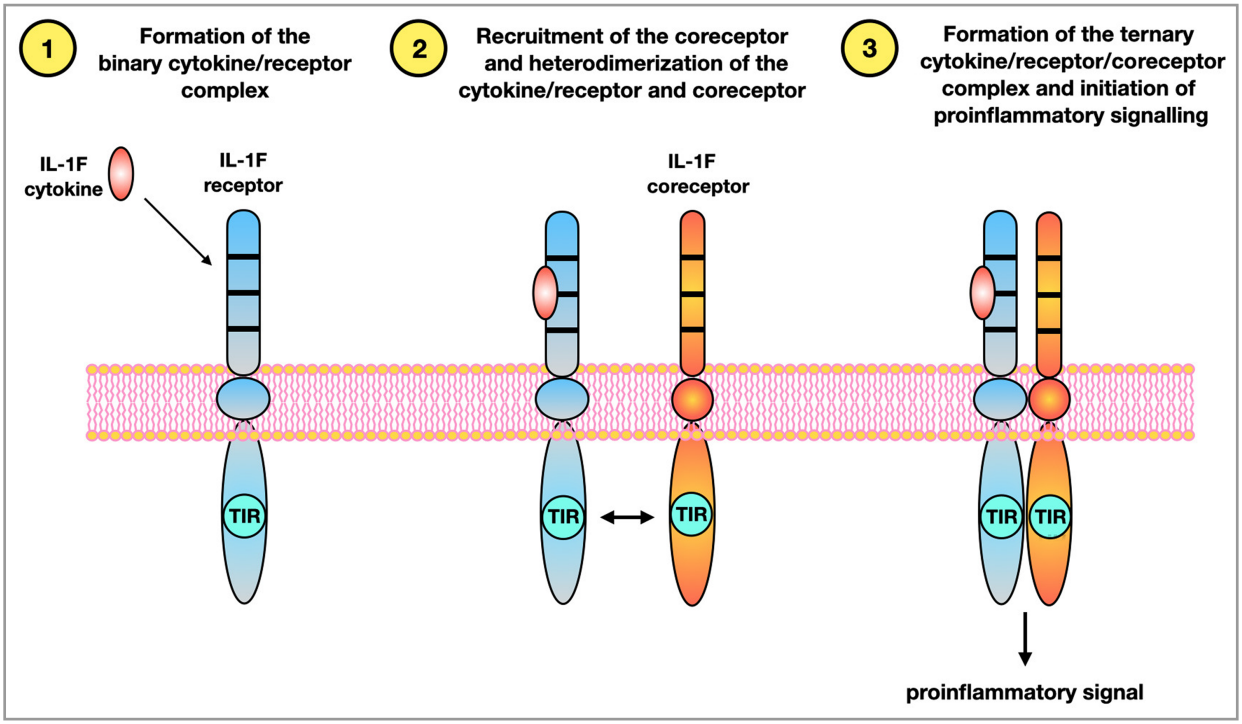

Figure 1 Most interleukin (IL)-1 family cytokines bind the cognate membrane receptor to form a so-called binary complex. Thereupon, the coreceptor, necessary for proinflammatory signal transmission, is recruited (ternary complex).

Table 2 Receptors of the interleukin (IL)-1R family

Name	Alternative name(s)	Ligands	Coreceptor (alternative names)	Human gene	Human chromosome
IL-1R1	IL-1RI, CD121a	IL-1α, IL-1β, IL-1Ra, IL-38	IL1-R3 (IL-1RacP, IL1RAP)	*IL1R1*	2q12
IL-1R2	IL-1RII, CD121b	IL-1α, IL-1β, IL-1Ra, pro-IL-1α		*IL1R2*	2q12
IL-1R3	IL-1RacP	No ligand known, accessory chain		*IL1RAP*	3q28
IL-1R3b	IL-1RacPb	No ligand known, accessory chain		*IL1RAP*	2q12
IL-1R4	T1, ST2, ST2L, DER4, Fit-1, IL-33Rα	IL-33	IL1-R3 (IL-1RacP, IL1RAP)	*IL1RL1*	2q12
IL-1R5	IL-18Rα, IL-1Rrp, IL-1Rrp1, CD218a	IL-18, IL-37	IL-R8 (TIR8, SIGIRR)	*IL18R1*	2q12
IL-1R6	IL-1Rrp2, IL-1RL2, IL-36R	IL-36α, IL-36β, IL-36γ, IL-36Ra, IL-38	IL1-R3 (IL-1RacP, IL1RAP)	*IL1RL2*	2q12
IL-1R7	IL-18Rβ, IL-18RAcP, AcPL, CD218b	No ligand known, accessory chain		*IL18RAP*	2q12
IL-1R8	TIR8, SIGIRR	No ligand known, inhibitory receptor		*SIGIRR*	11p15.5
IL-1R9	TIGIRR-2				
IL-1R10	TIGIRR-1				

IL-1R4 (ST2, IL-33Rα) and IL-1R6 (IL-36R, IL-1Rrp2) are the ligand-binding chains for IL-1, IL-33 and IL-36, respectively.[11] They all use IL-1R3 as an accessory protein to form the ternary complex and induce intracellular signalling. In contrast, the ternary receptor complex of IL-18 consists of the main receptor IL-18Rα and the accessory protein IL-18Rβ.[12] Soluble forms of IL-1 family receptors also exist, mostly acting as negative regulators (Table 3).[13]

Interleukin-1 receptor accessory protein

First described in 1995,[14] IL-1R3 is an accessory receptor of the IL-1 family. It is not directly involved in ligand binding, although it is crucial for the constitution of the three high-affinity ternary complexes necessary for IL-1, IL-33 and IL-36 signal transmission. IL-1R3 interacts with a composite surface created by IL-1R bound to the ligand, allowing the formation of a ternary complex and the initiation of an intracellular signalling pathway.[15] Subsequent activation of several kinases, especially nuclear factor-κB and mitogen-activated protein kinase, promotes the transmission of a strong proinflammatory signal to the cell nucleus.

Table 3 Soluble receptors of the interleukin (IL)-1R family

Name	Other names	Ligands
sIL-1R1	sIL-1RI	IL-1α, IL-1β, IL-1Ra, IL-38
sIL-1R2	sIL-1RII	IL-1α, IL-1β, (IL-1Ra), pro-IL-1β
sIL-1R3	sIL-1RacP, sIL-1RAP	None (accessory chain)
sIL-1R3β	sIL-1RacP, sIL-1RAP-b	None (accessory chain)
sIL-1R4	sST2	IL-33
sIL-1R5		IL-18 (IL-37)
sIL-1R6		IL-36α, IL-36β, IL-36γ, IL-36Ra, IL-38
sIL-1R7		None (accessory chain)
sIL-1R8		No ligand known
sIL-1R9		IL-38
sIL-1R10		No ligand known
IL-18BP		IL-18, IL-37

Recent research has demonstrated a major role of IL-1 family cytokines in certain chronic inflammatory skin diseases (Figure 2), and the potential of blocking one or more of the family members is being explored in depth (Figure 3).[16,17] The aim of this review is to thoroughly describe the consequences of pathological dysregulation of IL-1 family signalling in chronic inflammatory skin disorders and to provide an update on the therapeutic strategies targeting these pathways.

Interleukin-1 in skin diseases

IL-1α is expressed constitutively in epithelial and mesenchymal cells of healthy individuals. This cytokine is active in its pro-form and can perform a dual function, either in the nucleus as a transcription factor or in the extracellular environment.[18] Conversely, activation of IL-1β requires proteolytic cleavage mediated by the NLRP3 inflammasome, a cytoplasmic innate immune protein complex.[19] This cytokine is produced mainly by activated macrophages, but also by other cell types including keratinocytes.[20] Activation of the IL-1 pathway promotes a proinflammatory signal, well described in the pathogenesis of various chronic skin diseases (Table 4).[21]

Interleukin-1 in monogenic autoinflammatory skin disorders

Autoinflammatory diseases (AIDs) are primarily characterized by sterile inflammation, with innate immunity playing the primary pathophysiological role. The stigmata of classic autoimmune diseases are typically absent.[22] Among AIDs, the so-called inflammasomopathies are directly caused by gain-of-function mutations in components of the inflammasome.

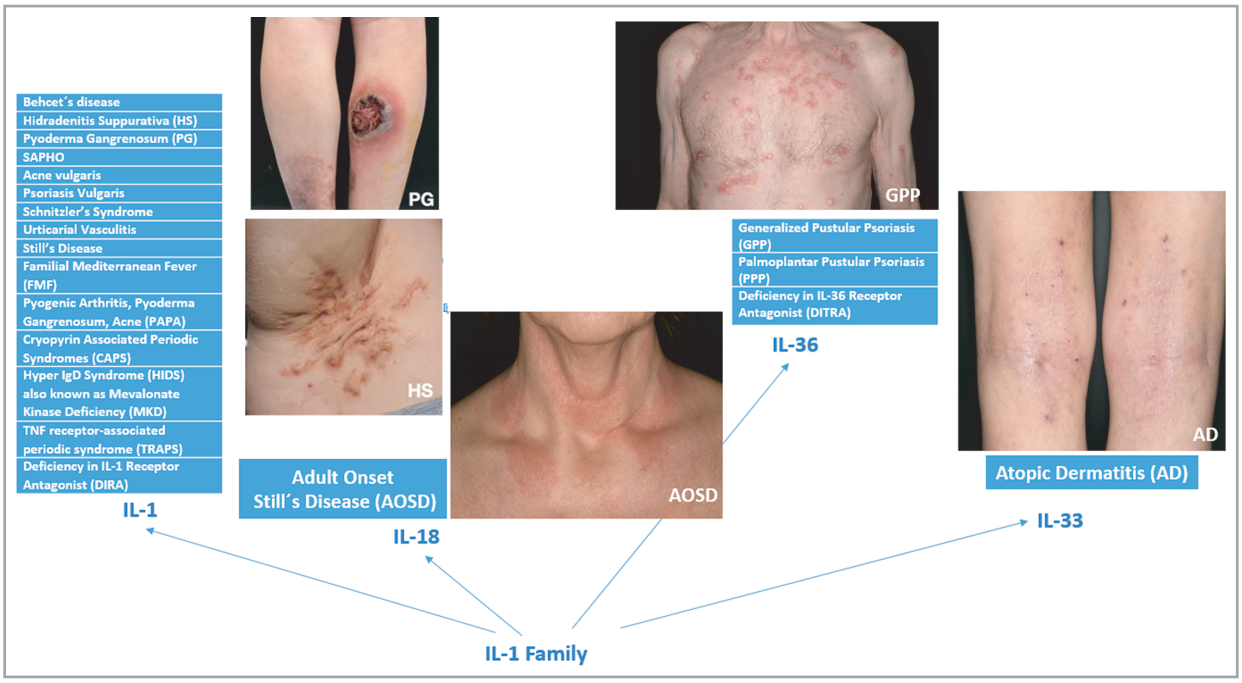

Figure 2 The main dermatological diseases with solid evidence of involvement of interleukin (IL)-1, IL-36, IL-33 and IL-18 in their pathogenesis. SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis; TNF, tumour necrosis factor.

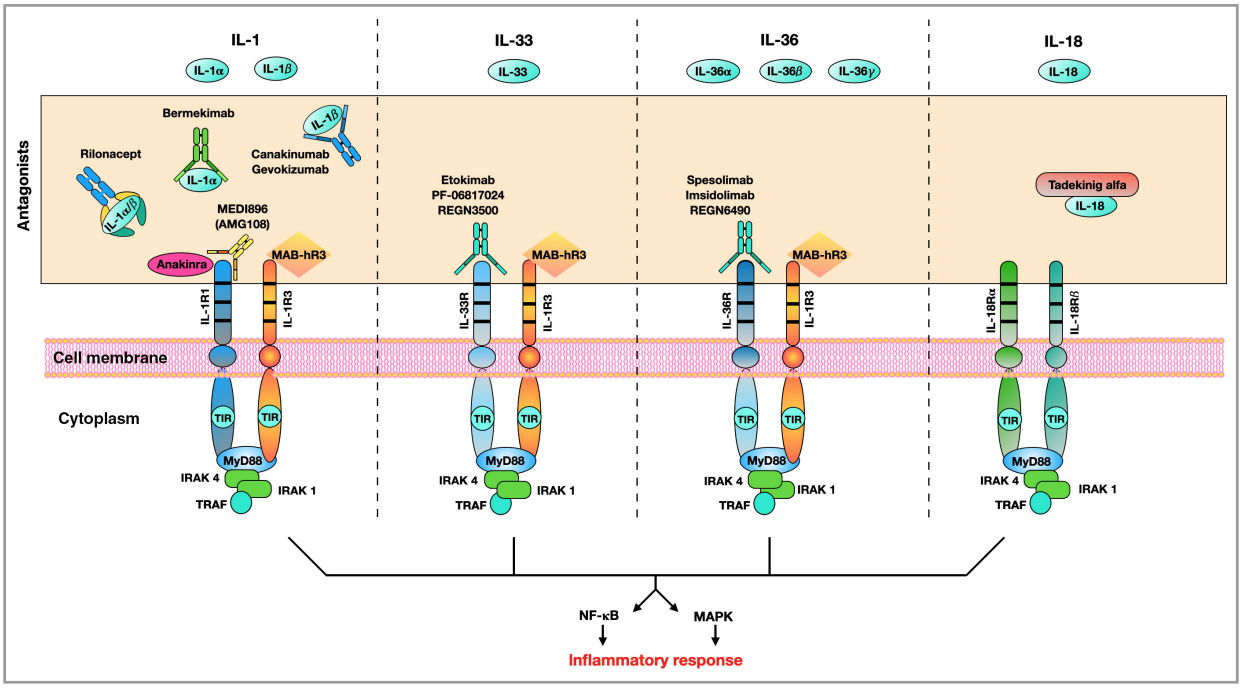

Figure 3 Schematic representation of seven members of the interleukin (IL)-1 family (IL-1α, IL-1β, IL-33, IL-36α, IL-36β, IL-36γ and IL-18) acting on their receptor complex with transmission of a proinflammatory signal to the nucleus. Multiple inhibitors of the inflammatory cascade at different levels are also shown. IRAK, interleukin-1 receptor-associated kinase; MAB-hR3, monoclonal antibody targeting IL-1R3; MAPK, mitogen-activated protein kinase; NF, nuclear factor; TIR, Toll–interleukin-1 receptor; TRAF, tumour necrosis factor receptor-associated factor.

These mutations lead to dysregulation of IL-1β signalling, as is the case in two prototypical AIDs: familial Mediterranean fever and cryopyrin-associated periodic syndromes.[23–25]

Additionally, the IL-1 pathway can be imbalanced by the lack of counter-regulatory mechanisms, as in deficiency of IL-1Ra (DIRA), first described in 2009.[26] DIRA is caused by

Table 4 Current evidence for a pathogenic role of interleukin-1 in cutaneous diseases

Strong[a]	Possible[b]	Uncertain[c]
Adult-onset Still disease[123,153,154]	Sweet syndrome[125,155,156]	PAPASH[128]
Behçet disease[121,157–160]	PASH[161]	Rosacea[162]
Hidradenitis suppurativa[135,136,140]	PFAPA[163]	Acute generalized exanthematous pustulosis (AGEP)[90]
Pyoderma gangrenosum[35]	Generalized pustular psoriasis (GPP) [132–134]	Atopic dermatitis[164,165]
SAPHO[130]	Palmoplantar pustular psoriasis (PPP)[134]	Allergic contact dermatitis[166,167]
Acne vulgaris[142]	Dermatomyositis[168]	Irritant contact dermatitis[169,170]
Psoriasis vulgaris[142]	Panniculitis[128]	Mastocytosis[171]
Schnitzler syndrome[119–121,172]	Erdheim–Chester syndrome[173–175]	Systemic sclerosis[176,177]
Urticarial vasculitis[178]	Deficiency of adenosine deaminase (DADA2)[179]	Chronic spontaneous urticaria[180]
Familial Mediterranean fever (FMF)[181]	Majeed syndrome[182]	Autoimmune blistering diseases[183]
Pyogenic arthritis, pyoderma gangrenosum, acne (PAPA)[184]	Deficiency of IL-36 receptor antagonist (DITRA)[132]	Vitiligo[185]
Cryopyrin-associated periodic syndromes (CAPS)[186]	Haploinsufficiency of A20 (HA20)[187]	CARD-14 mediated pustular psoriasis (CAMPS)[22]
Hyper-IgD syndrome (HIDS), also known as mevalonate kinase deficiency (MKD)[188]		Familiar keratosis lichenoides chronica (FKLC), multiple self-healing palmoplantar carcinoma (MSPC)[23]
TNF receptor-associated periodic syndrome (TRAPS)[188]		Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)[189]
Deficiency of IL-1 receptor antagonist (DIRA)[26]		NLRC4-related macrophage activation syndrome (NLRC4-MAS)[23]

PASH, pyoderma gangrenosum, acne, hidradenitis suppurativa; PAPASH, pyogenic arthritis, pyoderma gangrenosum, acne, hidradenitis suppurativa; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis. [a]Strong evidence: clinical trials showing efficacy of selective cytokine antagonism in a cohort of patients. [b]Possible: case reports or series reporting efficacy of selective cytokine antagonism in a single patient or a small number of patients. [c]Uncertain: biological evidence concerning the role of interest of the cytokine in the disease.

mutations in the *IL1RN* gene and presents clinically as neonatal onset of generalized cutaneous pustulosis, multifocal osteomyelitis, and high levels of acute-phase reactants.

Interleukin-1 in neutrophilic dermatoses

Neutrophilic dermatoses (NDs) are chronic inflammatory skin disorders characterized by neutrophil-driven sterile cutaneous inflammation. Two of the most prototypical NDs include Sweet syndrome and pyoderma gangrenosum (PG). Sweet syndrome typically occurs in individuals aged 47–57 years, with a slight female predominance, and is characterized by the sudden appearance of painful, oedematous and erythematous papules, plaques or nodules on the skin associated with fever and leucocytosis. PG presents, in its classic form, with rapidly developing, painful skin ulcers with undermined borders and violaceous peripheral erythema. The incidence of PG is approximately six cases per million person-years, with an average age of onset between 40 and 60 years.[27] The pathogenesis of ND is so far not completely elucidated. A complex interplay between an imbalanced expression of inflammatory molecules, abnormal neutrophil function, and genetic predisposition contributes to the onset of ND. In the end, extravasation of activated neutrophils and migration towards the source of the inflammatory chemoattractant cause inflammation and tissue damage.[28]

Dysregulation of innate immune pathways is regarded as one of the predominant mechanisms underlying the pathophysiology of ND.[29] Indeed, IL-1β has been shown to promote the generation of T helper (Th)17 cells, which can amplify the recruitment of neutrophils.[30,31] This cytokine both acts on neutrophils, exerting antiapoptotic effects and thus promoting their survival,[32] and is produced by neutrophils, mainly in an inflammasome-dependent manner.[33] Because of numerous clinical and pathogenic similarities and the frequent response to IL-1-targeted therapy, NDs are now considered to be predominantly autoinflammatory in nature.[22] Indeed, IL-1β gene expression and protein levels were found to be elevated in two prototypical NDs, Sweet syndrome[34] and PG.[35] Similarly, elevated serum levels of IL-1β have been described in Behçet disease,[36] and IL-1α was found to be upregulated in skin from a patient with amicrobial pustulosis of the folds.[37]

Interleukin-1 in hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder that affects approximately 1% of the general population, with the highest prevalence reported in young adults. The disease manifests clinically as recurrent episodes of neutrophilic inflammation mostly involving skin bearing pilosebaceous and apocrine units (predominantly the axillary and inguinal folds and perianal area). The pathogenesis of HS has not been completely elucidated, although it is known that genetic, hormonal, immunological and microbial factors, together with tobacco smoking and obesity, contribute to

disease occurrence and/or severity. The main events leading to the development of HS lesions encompass aberrant infundibular keratinization with consequent hyperkeratosis and occlusion, and the aberrant activation of innate immune pathways with a massive neutrophil-rich inflammatory infiltrate.[38] The pathogenic role of IL-1β has recently been investigated in HS.[39]

van der Zee *et al.* found a significant increase in IL-1β, tumour necrosis factor (TNF)-α and IL-10 in the supernatants of *ex vivo* cultured HS lesional skin, compared with healthy controls and with psoriatic skin.[40] Kelly *et al.* described augmented protein levels of IL-1β, IL-17 and TNF-α and enhanced *NLRP3* and *IL18* gene expression in lesional HS skin, supporting the pathogenic involvement of the inflammasome and IL-1β.[41] Furthermore, Witte-Händel *et al.* showed that the IL-1β pathway is clearly hyperactive in HS lesions, compared with psoriasis lesions and healthy skin, thus likely contributing to local and systemic inflammation.[39] In HS skin, IL-1β was found to be produced mainly by monocytes and macrophages, whereas fibroblasts were the most potent producers of IL-1β target molecules. Interestingly, this strong IL-1β signature with downstream upregulation of matrix metalloproteinases, chemokines (including CXCL1, CXCL6, CXCL10 and CCL7) and several cytokines (IL-1β, IL-6, IL-32 and IL-36), could be specifically reversed *ex vivo* by inhibition of IL-1β signalling with IL-1Ra.[39]

Given the above experimental data, it would be expected that IL-1 pathway blockade could be of therapeutic benefit in patients with HS, and indeed, as discussed later in this review, some evidence for this exists.

Interleukin-1 in psoriasis

Psoriasis is an immune-mediated inflammatory disease with a chronic course and a multifactorial pathogenesis, which manifests as scaly itchy and/or painful patches and plaques on the skin. The prevalence of the disease varies among populations and ages within a range from 0.09% to 5.1%.[42] The pathogenesis of psoriasis is based on a complex interaction between innate and adaptive immune compartments and relies on a predominant Th1/Th17 signature.[43]

In psoriasis, the IL-1 pathway has a well-documented pathogenic role, albeit early in the pathogenesis.[44] IL-1α is essential for the development of neutrophilic abscesses in the imiquimod-induced murine psoriasis-like model.[45] IL-1β, produced by macrophages, dendritic cells and keratinocytes, is critical in Th17-cell differentiation and activation.[46–48]

Interleukin-33 in dermatological diseases

IL-33 primarily plays a defensive role at barrier sites, being constitutionally expressed by keratinocytes.[49] Like IL-1α, IL-33 can transmit its signal by acting as a transcription factor in the cell nucleus or in the extracellular environment.[50] This cytokine can stimulate group 2 innate lymphoid cells[51] and predominantly drives Th2 polarization, thus playing a role in allergic diseases and eosinophilic inflammation.[52] IL-33 dysfunction has been investigated in a wide range of inflammatory skin diseases, including AD and psoriasis (Table 5).[53]

Interleukin-33 in atopic dermatitis

Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder, affecting an increasing number of patients globally, with a prevalence of up to 7% in adults and up to 25% among children.[54] The disease clinically manifests as itchy eczematous lesions predominantly localized on flexural areas and the face, neck and distal extremities. Classically considered to be mediated by a Th2-skewed adaptive immune response,[55] the immune map of the disease is actually far more complex and involves multiple inflammatory pathways guided by Th22, Th17/IL-23 and Th1 cytokines.[54]

Transgenic mice with enhanced skin-selective expression of the *IL33* gene have been shown to have AD-like dermatitis.[56] Also, serum IL-33 in AD skin, as well as IL-33 mRNA and protein levels, were found to be elevated.[57,58] Current knowledge also indicates that IL-33 is able to induce Th2 cell differentiation and to promote IL-31 expression by Th2 cells, alone or in combination with IL-4.[59] IL-31 further stimulates the onset and persistence of itching, and directly downregulates the expression of claudin-1 and filaggrin, thus contributing to skin barrier impairment.[60,61]

Interleukin-33 in psoriasis

Despite its original description as a Th2-driving cytokine, IL-33 also plays a role in psoriasis, classically considered a Th1/Th17-mediated disease. IL-33 has been shown to be produced primarily by keratinocytes following psoriatic inflammatory stimuli and to induce the transcription of inflammation-related

Table 5 Current evidence for a pathogenic role of interleukin-33 in cutaneous diseases

Strong[a]
Atopic dermatitis[149,150]
Uncertain[b]
Allergic contact dermatitis[166]
Irritant contact dermatitis[190]
Rosacea[191]
Psoriasis vulgaris[65,192,193]
Pustular psoriasis[67]
Mastocytosis[171]
Systemic lupus erythematosus[194]
Systemic sclerosis[195,196]
Chronic spontaneous urticaria[197]
Autoimmune blistering diseases[198]
Behçet disease[199]
Vitiligo[200]

[a]Strong evidence: clinical trials showing efficacy of selective cytokine antagonism in a cohort of patients. [b]Uncertain: biological evidence concerning the role of interest of the cytokine in the disease.

genes (such as *CCL2*, *CXCL1*, *CXCL2*, *Cxcl15* and vascular endothelial growth factor genes) in keratinocytes, in an autocrine manner.[62]

Also, in a murine model, IL-33 induced psoriasis-like lesions through interaction with mastocytes and neutrophils.[63] Additionally, several studies have found higher IL-33 expression levels in psoriatic lesions than in healthy skin,[64–66] and some data are suggestive of an increase in IL-33 levels in the serum of patients with psoriasis.[67,68]

Interleukin-36 in skin diseases

The three splice variants of IL-36 (IL-36α, IL-36β and IL-36γ) are potent proinflammatory cytokines, mainly produced in barrier sites of the body (cutaneous, bronchial and intestinal epithelium).[69] In the skin, IL-36γ is predominantly expressed in epidermal keratinocytes.[70,71] These cytokines play a first-line defensive role against exogenous insults and contribute to maintaining cutaneous homeostasis. Furthermore, they contribute to crosstalk between the innate and adaptive immune responses, for example by stimulating Th-cell activation and Th1 polarization.[72] IL-36 pathway dysfunction is associated with selected inflammatory skin diseases (Table 6).[73]

Interleukin-36 in psoriasis

The role of IL-36 in skin diseases received great attention when loss-of-function mutations in the gene *IL36RN*, encoding IL-36Ra, were discovered as a cause of a severe recessive autoinflammatory syndrome named deficiency of IL-36 receptor antagonist (DITRA).[74] The reported mutations influence the stability of IL-36Ra and its ability to bind to IL-1R6, thus limiting its ability to inhibit IL-36 signalling. DITRA presents clinically with episodic fever and generalized pustular psoriasis (GPP). Loss-of-function mutations or single-nucleotide polymorphisms of *IL36RN* have also been identified in 23–37% of sporadic forms of GPP.[75–77] Although the frequency of *IL36RN* gene mutations in palmoplantar pustular psoriasis (PPP) is < 5%,[78] gene expression levels of *IL36G* in PPP are higher than in normal skin, suggesting that IL-36 pathway signalling is also upregulated in PPP.[79]

Furthermore, a severe pustular or erythrodermic psoriasis phenotype named CAMPS (CARD-14-mediated pustular psoriasis) has been described, caused by autosomal dominant gain-of-function mutations in CARD-14.[80] CARD-14 is strongly expressed in keratinocytes and drives IL-1β production and subsequent increased transcription of IL-8 and IL-36γ.[81]

IL-36 cytokines are also relevant in the most frequent form of psoriasis, namely psoriasis vulgaris.[82] These cytokines are released mainly by keratinocytes upon stimulation by Toll-like receptor agonists or proinflammatory cytokines (TNF-α, IL-17 and IL-22), but are also produced by endothelial and immune cells.[83] In psoriasis, IL-36 cytokines influence the cornification processes in the epidermis by acting on keratinocytes, induce the production of Th17- and Th1-polarizing cytokines by myeloid dendritic cells and macrophages, and potently sustain neutrophil recruitment. In lesional psoriatic skin, IL-36α, IL-36γ and IL-36Ra are indeed highly expressed.[70,84] Conversely, the antagonist IL-38 is downregulated.[85] Particularly, the IL-36γ isoform, which is not normally expressed in healthy skin, appears to be crucial in psoriasis and has been suggested as a biomarker for disease activity.[86]

Table 6 Current evidence for a pathogenic role of interleukin (IL)-36 in cutaneous diseases

Strong[a]
Generalized pustular psoriasis[145]
Palmoplantar pustular psoriasis[146]
Deficiency of IL-36 receptor antagonist (DITRA)[74]
Uncertain[b]
Psoriasis vulgaris[86,194]
CARD14-mediated psoriasis[22]
Acute generalized exanthematous pustulosis[91]
Hidradenitis suppurativa[92–94]
Pyoderma gangrenosum[35]
Sweet's syndrome[22]
Systemic lupus erythematosus[201]
Systemic sclerosis[202]
Autoimmune blistering diseases[203]
Acne[95]
Atopic dermatitis[204]
Allergic contact dermatitis[166]
Folliculitis and eosinophilic pustular folliculitis[205]

[a]Strong evidence: clinical trials showing efficacy of selective cytokine antagonism in a cohort of patients. [b]Uncertain: biological evidence concerning the role of interest of the cytokine in the disease.

Interleukin-36 in neutrophilic dermatoses

IL-36 cytokines have a strong ability to recruit neutrophils to the skin[87] and, in turn, neutrophil-derived proteases process IL-36 cytokines, enhancing their biological activity.[88] This suggests that neutrophils are key players in escalating IL-36-driven inflammation, and that IL-36 may be central to the pathogenesis of NDs.[16] Indeed, in lesional PG skin, Kolios *et al.* reported selective upregulation of *IL36A* mRNA, whereas *IL36G* mRNA was not elevated.[35]

IL-36 has also been shown to play a role in acute generalized exanthematous pustulosis (AGEP), a severe adverse cutaneous drug reaction that shares certain phenotypical and histological features with GPP.[89,90] IL-36γ expression is strongly increased in the epidermis during AGEP, and culprit drugs can specifically stimulate keratinocytes to secrete IL-36γ with subsequent IL-8 production by macrophages and T cells, thus driving neutrophil recruitment and survival in lesional AGEP skin.[91]

Furthermore, IL-36 has been shown to be a driver in the pathogenesis of the acneiform eruption induced by epidermal growth factor receptor and MEK (MAPK kinase) inhibitors. In fact, these targeted drugs are able, by synergizing with the commensal *Cutibacterium acnes*, to potently induce keratinocyte

IL-36γ expression and drive IL-8-mediated neutrophil-rich inflammation.[92]

Interleukin-36 in hidradenitis suppurativa

As in psoriasis, in HS skin, keratinocytes are primarily responsible for the secretion of IL-36 cytokines. These cytokines can target different types of cells, from keratinocytes to dendritic cells, promoting the production of proinflammatory cytokines, such as IL-12 and IL-23, which selectively provoke adaptive immunity (Th1 and Th17 responses). In turn, dendritic cells also produce IL-36, thus establishing an autocrine loop that further amplifies inflammation.[93] Several studies have shown significantly high protein and gene expression levels of IL-36α, IL-36β and IL-36γ in lesional HS skin, as well as serum levels in patients with HS compared with healthy controls.[93–95] Furthermore, Wolk *et al.* demonstrated in HS skin high levels of granulocyte colony-stimulating factor, a major driver of neutrophil recruitment and survival, which were induced by IL-36.[96] Moreover, currently available data are supportive of a pivotal role of the IL-36 cytokine family in orchestrating the crosstalk between keratinocytes and immune cells in HS, thus likely contributing to the chronic inflammation.[93]

Interleukin-18 in dermatological diseases

Originally described as IGIF (interferon-γ-inducing factor), IL-18 can exert pleiotropic functions, mainly depending on the surrounding cytokine milieu.[97] IL-18 is constitutively expressed by human keratinocytes[98] and exerts strong proinflammatory activity. The biological action of IL-18 is neutralized by IL-18BP and IL-37. IL-18BP is an endogenous soluble factor that prevents IL-18 from binding to IL-18R, thus suppressing interferon (IFN)-γ production and inhibiting Th1 immune responses.[11] Dysregulation of the IL-18 pathway has been reported in several cutaneous diseases (Table 7).

Table 7 Current evidence for a pathogenic role of interleukin-18 in cutaneous diseases

Strong[a]
Adult-onset Still disease[151]
Uncertain[b]
Cutaneous lupus erythematosus[107,206]
Psoriasis[207,208]
Atopic dermatitis[209,210]
Chronic spontaneous urticaria[211]
Contact dermatitis[212]
Alopecia areata[213]
Cutaneous drug eruptions[214]
Graft-versus-host disease[215,216]
Cryopyrin-associated periodic syndromes[217]
Granulomatosis with polyangitis[218]
Systemic sclerosis[219]
Hidradenitis suppurativa[41]
Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA)[220]
Familial Mediterranean fever[221,222]
Rosacea[223]
Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO)[224]
Bullous pemphigoid[225]
Pemphigus vulgaris[226]
Behçet disease[227]
Schnitzler syndrome[228]

[a]Strong evidence: clinical trials showing efficacy of selective cytokine antagonism in a cohort of patients. [b]Uncertain: biological evidence concerning the role of interest of the cytokine in the disease.

Interleukin-18 in adult-onset Still disease

Adult-onset Still disease (AoSD) is a systemic inflammatory condition typically affecting young adults and traditionally characterized by four symptoms: fever, arthralgia, cutaneous eruption and leucocytosis. The estimated annual incidence is approximately 0.16 cases per 100 000 people.[99] Crucial for the pathogenesis of AoSD is an intense activation of the innate immune system, with several proinflammatory cytokines suggested to be involved, including IL-1β, IL-6, TNF-α, IFN-γ and IL-18.[100] Particularly, IL-18 and IL-1β appear to be crucial in initiating the proinflammatory cascade in AoSD.[101] IL-18 is produced mainly by macrophages in an NLRP3 inflammasome-dependent manner and further promotes immune cells to produce a large amount of proinflammatory cytokines, including IL-6, IL-8, IL-17 and TNF-α, thus contributing to the so-called 'cytokine storm' in AoSD.[100] Indeed, several studies have shown high levels of serum IL-18 in systemic forms of AoSD, so this cytokine has been proposed as a promising biomarker for the diagnosis of AoSD.[102–105]

Interleukin-18 in lupus erythematosus

Recent evidence has highlighted a relevant role of IL-18 pathway dysfunction in the pathogenesis of systemic lupus erythematosus. In particular, single-nucleotide polymorphisms in the *IL18* gene have been shown to be associated with predisposition to systemic lupus erythematosus,[106] and IL-18 was found to be overexpressed in skin samples[107] and serum[108] of patients with cutaneous lupus. Indeed, IL-18 has been proposed as a predictive marker of disease activity.[109] In cutaneous lupus, IL-18 has been shown to induce apoptosis of keratinocytes by stimulating TNF-α expression in these cells and reducing the expression of IL-12, which instead is able to protect keratinocytes from TNF-α- and ultraviolet-induced apoptosis.[110]

Interleukin-18 in psoriasis

In psoriasis, cathelicidin LL-37-stimulated keratinocytes are able to produce IL-18, via activation of the NLRP3 inflammasome.[111] Subsequently, IL-18 can enhance IFN-γ production by Th1 cells and IL-17 secretion by Th17 lymphocytes, thus maintaining the inflammatory circuit underlying disease pathogenesis. Elevated skin and serum levels of IL-18 have been reported in patients with psoriasis and these correlate with disease severity.[112,113]

Table 8 Current interleukin (IL)-1 family antagonists targeting chronic inflammatory skin diseases

Drug	Mechanism of action	Approved indications (FDA and/or EMA)	Published clinical trials beyond label indications	Ongoing clinical trial		
				Disease(s)	Phase	Clinical trial number
Anakinra (Kineret®)	Competitive binding of IL-1α and IL-1β to the IL-1 receptor	FDA: RA and CAPS. EMA: FMF, SJIA, AoSD, rheumatoid arthritis and CAPS	HS: Leslie 2014,[136] Tzanetakou 2016[137]	Inflammatory pustular skin diseases	II	NCT01794117
				AD (severe)	I	NCT01122914
Rilonacept (Arcalyst®)	Soluble decoy receptor that binds both IL-1α and IL-1β	FDA: CAPS, recurrent idiopathic pericarditis, maintenance of remission of DIRA	FMF: Hashkes 2012.[229] SSc: Mantero 2018.[230] Schnitzler syndrome: Krause 2012[121]	Cold contact urticaria	II	NCT02171416
				CAPS (MWS) or Schnitzler syndrome	II	NCT01045772
Canakinumab (Ilaris®)	Human monoclonal antibody specific for IL-1β	FDA: CAPS, TRAPS, HIDS/MKD, SJIA, FMF. EMA: CAPS, TRAPS, HIDS/MKD, SJIA, FMF, AoSD, gouty arthritis	PG: Kolios 2015[35]	Urticaria	II	NCT01635127
				Urticarial vasculitis	II	NCT01170936
				Schnitzler syndrome	II	NCT01245127
Gevokizumab	Humanized monoclonal antibody specific for IL-1β	None	None	PG	II	NCT01882504
				PG	III	NCT02318914
				PG	III	NCT02326740
				PG	III	NCT02315417
				Acne vulgaris	II	NCT01498874
				CAPS (FCAS/MWS) and Behçet disease	I/II	NCT01211977
Bermekimab	Human monoclonal antibody specific for IL-1α	None	HS: Gottlieb 2020,[141] Kanni 2018.[140] Acne vulgaris: Carrasco 2015.[142] Psoriasis: Coleman 2015[143]	AD	II	NCT04990440
				AD	II	NCT04791319
				HS	II	NCT04019041
				SSc	II	NCT04045743
				AD	II	NCT04021862
				HS	II	NCT04988308
				AD	II	NCT03496974
MEDI8968 (AMG 108)	Human monoclonal antibody targeting IL-1R1: inhibition of its activation by IL-1α and IL-1β	None	None	HS	II, lack of efficacy	
NCT01838499	RPH-104	Macromolecular compound binding human IL-1β	None	None		Schnitzler syndrome
II	NCT04213274					
Spesolimab (BI 655130)	Humanized monoclonal antibody targeting IL-36R	None	GPP: Bachelez 2019[145]	HS	II	NCT04762277
				HS	II	NCT04876391
				PPP	II	NCT04493424
				GPP	II	NCT04399837
				GPP	II	NCT03886246
				GPP	II	NCT03782792
				AD	II	NCT03822832
				AD	II	NCT04086121
				PPP	II	NCT03135548
				PPP	II	NCT04015518
Imsidolimab (ANB019)	Humanized monoclonal antibody targeting IL-36R	None	None	Acne vulgaris	II	NCT04856917
				HS	II	NCT04856930
				Acneiform rash	II	NCT04697069
				Ichthyosis	II	NCT04697056
				GPP	II	NCT03619902
				PPP	II	NCT03633396

(continued)

Table 8 (continued)

Drug	Mechanism of action	Approved indications (FDA and/or EMA)	Published clinical trials beyond label indications	Ongoing clinical trial		
				Disease(s)	Phase	Clinical trial number
REGN6490	Monoclonal antibody targeting IL-36R	None	None	Healthy volunteers Healthy volunteers	I I	NCT04616105 NCT04616079
Etokimab	Monoclonal antibody targeting IL-33	None	AD: Chen 2019[149]	AD	II	NCT03533751
PF-06817024	Monoclonal antibody targeting IL-33	None	None	Chronic rhinosinusitis with nasal polyps and AD	I	NCT02743871
REGN3500	Human monoclonal antibody targeting IL-33	None	None	AD AD	II II	NCT03736967 NCT03738423
CNTO 7160	Monoclonal antibody targeting IL-33R	None	None	Asthma or AD	II	NCT02345928
Tadekinig alfa	Recombinant human interleukin-18-binding protein	None	None	AoSD *NLRC4* mutation and *XIAP* deficiency	II III	NCT02398435 NCT03512314

AD, atopic dermatitis; AoSD, adult-onset Still disease; CAPS, cryopyrin-associated periodic syndromes; DIRA, deficiency of interleukin-1 receptor antagonist; EMA, European Medicines Agency; FCAS, familial cold autoinflammatory syndrome; FDA, US Food and Drug Administration; FMF, familial Mediterranean fever; HIDS/MKD, hyperimmunoglobulin D syndrome/mevalonate kinase deficiency; GPP, generalized pustular psoriasis; HS, hidradenitis suppurativa; MWS, Muckle–Wells syndrome; PG, pyoderma gangrenosum; PPP, palmoplantar pustulosis; RA, rheumatoid arthritis; SJIA, systemic juvenile idiopathic arthritis; SSc, systemic sclerosis; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

Registered and emerging therapies specifically targeting interleukin-1 family members

Interleukin-1 antagonists

To date, several different therapeutic approaches have been developed to antagonize the IL-1 pathway. Among these are anakinra,[114,115] a recombinant IL-1Ra that simultaneously inhibits IL-1α and IL-1β; rilonacept,[116] a recombinant soluble decoy receptor of IL-1β that binds IL-1β and, with lower affinity IL-1α and IL-1Ra; and canakinumab,[117,118] a monoclonal antibody targeting IL-1β. The above-mentioned drugs have received approval by the US Food and Drug Administration and/or the European Medicines Agency for certain inflammatory skin diseases and have been investigated in randomized clinical trials (Tables 4 and 8).

In detail, IL-1-blocking agents have shown therapeutic effects, albeit of differing levels, in Schnitzler syndrome,[119–121] Behçet disease,[122] Still disease,[123–125] Sweet syndrome,[126] PG,[35,127] neutrophilic panniculitis,[128] PG-associated autoinflammatory syndromes [PASH (PG, acne, HS) and PAPASH (pyogenic arthritis, PG, acne, HS)],[129] SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis)[130] and PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and adenitis).[131] In GPP, several reports have documented therapeutic efficacy of anakinra,[132,133] and also canakinumab,[134] whereas only partial and transient clinical remission was observed in patients with PPP treated with anakinra.[135] Anakinra has shown clinical efficacy also in more common diseases, such as HS, as demonstrated in a small open-label study[136] and in a randomized clinical trial.[137] Conversely, data concerning the efficacy of canakinumab in HS, from case reports and series, showed contrasting results, raising the possibility that IL-1α may, in addition to IL-1β, be an important inflammatory mediator in this disease.[138,139]

Three additional investigational mAbs targeting the IL-1 pathway have been investigated in clinical trials: bermekimab (anti-IL-1α), gevokizumab (anti-IL-1β) and MEDI8968 (AMG 108; anti-IL-1R1). Also reported is RPH-104, a heterodimeric fusion protein that inhibits IL-1β (Table 8). Bermekimab has already shown clinical efficacy in patients with HS, both in a randomized clinical trial[140] and in an open-label study.[141] Additionally, the drug has shown encouraging results in open-label studies in acne[142] and psoriasis.[143]

Interleukin-36 antagonists

Three IL-36 antagonists, directly inhibiting IL-36R, are currently in the clinical development phase, namely spesolimab (BI 655130), imsidolimab (ANB019) and REGN6490.

Spesolimab has shown efficacy in GPP treatment in a phase I clinical trial[144,145] and is currently being investigated in phase II studies (Table 8). In a randomized clinical trial conducted on patients with PPP treated with spesolimab, improvement of disease severity was reported in all treatment groups, although the primary endpoint of the trial was not met.[146,147] Spesolimab is currently being investigated in clinical trials for other skin disorders. Imsidolimab has shown a favourable safety profile in a phase I clinical trial in healthy volunteers.[148] Phase II clinical trials are currently ongoing. REGN6490 is currently being investigated in two phase I clinical trials on healthy volunteers (Table 8).

Interleukin-33 antagonists

Etokimab (ANB020) is a humanized IgG1 monoclonal antibody targeting IL-33, and encouraging data have been reported in a phase IIa proof-of-concept clinical trial conducted on patients with AD.[149] Currently etokimab is being investigated in a phase IIb trial (NCT03533751) in patients with AD. Two other monoclonal antibodies targeting IL-33 are currently under investigation in patients with AD: PF-06817024 and REGN3500 (Table 8).

Furthermore, blockade of IL-33 has been explored in AD using a monoclonal antibody targeting IL-33R (CNTO 7160). The safety and efficacy of this drug have been investigated in a phase I trial in patients with asthma, patients with AD and healthy individuals. While laboratory evidence showed inhibition of the IL-33 pathway, no significant clinical improvement was achieved.[150]

Interleukin-18 antagonist

A human recombinant IL-18-binding protein (tadekinig alfa) has been developed and investigated in a phase II open-label clinical trial on 23 patients with AoSD, randomized to receive tadekinig alfa 80 mg or 160 mg subcutaneously, three times per week for 12 weeks. Tadekinig alfa demonstrated a favourable safety profile at both doses and early signs of efficacy, with a response rate of 50%, as endorsed by clinical and laboratory assessment.[151]

Interleukin-1 receptor 3 antagonism

IL-1R3[14] is an accessory receptor of the IL-1 family, crucial for the constitution of the three high-affinity ternary complexes necessary for IL-1, IL-33 and IL-36 signal transmission.[15] IL-1R3 blockade was investigated by Højen *et al.*, by developing a humanized monoclonal antibody targeting IL-1R3 (MAB-hR3).[152] *In vitro*, MAB-hR3 was able to inhibit signalling by IL-1R1, IL-1R4 and IL-1R6. Blocking IL-1R3 had a greater impact in lowering the production of proinflammatory cytokines compared with the inhibition of individual receptors *in vitro* (IL-1R1, IL-1R4 and IL-1R6).The effects of IL-1R3 blockade were also explored *in vivo* using a chimeric mouse monoclonal antibody (MAB-mR3) in murine models of inflammatory diseases driven by IL-1β, IL-33 and IL-36. Treatment resulted in significant disease improvement,[152] suggesting that IL-1R3 blockade may have potential for the treatment of several types of inflammatory diseases in humans.

Conclusions and future directions

Thanks to recent advances in research, the complex pathophysiology of chronic inflammatory skin disorders, and their similarities, differences and driving pathways are being increasingly unravelled, thus identifying eligible targets for therapeutic intervention. Evidence that IL-1 family cytokines play a central role not only in rare monogenic AIDs, but also in some of the most common inflammatory skin diseases is rapidly growing. Further clinical and preclinical data, as well as further clinical trials, will hopefully lead to an extension of future indications and wider use of IL-1 family cytokine antagonists in daily clinical practice. The development of new drugs antagonizing IL-1 family pathways at multiple levels, such as via IL-1R3 antagonism, may have great potential, given that single-cytokine blockade in inflammatory diseases sometimes has limited efficacy.

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