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REVIEW

IRAK4 Targeting: A Breakthrough Approach to Combat Hidradenitis Suppurativa

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Abstract: Hidradenitis suppurativa (HS), a chronic inflammatory condition, features recurrent, painful lesions in the perineal area, severely impairing patients' quality of life. Despite its clinical significance, HS pathogenesis remains incompletely understood, and effective treatments are scarce. Interleukin-1 receptor-associated kinase 4 (IRAK4) is located downstream of IL-1R/TLR in the IL-1R/TLR signaling pathway, which is upstream of the end products of the pathway. IRAK4-targeted drugs can potentially block this pathway, reducing cytokine secretion and alleviating HS symptoms. This paper comprehensively reviews IRAK4 and its family members' physiological functions, systematically examines the IRAK family's roles in the IL-1R/TLR pathway, with a focus on IRAK4, analyzes IRAK4's specific role in HS, strengthening the theoretical basis for using IRAK4-targeted drugs. The text also covers representative drugs of the major biologics currently used in the treatment of HS and describes the IRAK4 inhibitor Zimlovisertib and the IRAK4 degrader KT-474, along with a discussion of the current status of drugs that inhibit IRAK4 in the treatment of HS and the challenges they face.

Keywords: Hidradenitis suppurativa, interleukin-1 receptor-associated kinase 4, IL-1R/TLR signalling pathway, cytokines

Introduction

IRAK4, a serine/threonine kinase in the IRAK family, is characterized by a conserved N-terminal death domain (DD) and a central kinase domain (KD). The DD binds to the adapter protein myeloid differentiation factor 88 (MyD88), while the KD is responsible for IRAK4's catalytic activity.[1,2] When IL-1R/TLR is activated, the signal is mediated through MyD88 to form a "Myddosome". MyD88 fulfils the function of a scaffolding protein, which in turn recruits IL-1R-associated kinases (IRAKs). The process of IRAK4 activation results in the phosphorylation of IRAK1, which subsequently forms a complex with TRAF6, thereby triggering the activation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Mitogen-activated protein kinase (MAPK) pathways. This process promotes Th1/Th17 cell-mediated inflammation characterised by increased levels of TNF-α, IL-6 and IL-17.[3–5]

Clinically, HS presents as nodules, abscesses, sinus tracts, and fistulas, accompanied by pain and inflammation, primarily affecting skin folds in areas like the axillae, groin, buttocks, and perianal region.[6–9] (shown in Figure 1) HS patients experience reduced quality of life due to physical discomfort, psychological stress, comorbidities such as metabolic and cardiovascular diseases, and a shorter life expectancy.[10–12] The true prevalence of HS may be underestimated due to misdiagnosis, with current estimates ranging from 0.05% to 4.1%.[13] Although many studies have investigated HS pathophysiology, its exact mechanisms remain unclear. It is widely believed that HS initiates with hair follicle occlusion and rupture, releasing keratin fibers into the dermis, attracting neutrophils and lymphocytes. In the presence of cytokines, this triggers immune responses, leading to dysregulation and HS progression.[13,14] The IL-1R/TLR signaling pathway plays an important role in the development of HS, and it has been shown that the expression of IRAK4 in HS lesions is much higher than that of non-lesional skin, and the role of IRAK4 in the IL-1R/TLR signaling pathway

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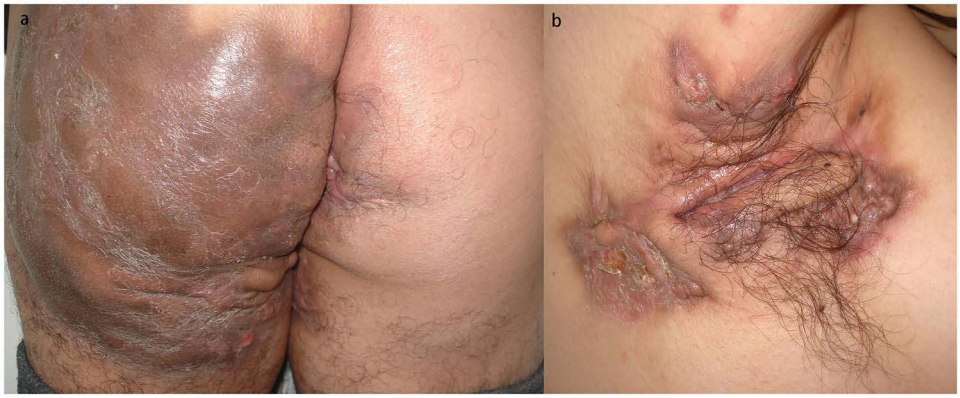

Figure 1 Typical skin lesions of hidradenitis suppurativa. Representative images of the various lesions that are typically found in patient with hidradenitis suppurativa (HS). (**a** and **b**) The patient is a 35-year-old male with an onset of symptoms four years. Large dark brown patch on the left buttock with multiple abscesses, sinus tracts, scar formation, and multiple abscesses penetrating on extrusion. Atrophy, scar formation, and multiple abscesses were seen in the axilla, with yellowish pus coming out on extrusion.

is well recognized. IRAK4 expression increases the secretion of pathogenic cytokines through the relevant signaling pathways, thereby exacerbating disease progression in HS.[15,16] Currently, clinical trials of IRAK4 inhibitors are underway. Further investigation of the specific molecular mechanisms is likely to be beneficial for the subsequent development of drug trials and to provide a theoretical foundation for the marketing of IRAK4 inhibitors.[17]

Physiological Functions of IRAK Family Proteins

The IRAK family, consisting of IRAK1, IRAK2, IRAK3 (IRAKM), and IRAK4, is vital in innate immune system.[18] The involvement of IRAKs in the IL-1R/TLR signaling pathway depends on specific ligands and cell types, and each member has distinct functions. IRAK4 is the primary mediator in HS.[19]

IRAK4

IRAK4, a threonine/serine kinase consisting of 460 amino acids, exhibits dual functions of kinase activity and scaffolding.[20,21] It is a core mediator in the IL-1R/TLR pathways. Upon the binding of IL-1R/TLRs to DAMPs and PAMPs, IRAK4 is drawn to the MyD88 oligomeric complex. In this complex, IRAK4 serves as a scaffold and displays kinase functions. IRAK4's kinase activity is crucial for MyD88-dependent cytokine production and plays a key role in Myddosome assembly.[22] These roles are indispensable for the downstream signaling processes mediated by NF-κB and MAPK.[23–27]

Currently, IRAK4-targeted drugs are in clinical trials. These drugs have relieved symptoms in experimental atopic dermatitis (AD) and HS, indicating IRAK4 as a promising target for inflammatory diseases.[28] Emavusertib, a selective oral IRAK4 inhibitor, shows safety and efficacy in B-cell non-Hodgkin lymphoma and myeloid malignancies, either as monotherapy or in combination.[29–32] Edecesertib, another IRAK4 inhibitor, is being developed for cutaneous lupus erythematosus and rheumatoid arthritis and is well-tolerated and non-toxic.[33] Inhibiting IRAK4 kinase activity blocks the NF-κB pathway and reduces chemokine and cytokine production, making IRAK4-targeted drugs a valuable option for HS treatment.[22]

IRAK1 and IRAK2

IRAK1 and IRAK2 are also members of the IRAK family.[34] Unlike IRAK4, under basal conditions, IRAK1 is predominantly in an inactive state and necessitates upstream stimulation to be activated. Serving as a phosphorylation target of IRAK4, IRAK1 experiences extensive ubiquitination and autophosphorylation following the stimulation of IL-1R/TLR.[20,35,36] While IRAK1 is not a fundamental component of the Myddosome, it engages in interaction with IRAK4 during the process of Myddosome assembly.[18,37] IRAK2, similar to IRAK4, is a crucial Myddosome component and is predicted to be a pseudokinase.[38,39] Myddosome formation promotes auto-activation of IRAK4, followed by sequential

motivation of IRAK1 and IRAK2.[40] Putative binding motifs in IRAK1 and IRAK2 have the capacity to mediate the stimulation of TNF receptor-associated factor 6 (TRAF6) via transient recruitment of the latter to the receptor complex. Upon stimulation, TRAF6 is secreted into the cytoplasm, where it stimulates the NF-κB pathway. Moreover, TRAF6 signalling initiates the MAPK pathway, which in turn leads to the stimulation of activator protein 1 (AP-1) and cAMP-responsive element-binding proteins, leading to the production of proinflammatory cytokines and chemokines.[22,41,42]

Pacritinib, a highly effective kinase inhibitor, exhibits selective targeting of JAK2/FLT3 and IRAK1.[43,44] It suppresses the proliferation of acute myeloid leukemia (AML) cells harboring gene mutations. Primarily, it is utilized in the treatment of hematological malignancies such as primary myelofibrosis.[45–47]

IRAK3

Like other IRAKs, IRAK3 has an N-terminal death domain and a C-terminal TRAF6 binding site.[41] While certain IRAKs play a positive role in regulating the IL-1R/TLR pathway, IRAK3 functions as a negative modulator.[48,49] It downregulates the inflammatory response by impeding the dissociation of IRAK1 or IRAK2 from Myddosome complexes. Reduced IRAK3 expression is associated with increased NF-κB activity and elevated inflammatory cytokines.[50,51] It downregulates the inflammatory response by impeding the dissociation of IRAK1 or IRAK2 from Myddosome complexes. This inhibitory mechanism of IRAK3 is distinct from the positive regulatory effects of other IRAKs in the IL-1R/TLR signaling cascade. Reduced IRAK3 expression is associated with increased NF-κB activity and elevated inflammatory cytokines.[39]

The Pivotal Function of IRAK4 in Triggering the IL-1R/TLR Pathway within HS

When a ligand binds to IL-1R/TLR, IRAK4 is attracted to the MyD88 oligomerization complex. Here, it serves dual functions as both a scaffolding molecule and a kinase.[17,52] There are two main pathways for IL-1/TLR signaling, the MyD88-dependent pathway and the Toll-IL-1 receptor (TIR)-containing structural domain articulin-induced interferon-β (TRIF) pathway. In the MyD88-dependent pathway, the ligand mediates initial activation, which results in the recruitment of MyD88 to the TIR, followed by the recruitment of IRAK4 to the complex and binding to MyD88 and consequent activation of IRAK1.[53] Activation of IRAK1 results in its binding to TRAF6. Subsequently, IRAK1 and TRAF6 are released from the receptor complex and bind to TGF-β-activated kinase 1 (TAK1) and the TAK1-binding protein (TAB) complexes.[54] At this point, the inhibitor of κB kinase (IKK) complex promotes the degradation of IκB (NF-κB inhibitor), which in turn translocates the dissociated NF-κB to the nucleus to induce target gene transcription. On the other hand, TAK1 activates MAPK, which further activates AP-1 (a heterodimer of c-Jun), which translocates to the nucleus and coordinates with NF-κB to initiate transcription of various inflammatory cytokines, chemokines, and co-stimulators. The TRIF signaling pathway manifests itself in the binding of TLRs and ligands to activate TRAF3 and TBK1, resulting in the transcription of interferons.[55,56] It has been established that, in the presence of TLR3, activation of downstream signalling is initiated through the MyD88 non-dependent pathway.[57] Conversely, TLR4 has been demonstrated to activate both MyD88-dependent and non-dependent signalling pathways.[58]

Cytokines secreted by the IL-1/TLR signaling pathway, in which IRAK4 is involved, such as IL-36, IL-17, TNF-α, IFN-γ, and IL-1β, assume important roles in the pathogenesis of HS. IRAK4 oligomerizes through MyD88 to form the "Myddosome" complex, a central platform for IL-1R/TLR signaling, and phosphorylated IRAK4 activates downstream IRAK1, which together promote activation of the TRAF6/NF-κB pathway.[59,60] IL-1β and TNF-α, which are directly upregulated by NF-κB, activate hair follicle epithelial cells and immune cells (such as macrophages), leading to an increase in local vascular permeability and resulting in redness, swelling and pruritus.[61] IL-8 (CXCL8) and CXCL1/CXCL2 attract neutrophils to gather around the follicle, and a chemokine gradient directs neutrophils to penetrate the follicle wall, releasing toxic substances such as elastase and myeloperoxidase.[62] AP-1 and MAPK synergistically upregulate the transcription of matrix metalloproteinases,[63,64] which degrade the follicular basement membrane (eg collagen type IV) and extracellular matrix (ECM), weakening the mechanical stability of the hair follicle and leading to follicular rupture. In skin lesion tissues of HS patients, IRAK4 protein levels were significantly higher than in non-lesion areas and positively correlated with disease

severity. Preclinical models showed that IRAK4 inhibitors reduced NF-κB p65 expression,[65] neutrophil marker MPO levels and abscess diameter in skin lesion areas.[28] This provides substantial evidence in support of the utilisation of IRAK4 inhibitors as a therapeutic intervention for HS. (shown in Figure 2)

Current Treatments for Hidradenitis Suppurativa

Current HS treatments are mainly pharmacological and surgical. Pharmacological treatments range from local and intralesional therapies for mild cases to systemic medications, including antibiotics, hormones, retinoids, immunosuppressants, and biologics, for moderate to severe cases.[66,67] The development of biopharmaceuticals has enabled innovative therapeutic strategies.[68]

Surgical Treatment for HS

Improved reconstructive surgical techniques are changing the role of surgery in HS treatment from a last resort to an early option. Reconstructing larger defects is now more straightforward, facilitating complete excision of diseased areas. Surgical techniques encompass "de-roofing", "local excision", "wide excision", and "radical excision", along with the utilization of fascia post-excision.[69,70] The application of local regional flaps, perforator flaps, and propeller flaps

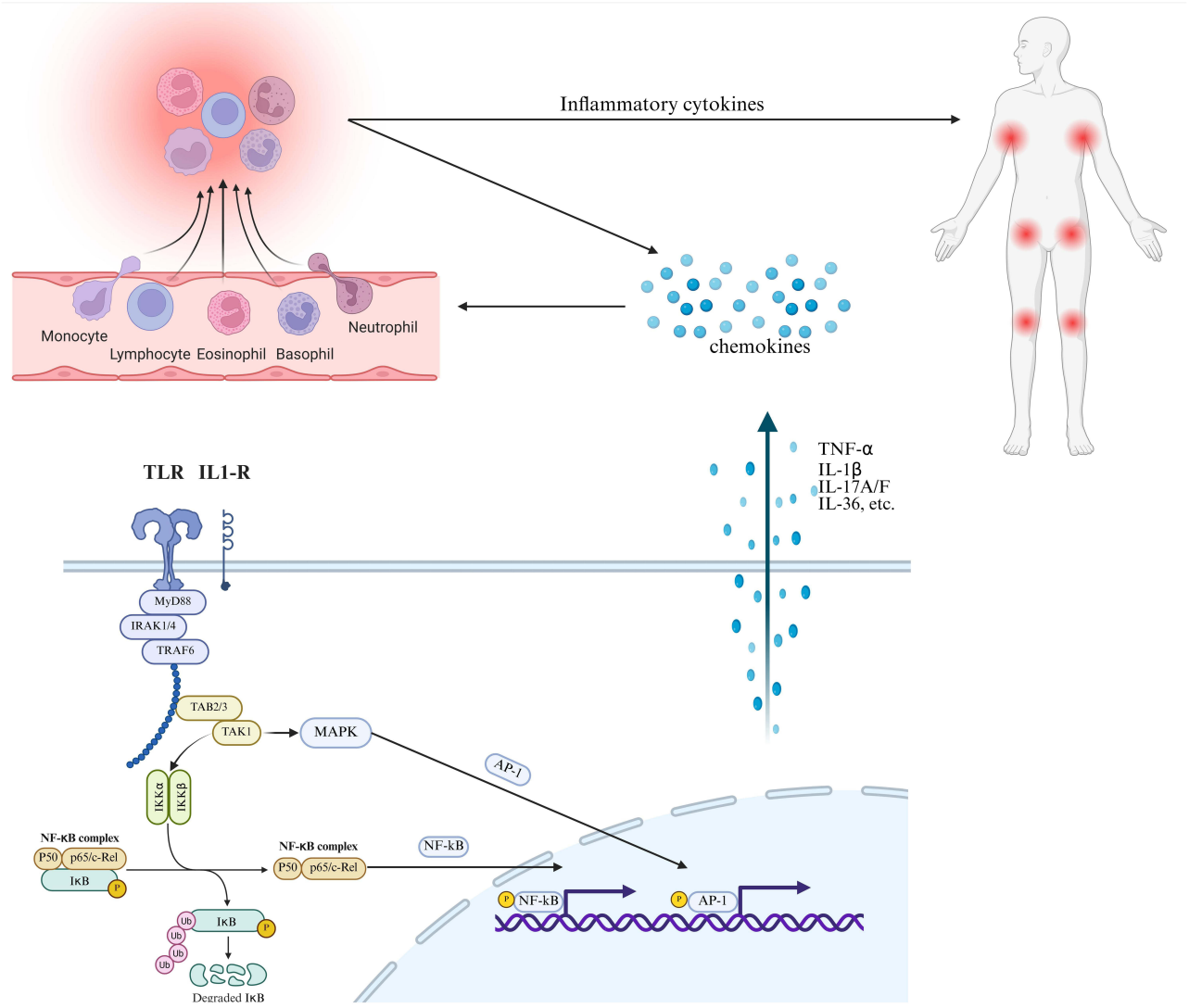

Figure 2 Mechanisms of IRAK4 involvement in IL-1R/TLR signaling pathways.

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composed of fascial skin tissue can lead to superior cosmetic and functional results.[71–75] However, in cases with tunnels and deep nodules, insufficient excision may lead to local recurrence. Combining biological therapy with surgery is recommended, as it has a higher probability of reducing active nodules by 75%.[76]

Biological Agents Currently used in the Treatment of HS

Adalimumab

Adalimumab, a TNF-α inhibitor, is the first approved biologic for moderate-to-severe HS. It is a human-derived recombinant IgG1 monoclonal antibody. Its mechanism lies in impeding the interaction between TNF-α and its receptors.[77–80] By doing so, it effectively alleviates painful nodules and abscesses, thereby enhancing the skin's condition.[81] However, only 50% of HS patients respond to treatment.[82] The most common side effects of Adalimumab include injection site reactions, upper respiratory tract infections, and headache, in addition to the risk of infection (eg, recurrence of tuberculosis) and the risk of potential malignancy, similar to other TNF-α inhibitors.[83–85]

Secukinumab

Secukinumab, a human monoclonal antibody, selectively blocks the binding of IL-17A to its receptor and is the first approved anti-IL-17A drug for HS.[86–88] Secukinumab had a favorable safety profile in Phase III trials, with common side effects of nasopharyngitis, headache, and upper respiratory tract infections,[89,90] and no increased risk of serious infections or Candida infections compared to placebo.[91] Long-term use (52 weeks) maintained efficacy and a stable safety profile.[87]

Bimekizumab

Bimekizumab, a humanized antibody binding to IL-17A, IL-17F, and their heterodimers, may block the activation of the IL-17 receptor A and C heterodimer complex. It has a favorable safety profile and provides symptomatic improvement for moderate-to-severe HS patients.[82,92–95] Bimekizumab is currently undergoing a review process with the FDA to determine its suitability as a treatment for HS. Bimekizumab showed common side effects of oral candidiasis and mild gastrointestinal reactions in Phase III clinical trials, with a favorable safety profile, rapid onset of action, and significant improvement in HiSCR over 48 weeks.[92,95,96]

Povorcitinib

Povorcitinib, a selective JAK1 inhibitor, has shown a 29.30% improvement in the dermatological quality of life index in patients, but its efficacy is still under investigation.[86,97] Povorcitinib had a manageable safety profile in Phase II clinical trials in the 15–75 mg dose group, with common side effects of mild infections (eg, nasopharyngitis) and dyslipidemia, and was administered orally with dose-dependent inhibition of the JAK1 pathway, which resulted in significant reductions in inflammatory markers over 16 weeks.[98,99]

Guselkumab

Guselkumab is a fully human IgG1λ monoclonal antibody that selectively targets the p19 subunit of IL-23.[100] It has demonstrated encouraging efficacy, primarily in the treatment of psoriasis, and is currently being investigated for potential use in other chronic inflammatory skin diseases. The present study reports on the ongoing clinical trials of the drug in HS. Although case reports and series have demonstrated positive results with Guselkumab, Phase 2 studies have yet to confirm this encouraging trend.[101] Guselkumab has demonstrated its efficacy in the treatment of paradoxical HS, as well as cases of HS in patients with paradoxical psoriasis-like reactions following adalimumab treatment. In addition, evidence has demonstrated the efficacy of guselkumab in the treatment of HS patients who also suffer from other comorbidities, such as Crohn's disease.[102] Guselkumab 200 mg subcutaneously every 4 weeks was well tolerated in phase II trials, with side effects comparable to placebo (eg, injection site reactions), and some patients achieved HiSCR at 16 weeks, but efficacy data are more limited.[101,103]

Zimlovisertib

Zimlovisertib, an IRAK4 inhibitor, has completed Phase II clinical trials and shows promise for HS treatment, though further verification of its clinical efficacy is needed.[104,105]

KT-474

KT-474 is a highly selective degrader of IRAK4 among proteolysis-targeting chimeras (PROTAC) degraders. It is composed of three key components: a ligand for Cereblon (CRBN), a linker, and a ligand for IRAK4. This unique composition endows KT-474 with its selectivity in targeting IRAK4 for degradation, which is a significant feature in the realm of PROTAC-based molecular regulation.[106] It leads to IRAK4 ubiquitylation and proteasomal degradation. In early clinical trials, it exhibited anti-inflammatory properties, was more effective than IRAK4 inhibitors, and had a favorable safety profile, reducing lesion severity and cytokine release in moderate-to-severe HS and AD patients.[15,107] (shown in Table 1)

Expectations for IRAK4-Targeted Drugs in Therapeutic Management of HS

Possibility of IRAK4-Targeted Drugs for HS Treatment

Multiple immune pathways are upregulated in lesion tissues, including IFN-γ, IL-36, IL-1, IL17A, IL17F, IL-3/IL-5/GM-CSF, etc. In HS skin, notable responses are observed towards IFN-γ and IL-36. However, it fails to respond to Th2 cytokines such as IL-4, as well as to IL-17A or TNF stimulation. In contrast to AD and psoriasis, HS lacks a dominant Th cytokine axis. Distinct cytokine response pattern in HS may reflect unique immunological mechanisms underlying the disease, setting it apart from AD and psoriasis in terms of cytokine-mediated immune regulation. This may explain the limited efficacy of some targeted drugs in HS.[108,109] In skin samples from patients with HS, the levels of IRAK4 protein are elevated. Additionally, an increase in the infiltration of IRAK4-positive immune cells is associated with the severity of the disease. In HS lesions, there is an upregulation of inflammatory mediators, which is correlated with the overexpression of IRAK4.[15,17] In clinical trials of IRAK4 inhibitors targeting HS, the IRAK4 degrader KT-474 significantly reduced IRAK4 levels in immune cells from PBMCs of healthy volunteers and HS patients and inhibited the production of inflammatory cytokines (eg, TNF-α, IL-6), which may reduce inflammatory infiltration and cytokine release, improve skin lesion severity, and possibly affect the fibrosis process.[15,16,110] The mechanism involves the regulation of the MyD88/IRAK4 signaling pathway, but the specific clinical efficacy still needs to be verified in further trials.

Challenges Faced by IRAK4-Targeted Drugs

Despite the potential of IRAK4-targeted drugs, obstacles exist. The KD amino-acid sequences of IRAK1 and IRAK4 exhibit a high degree of homology. As a result, inhibitors designed for IRAK4 might inadvertently act on IRAK1 as well. Although there is currently no reported resistance data, the potential for drug resistance due to active-site mutations exists. Traditional IRAK4 inhibitors cannot fully inhibit all IRAK4 functions due to its dual kinase and scaffolding roles. IRAK4 degraders may address this issue, and the development and application of these drugs will be a focus in the coming years.

Table 1 Small Molecule Drugs for the Treatment of HS

Medication	Target	Route of Administration	Phase	Trial Status
Adalimumab	TNF-α	Subcutaneous	IV	√(completed)
Secukinumab	IL-17A	Subcutaneous	III	√(completed)
Bimekizumab	IL-17A IL-17F IL-17A/F	Subcutaneous	III	√(completed)
Povorcitinib	JAK	Oral	III	Δ(ongoing)
Guselkumab	IL-23	Subcutaneous	II	Δ(ongoing)
Zimlovisertib	IRAK4	Oral	II	√(completed)
KT-474	IRAK4	Oral	II	Δ(ongoing)

Conclusion

HS affects the quality of life of patients and causes considerable psychological and physical distress. However, the existing treatment options, which include various medications and surgical interventions, have been ineffective or recurrent in a substantial proportion of patients with HS. IRAK4 has emerged as a prominent research focus, with its potential as a therapeutic target for inflammatory skin diseases being a key area of investigation. Clinical trials of IRAK4-targeted drugs, including inhibitors and degraders, are underway, showing early promise in alleviating AD and HS symptoms with satisfactory safety. KT-474, the most advanced IRAK4-selective degrader, significantly reduced IRAK4 levels in immune cell types from healthy volunteers and HS patients. Despite the significant clinical potential of IRAK4-targeted therapeutics, several challenges remain. However, it is important to note that a range of issues, including drug resistance, may emerge in the future. The integration of genomic or proteomic profiles of HS patients has the potential to facilitate the personalisation of IRAK4-targeted therapies and to address the challenges posed by emerging resistance mechanisms.

Data Sharing Statement

There are no additional data available.

Author Contributions

Conceptualization: HZ, ZL, XB; Data Curation: HZ, ZL; Formal Analysis: BQ, DC, PC; Validation: HZ, ZL; Supervision and Project Administration: XB; Writing-Review and Editing: HZ, ZL, BQ, DC, PC, XB. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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