REVIEW

The Role of TYK2 Inhibitors in the Pathogenesis and Treatment of Psoriasis

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BACKGROUND: Psoriasis is a chronic, inflammatory condition that has a substantial effect on quality of life. Tyrosine kinase 2 (TYK2) inhibitors have emerged as a promising class of agents for treating psoriasis. **OBJECTIVE:** To summarize the current evidence on TYK2 inhibitors and their role in the management of psoriasis. **METHODS:** A comprehensive literature search was conducted using a combination of the keywords "psoriasis," "tyrosine kinase," "pathogenesis," "mechanism of action," and "emerging therapies." The authors reviewed all studies and included those that addressed the topic of the review. **RESULTS:** TYK2 plays an integral role in the pathogenesis of psoriasis. Targeting TYK2 as a therapeutic pathway has led to significant improvement in disease severity and quality of life. Deucravacitinib was the first TYK2 inhibitor approved by the Unitefor moderate-to-severe plaque psoriasis. Zasocitinib and envudeucitinib are 2 agents currently undergoing late-stage clinical trials for psoriasis. The mechanism of action for these therapies is similar, targeting the JH2 pseudokinase domain of TYK2, but each has distinct features that differentiate their effectiveness and safety. Several other TYK2 inhibitors are in earlier development, including D-2570, ICP-488, AC-201, and TLL-018. **LIMITATIONS:** This review is limited by the information available in the published literature. In addition, comparisons between studies are limited as varying methodologies were used. **CONCLUSION:** TYK2 inhibition represents a significant advancement for the treatment of psoriasis. Continued research will enable optimization of these agents in managing psoriasis and related immune-mediated diseases. **KEYWORDS:** Psoriasis, systemic therapy, tyrosine kinase 2, TYK2, mechanism of action, efficacy, safety

Psoriasis is a chronic, immune-mediated, inflammatory condition affecting skin, joints, and other internal systems.[1] It affects approximately 1% to 3% of the global population, with an incidence rate of 63.8 cases per 100,000 person-years (PY) in the United States.[2,3] As a chronic relapsing-remitting disease, psoriasis has a substantial effect on quality of life.[4] A wide range of treatment options are available, including both topical and systemic therapies. Tyrosine kinase 2 (TYK2) inhibitors have emerged as a promising class of agents for treating various autoimmune and inflammatory disorders, including psoriasis.[5]

TYK2, a member of the Janus kinase (JAK) family, mediates interleukin (IL)-23–dependent signaling that promotes the differentiation of naive T cells into helper T cell (Th) 17.[6] Th17 subsequently secretes IL-17, a key cytokine that drives the chronic inflammatory cascade of psoriasis.[6] Unlike traditional JAK inhibitors that act through broader, nonselective inhibition, selectively targeting TYK2 results in more precise downstream signaling modulation and a narrower cytokine inhibition profile.[6] Deucravacitinib is a first-in-class, oral, selective, allosteric TYK2 inhibitor that was approved by the United States Food and Drug Administration (FDA) for the treatment of moderate-to-severe plaque psoriasis in adults.[7] Several additional TYK2-targeted therapies are currently under development for psoriasis, highlighting the importance of understanding the distinct mechanisms of action among these agents. This review aims to summarize the current evidence on TYK2 inhibitors and their role in the management of psoriasis.

TYK2 AND ITS ROLE IN PSORIASIS

The pathway between JAK and signal transducer and activator of transcription (STAT) is a mediator of cellular responses signaled by

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various cytokines and growth factors.[8] The signaling cascade that results from activation of the JAK/STAT pathway is fundamental to cellular processes, such as proliferation and differentiation, and the specific response is dependent on the signal inducers and tissue context.[9,10] The mechanism of the JAK/STAT pathway is a complex interplay of cytokine binding and receptor phosphorylation.[11] When a cytokine binds to a JAK receptor, it induces dimerization of the receptors.[10,11] Tyrosine residues on the receptors are then phosphorylated, which generates binding sites for STAT proteins and results in receptor assembly and activation.[10,11] The STAT proteins subsequently undergo phosphorylation and activation, translocating into the cell nucleus to regulate gene expression via binding to specific sites on DNA.[12] There are a total of 4 JAK proteins: JAK1, JAK2, JAK3, and TYK2; JAK1 can pair with each of the other JAK proteins.[13,14] Specifically, JAK2 and TYK2 heterodimers transmit signals induced by type 1 interferon (IFN), IL-12, and IL-23.[15]

TYK2 has the ability to regulate cytokine receptor signaling via its enzymatic activity and through its kinase-independent scaffolding function.[16] In psoriatic disease, TYK2 modulates the downstream signaling of receptors that bind to IL-12, IL-23, IFN-β, and IFN-α.[17,18] In turn, these cytokines control the diverse functions of immune cells such as Th1, Th17, and Th22, which all have a role in the pathogenesis of psoriasis.[17] Studies have shown that the absence of TYK2 decreases the production of psoriasis-related cytokines and the development of epidermal proliferation from IL-23 activation.[15,19]

DEUCRAVACITINIB

Deucravacitinib was approved by the FDA in 2022 for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[20] It is a highly selective allosteric TYK2 inhibitor that specifically targets the Janus homology 2 (JH2) pseudokinase (regulatory) domain.[21–23] By binding to this domain through allosteric means instead of the conserved adenosine triphosphate-binding site in the catalytic domain, deucravacitinib keeps the regulatory domain in an inhibitory configuration, which maintains TYK2 in its inactivated state and halts downstream inflammatory signaling.[21–23] Studies have shown that deucravacitinib has potent binding to TYK2 with minimal to no activity against JAK1, JAK2, or JAK3 at clinical doses.[21–23]

The efficacy of deucravacitinib has been evaluated in multiple phase 2 and 3 clinical trials.[24–29] In a phase 3 clinical trial, patients were randomized to receive either deucravacitinib 6 mg daily, apremilast 30 mg twice daily, or placebo for 52 weeks.[24] After 16 weeks, the deucravacitinib arm experienced significantly higher rates of achieving a ≥75% improvement in Psoriasis Area and Severity Index score (PASI75) compared to apremilast (58.4% vs 35.1%, $P<0.0001$) and placebo (58.4% vs 12.7%, $P<0.0001$).[24] Further, 53.6% achieved a static Physician's Global Assessment (sPGA) score of 0 or 1 compared to 32.1% with apremilast and 7.2% with placebo ($P<0.0001$ for both).[24] Another phase 3 clinical trial reported similar results in patients treated with deucravacitinib compared to placebo and apremilast at Week 16, with a significant difference in achieving PASI75 (53% vs 9.4%, $P<0.0001$ and 39.8%, $P<0.0004$, respectively) and sPGA 0/1 response (49.5% vs 8.6%, $P<0.0001$ and 33.9%, $P<0.0001$, respectively).[28] A significantly greater percentage of patients receiving deucravacitinib achieved a ≥90% improvement in Psoriasis Area and Severity Index score (PASI90; 35.5%) and a ≥100% improvement in Psoriasis Area and Severity Index score (PASI100; 14.2%) compared to other groups (PASI90: apremilast 19.6%, placebo 4.2%, $P<0.0001$ for both; PASI100: apremilast 4.8%, placebo 0.6%, $P<0.0001$ for both).[24] Patients treated with deucravacitinib were monitored through Week 24 and Week 52, demonstrating sustained response rates for PASI75 and sPGA 0/1.[24,28] The long-term extension trial of deucravacitinib demonstrated maintained clinical and patient-reported outcomes at the 2-, 3-, and 4-year evaluations.[30–32] After 4 years of treatment with deucravacitinib, 47.5% of patients maintained PASI90 and 49.4% achieved Dermatology Life Quality Index (DLQI) of 0 or 1.[32]

A phase 4 multicenter, randomized,a controlled study evaluated the effect of deucravacitinib on quality of life in patients with plaque psoriasis who were treated in a community setting.[33] Patients who received deucravacitinib had superior responses compared to placebo for DLQI 0/1 (33.3% vs 6.7%, $P=0.0001$), DLQI meaningful change threshold response rates (72.5% vs 53.3%, $P=0.011$), and adjusted mean change from baseline in whole-body itch numeric rating scale (-3.9% vs -1.8%, $P<0.0001$) at Week 16.[33] The long-term extension reported that DLQI 0/1 responses were maintained through Week 52 across all of the endpoints analyzed.[34]

Given its mechanism of action, deucravacitinib causes less modification of cytokine signaling vs other JAK inhibitors, resulting in a narrower adverse effect (AE) profile. It is the only JAK or TYK2 inhibitor indicated for psoriasis that does not have a boxed warning.[35,36] In 2 phase 3 trials, deucravacitinib was well tolerated, with AE rates consistent with placebo and apremilast, and most AEs were mild and self-resolved.[24,28] Patients discontinued deucravacitinib at a lower rate than the other groups at Week 16 and Week 52, and discontinuation rates were similar through 3 years of treatment.[29,31,32,36] The most common AEs for deucravacitinib were nasopharyngitis and upper respiratory tract infections, which were similar to placebo and apremilast.[29,37] Other common AEs included nausea, headache, and diarrhea, though these rates were lower than those seen with apremilast.[29,37] Further, rates of serious AEs were also similar between deucravacitinib, apremilast, and placebo, and no serious AEs led to treatment discontinuation.[29] In particular, rates of major adverse cardiovascular events (MACE; 0.3/100 PY, 0.9/100 PY, and 1.2/100 PY), venous thromboembolic events (VTEs; 0.2/100 PY, 0, and 0), and malignancies (1.0/100 PY, 0.9/100 PY, and 0) were all low and consistent among deucravacitinib, apremilast, and placebo, respectively.[29] In the long-term extension trial reporting 4 years of safety data for deucravacitinib, exposure-adjusted incidence rates per 100 PY were comparable or decreased from 1 year to 4 years for all AEs, serious AEs, deaths, discontinuations due to AEs, herpes zoster, malignancies, MACE, and VTEs.[32]

A recent expert consensus panel provided recommendations regarding the efficacy and safety of deucravacitinib.[38] The panel concluded that deucravacitinib has a superior safety profile compared to traditional JAK inhibitors and did not find evidence of a causal role for deucravacitinib in inducing laboratory abnormalities.[38]

ZASOCITINIB (TAK-279)

Zasocitinib is an oral allosteric inhibitor of TYK2 that, like deucravacitinib, binds to the JH2 pseudokinase domain of TYK2.[39,40] The difference between these 2 agents lies in the design of zasocitinib. This molecule was identified via an artificial intelligence-assisted, computationally enabled design strategy, therefore resulting in a reported higher level of selectivity compared to deucravacitinib.[39] The molecular structure of zasocitinib includes a methoxycyclobutyl ring that fits into the TYK2/JH2 domain-binding pocket but is obstructed from JAK1-JAK2/JH2 domains.[39] The molecule demonstrated strong cellular potency, with >1,000-fold selectivity over other JAK isoforms, as well as favorable pharmacokinetic and metabolism profiles.[39]

One study found that zasocitinib has a 1 million-fold greater biochemical selectivity to the TYK2/JH2 domain, with no detectable binding to the JAK1/JH2 domain.[40] In contrast, deucravacitinib has an 87-fold greater biochemical selectivity for the TYK2/JH2 domain compared to the JAK1/JH2 domain.[40] Further, pharmacologic testing revealed that zasocitinib had potent inhibition of TYK2 signaling from IL-23 and IL-12–stimulated phosphorylated STATs, greater than the most potent JAK inhibitor, baricitinib.[40] Zasocitinib 30 mg daily showed >90% inhibition of TYK2 while having no impact on JAK1, JAK2, or JAK3.[40] Zasocitinib has also demonstrated greater sustained inhibition of TYK2-dependent pathways compared to other TYK2 inhibitors.[40,41]

A phase 1 clinical trial of 25 patients evaluated varying doses of zasocitinib (5 mg, 10 mg, or 30 mg) compared to placebo for a total of 28 days.[42] Results demonstrated decreases in the thickness of lesional skin ($P<0.05$) as well as in the expression of psoriasis-related genes (*KRT16*, IL-17A, IL-17F, and IL-22).[42] There was also up to 50% improvement in the activity of several pathways ($P<0.01$ vs placebo) associated with psoriasis via microarray analysis.[42]

In a phase 2b clinical trial, patients were randomized to receive zasocitinib 2 mg, 5 mg, 15 mg, or 30 mg once daily or placebo for 12 weeks.[43] After 12 weeks of treatment, PASI75 was achieved by 18%, 44%, 68%, and 67% of patients receiving zasocitinib 2 mg, 5 mg, 15 mg, and 30 mg, respectively (compared to 6% receiving placebo).[43] PASI90 was achieved by 46% of patients treated with zasocitinib 30 mg daily; PASI100 was achieved by 33%, and a Physician's Global Assessment (PGA) score of 0 or 1 was reached by 52% of patients taking the same dose.[43] Patients receiving zasocitinib 30 mg also experienced greater reduction in DLQI from baseline compared to other doses and placebo, denoting a dose-dependent improvement in health-related quality of life.[43]

Treatment-emergent adverse events (TEAEs) occurred in 53% to 62% of patients receiving the 4 different doses of zasocitinib and 44% receiving placebo.[43] The most frequent TEAEs were COVID-19, acne, acneiform dermatitis, and diarrhea.[43] There was no dose dependency for TEAEs and no clinically meaningful differences in laboratory parameters.[43] Similar to other TYK2 inhibitors, there was a lack of JAK-related safety signals, substantiating the high level of selectivity for TYK2 by zasocitinib.

ENVUDEUCITINIB (ESK-001)

Another selective allosteric TYK2 inhibitor in development is envudeucitinib. Like other TYK2 inhibitors, this molecule binds to the JH2 domain of TYK2; preclinical studies reported envudeucitinib was highly selective for TYK2, with no off-target effects on JAK1, JAK2, and JAK3.[44] Envudeucitinib has a molecular structure that separates it from other TYK2 inhibitors, with a modified arrangement and strategic deuteration sites that contribute to its metabolic stability and pharmacodynamic properties.[44] In fact, there is no measurable inhibition of JAK1, JAK2, or JAK3 by envudeucitinib.[45] It also exhibits >24 hours of steady state time above IC50 and IC90, indicating prolonged and consistent TYK2 targeting.[45] In a phase 1 clinical trial, envudeucitinib was found to inhibit the downstream TYK2 pathway and showed dose-dependent inhibition of IFN-induced genes and SIGLEC1, a novel TYK2-responsive biomarker.[45] Most TEAEs were mild and no serious TEAEs were noted.[45]

A phase 2 clinical trial (STRIDE; NCT05600036) evaluated patients treated with envudeucitinib, ranging in dosages of 10 mg once daily to 40 mg twice daily, compared to placebo.[46] Similar to the phase 1 trial, a dose-dependent relationship was seen, with 40 mg twice daily dosing having maximal efficacy.[46] After 12 weeks of treatment, a greater percentage of patients achieved PASI75 in each envudeucitinib dose arm vs placebo (64% in the 40 mg twice daily arm vs 0% in the placebo group, $P<0.001$).[46] Further, in patients treated with the 40-mg twice-daily dosage, 39% ($P<0.0001$) achieved PASI90 and 15% ($P=0.013$) achieved PASI100, compared to 0% with placebo.[46] sPGA 0/1 and sPGA 0 were achieved by 59% ($P<0.0001$) and 23% ($P=0.0017$), respectively.[46] Patients also showed improvement in DLQI, with 64% receiving 40 mg twice daily achieving DLQI 0/1 compared to 18% who received placebo ($P<0.0001$).[46] A durability of over 4 weeks was reported after the last dose of envudeucitinib; 83% of patients receiving 40 mg twice daily maintained PASI75 and 85% maintained PASI90.[46] In vivo analysis of a novel TYK2 biomarker, SIGLEC1, confirmed that the 40-mg twice-daily dosage had the greatest and continuous inhibition of TYK2.[46] In the open-label extension study out to 52 weeks, 78% of patients treated with envudeucitinib 40 mg twice daily achieved PASI75, while 61%, 39%, and 39% achieved PASI90, PASI100, and sPGA 0, respectively.[47] Notably, the 52-week rates were greater than the original 12-week trial. Further, 62% of patients continued to demonstrate improvement in PASI over time.[47]

TEAEs were experienced in 50.3% of patients receiving any dose of envudeucitinib, and only 2.6% of patients discontinued envudeucitinib due to an AE.[46] Similarly, the open-label extension study reported that only 3.7% of patients discontinued envudeucitinib due to an AE.[47] The most frequent TEAEs included headache, upper respiratory tract infection, and nasopharyngitis.[46] Additionally, Grade ≥3 TEAEs were only reported in 5.3% of patients.[46]

EMERGING THERAPIES

Several other TYK2 inhibitors are currently undergoing clinical development for psoriasis. D-2570 is an oral TYK2 inhibitor that selectively inhibits the JH2 pseudokinase domain of TYK2.[48] A recent phase 2 clinical trial completed in China found that patients treated with D-2570 (at doses 18 mg, 27 mg, or 36 mg once daily) had a significantly higher response rate for PASI75 (85.0%–90.0% vs 12.5% for placebo, $P<0.001$ for all), PASI90 (70.7%–77.5% vs 5.0% placebo, $P<0.001$), PASI100 (39.0%–50.0% vs 2.5% placebo, $P<0.005$), and sPGA 0/1 (80.5%–87.5% vs 20.0% placebo, $P<0.001$) at all dosages compared to placebo after 12 weeks of treatment.[48] D-2570 also had greater efficacy vs placebo at Weeks 4 and 8.[48] TEAEs occurred in 70.2% of patients receiving D-2570 and 62.5% of patients receiving placebo.[48] Most TEAEs were

mild or moderate, with the most common being upper respiratory tract infection.[48] In analyzing pharmacokinetics, D-2570 showed sustained suppression of IL-17A over 12 weeks.[48]

ICP-488 is another TYK2 inhibitor that is being studied in clinical trials in China.[49] As an allosteric TYK2 inhibitor, it also binds to the JH2 domain. A phase 2 clinical trial reported that following treatment with 6 mg or 9 mg once daily, 77.3% and 78.6% achieved PASI75, respectively (vs 11.6% with placebo, $P<0.001$).[49] Rates of achieving PASI90, PASI100, and sPGA were also statistically significant.[49]

Additionally, AC-201 is a small molecule that binds to the JH2 domain and inhibits TYK2 and JAK1.[50] A phase 2 clinical trial conducted in China revealed significantly greater rates of PASI75, PASI90, and sPGA with all doses compared to placebo.[50] AC-201 was well tolerated with no serious AEs.[50]

Another TYK2/JAK1 inhibitor, TLL-018, recently completed a phase 1B clinical trial.[51] This study reported that the drug was well tolerated, with most TEAEs being mild to moderate in severity.[51] Efficacy data at Week 12 were promising.[51]

CONCLUSION

TYK2 inhibition represents a significant advancement in the treatment landscape of psoriasis, offering a novel mechanism that selectively targets key inflammatory pathways. Deucravacitinib has demonstrated both efficacy and safety, establishing proof of concept for this therapeutic class. As more TYK2 inhibitors, such as zasocitinib and envudeucitinib, emerge, additional studies will be essential to delineate differences in efficacy, safety, and long-term outcomes. Continued research into TYK2 signaling and its broader immunologic implications will enable optimization of these agents in managing psoriasis and related immune-mediated diseases.

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