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REVIEW

Deucravacitinib for the treatment of psoriatic arthritis: the evidence so far

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Abstract

Psoriatic arthritis (PsA) is a heterogeneous disease that may develop in up to 30% of patients with psoriasis. PsA mainly involves peripheral joints; however, axial skeleton and entheses can also be involved. PsA is the result of a complex interplay between an individual's genotype and environmental factors that triggers an immune response and leads to the production of a cytokine cascade. Even though there are about 17 targeted therapies for PsA, a significant percentage of patients fail to respond to such treatments, have a partial response or develop side-effects. This article aims to review the current knowledge on deucravacitinib, a new oral small molecule that selectively inhibits tyrosine kinase 2 (TYK2), for the treatment of PsA. TYK2, a member of the Janus kinase (JAK) family, is responsible for mediating intracellular signalling of cytokines involved in the pathogenesis of PsA and psoriasis, namely IL-12, IL-23, and type I interferons. Recently, deucravacitinib was approved by the FDA for the treatment of moderate-to-severe plaque psoriasis and is currently being evaluated in phase III clinical trials in PsA. In a phase II clinical trial, deucravacitinib showed sustained effectiveness in several domains of PsA, namely arthritis, enthesitis and dactylitis, was well tolerated, and had a favourable safety profile. In patients with psoriasis, deucravacitinib had shown a higher efficacy than placebo and apremilast. Deucravacitinib is a promising therapy, with a unique mechanism of action. Results from the phase III programme and studies evaluating long-term response and head-to-head comparisons with other targeted agents will be important to establishing the position of deucravacitinib in the management of PsA.

Keywords: deucravacitinib, psoriatic arthritis, tyrosine kinase inhibitor.

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease that may develop in up to 30% of patients with psoriasis.[1] This disease affects men and women equally, usually starts between 40 and 50 years of age, and has a prevalence of 0.10–0.25% in adults.[2,3] PsA is a heterogeneous disease that mainly involves peripheral joints; however, axial skeleton and entheses can also be involved.[4] The most frequent PsA subtypes are peripheral polyarthritis (rheumatoid-like) and asymmetric oligoarthritis. However, other recognisable PsA phenotypes include monoarthritis, predominantly distal interphalangeal disease, dominant axial disease and 'arthritis mutilans', a mutilating subtype of the disease with osteolysis of the digits.[5] Many patients may also develop dactylitis, a sausage-shaped swelling of the digits, and nail lesions such as nail pitting, subungual hyperkeratosis, onycholysis and oil-drop discolouration.[5]

PsA is the result of a complex interplay of genetics and environmental factors that triggers an immune response, which leads to the production of a cytokine cascade that includes tumour necrosis factor (TNF), IL-17 and IL-23.[6] The IL-23–IL-17 signalling pathway is currently considered the main pathogenic pathway.[7,8]

Regarding genotype factors, studies have revealed a strongest genetic association between PsA and class I major histocompatibility complex (MHC) genes, namely *HLA-B**27, *HLA-B**38, *HLA-B**08 and *HLA-B**39.[9] Furthermore, some environmental risk factors for PsA were identified, including obesity, severe psoriasis, scalp,

genital and inverse psoriasis, nail disease, and trauma or mechanical stress (Koebner's phenomenon).[10,11]

Over the last decade, an improved understanding of the pathogenesis of PsA has led to the development of effective biological disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs, which granted a better disease control and an improvement in the quality of life of patients with PsA. Even though there are about 17 targeted therapies for PsA, a significant percentage of patients fail to respond to such treatments or have a partial response.[12] Furthermore, the majority of the approved therapies are injectable, which may cause pain, anxiety and local reactions in the injection site in some patients.[13] Oral agents have the advantage of being painless and practical, which may improve therapeutic compliance, especially in patients with needle phobia. Unfortunately, few approved oral therapies are available and include Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib) and a phosphodiesterase 4 (PDE4) inhibitor (apremilast).

This article aims to review the current knowledge on deucravacitinib, a new oral small molecule that selectively inhibits tyrosine kinase 2 (TYK2), for the treatment of PsA.

Review

Role of TYK2 in the pathogenesis of PsA

TYK2, a member of the JAK family, plays an integral role in immune responses of innate immunity cells. TYK2 is responsible for mediating signals by cytokines involved in the pathogenesis of PsA and psoriasis, namely IL-12, IL-23 and type I interferons (IFNα and IFNβ), leading to inflammatory cascade responses.[14,15]

Previous studies have demonstrated that TYK2 deficiency leads to specific impairment of immune response pathways in mice, such as the incapacity of T helper 1 (T_H1) cell differentiation and *IFNG* gene transcription induced by IL-12, the inability of IL-23 to stimulate the secretion of other cytokines by T_H17 cells, and the reduced ability of IFNα to induce gene expression or antiviral and immune responses.[16,17] According to previous case reports, patients with loss-of-function mutations in the *TYK2* gene have a primary immunodeficiency disease characterized by an increased susceptibility to intracellular bacterial and viral infections.[18,19] On the other hand, previous literature supports that *TYK2* inactivation provides protection against multiple autoimmune diseases, including psoriasis.[20–23] Considering that TYK2 is involved in the signalling process of important cytokines linked to the pathogenesis of PsA, its inhibition presents as a promising therapeutic target for PsA.

Deucravacitinib

Deucravacitinib is an oral, highly selective TYK2 inhibitor recently approved by the FDA for the treatment of moderate-to-severe plaque psoriasis.[24] This molecule has a distinct mechanism of action from other JAK inhibitors. Whilst JAK inhibitors bind to the conserved active domain at the adenosine triphosphate (ATP) binding site (competitive inhibition), deucravacitinib binds to the regulatory pseudokinase (JH2) domain of TYK2 (allosteric inhibition), showing minimal or no inhibition of JAK1, JAK2 and JAK3.[25,26] Other JAK inhibitors, such as tofacitinib, baricitinib and upadacitinib, variably inhibit JAK1, JAK2 and JAK3 but not TYK2.[27] The high selectivity of deucravacitinib for TYK2 is expected to grant a better safety profile than other JAK inhibitors, with fewer side-effects, namely dyslipidaemia and cytopenias (anaemia, leukopenia or thrombocytopenia).[27,28]

Efficacy and safety of deucravacitinib in the treatment of PsA

A randomized, double-blind, placebo-controlled, multicentre phase II trial was started in March 2019 (NCT03881059). Patients with a PsA diagnosis for at least 6 months and who met ClASsification criteria for Psoriatic Arthritis (CASPAR), had active disease (defined as at least three tender and at least three swollen joints), C-reactive protein levels ≥3 mg/L, and at least one psoriatic lesion 2 cm or larger, were included. Patients also had to have failed or be intolerant to at least one non-steroidal anti-inflammatory drug (NSAID), corticosteroid, and/or conventional synthetic DMARD, or one anti-TNF agent.[29] Patients were randomized 1:1:1 to deucravacitinib 6 mg once daily (n=70), deucravacitinib 12 mg once daily (n=67) or placebo (n=66). American College of Rheumatology-20 (ACR-20) response at week 16 was considered the primary endpoint. Key secondary endpoints included improvement from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) and Short Form-36 Physical Component Score (SF-36 PCS). Additional endpoints included ACR-50/70 responses, HAQ-DI response (≥0.35 improvement from baseline), minimal disease activity (MDA, defined by the presence of at least five of the seven following criteria: tender joint count ≤1, swollen joint count ≤1, Psoriasis Area and Severity Index (PASI) ≤1 or body surface area ≤3, patient pain visual analogue score ≤15, patient global disease activity ≤20, HAQ ≤0.5, and tender entheseal points ≤1), enthesitis resolution (Leeds Enthesitis Index), adjusted change from baseline in the Psoriatic Arthritis Disease Activity Score (PASDAS) and in the Disease Activity Index for Psoriatic Arthritis Score (DAPSA), and adverse events (AEs).[29]

Of the 203 randomized patients, 180 (89%) completed 16 weeks of treatment. The main reasons of discontinuation were AEs (*n*=8, 34.8%) and patient withdrawal across the treatment arms (*n*=10, 43.5%).

Demographic and baseline disease characteristics were similar across the two treatment groups and the control group. Sixty-five percent of patients were using conventional synthetic DMARDs at baseline, 12.3% were using oral steroids and 15.8% were using anti-TNF agents.[29] ACR-20 response was significantly higher in patients receiving deucravacitinib 6 mg daily (52.9%, *p*=0.0134) and 12 mg daily (62.7%, *p*=0.0004) when compared to placebo (31.8%) at week 16. Furthermore, ACR-50 response were higher in both treatment groups (24.3%, *p*=0.0326 and 32.8%, *p*=0.0016 for deucravacitinib 6 mg and 12 mg groups, respectively) than in the placebo group (10.6%) at week 16. For ACR-70 response, similar results were observed with significantly higher response rates in the treatment groups.[29] At week 16, all key secondary endpoints were achieved (Table 1).

Rates of treatment-related AEs were 25.4% in the deucravacitinib 6 mg group, 31.4% in the deucravacitinib 12 mg group and 9.1% in the placebo group. Nasopharyngitis, sinusitis, headache, rash and diarrhoea were the

Table 1. Secondary and additional efficacy endpoints at week 16.

	Placebo (*n*=66)	Deucravacitinib	
		6 mg daily (*n*=70)	12 mg daily (*n*=67)
Primary endpoint			
ACR-20 Response rate, % (95% CI); *p* value	31.8 (20.6 to 43.1)	52.9 (41.2 to 64.6); 0.0134	62.7 (51.1 to 74.3); 0.0004
Secondary endpoints			
HAQ-DI Adjusted mean change from baseline (95% CI); *p* value	−0.1 (−0.2 to 0.0)	−0.4 (−0.5 to −0.2); 0.0020	−0.4 (−0.5 to −0.3); 0.0008
SF36-PCS Adjusted mean change from baseline (95% CI); *p* value	2.3 (0.4 to 4.2)	5.6 (3.8 to 7.5); 0.0062	5.8 (3.9 to 7.7); 0.0042
Additional endpoints			
ACR-50 Response rate, % (95% CI); *p* value	10.6 (3.2 to 18.0)	24.3 (14.2 to 34.3); 0.0326	32.8 (21.6 to 44.1); 0.0016
ACR-70 Response rate, % (95% CI); *p* value	1.5 (0.0 to 4.5)	14.3 (6.1 to 22.5); 0.0044	19.4 (9.9 to 28.9); 0.0003
Enthesis resolution (LEI) Response rate, % (95% CI); *p* value	*n*=31 22.6 (7.9 to 37.3)	*n*=39 51.3 (35.6 to 67.0); 0.0138	*n*=26 50.0 (30.8 to 69.2); 0.0393
Dactylitis resolution Response rate, % (95% CI); *p* value	*n*=25 60.0 (40.8 to 79.2)	*n*=30 76.7 (61.5 to 91.8); NA	*n*=24 79.2 (62.9 to 95.4); NA
PASDAS Adjusted mean change from baseline (95% CI); *p* value	−1.1 (−1.5 to −0.7)	−2.0 (−2.4 to −1.6); 0.0003	−2.1 (−2.5 to −1.8); <0.0001
DAPSA Adjusted mean change from baseline (95% CI); *p* value	−13.3 (−17.7 to −9.0)	−23.2 (−27.5 to −19.0); 0.0004	−25.6 (−30.0 to −21.2); <0.0001
MDA Response rate, % (95% CI); *p* value	7.6 (1.2 to 14.0)	22.9 (13.0 to 32.7); 0.0119	23.9 (13.7 to 34.1); 0.0068

ACR, American College of Rheumatology; DAPSA, Disease Activity Index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire – Disability Index; LEI, Leeds Enthesitis Index; MDA, Minimal Disease Activity; NA, not available; PASDASI, Psoriatic Arthritis Disease Activity Score; SF36-PCS, Short Form-36-Physical Component Summary.
Adapted from ref.[29]

most common AEs in patients treated with deucravacitinib. Most AEs were mild or moderate. No deaths and no serious AEs were reported in patients treated with deucravacitinib, including no serious infections, herpes zoster, opportunistic infections, cytopenias, major cardiovascular events or thrombotic events. No significant change from baseline in serum lipids was observed in any group.[29]

In part B (weeks 16–52) of the phase II PsA trial, patients who did not achieve MDA with deucravacitinib switched to ustekinumab at the approved PsA dose. Patients who achieve MDA with deucravacitinib continue this agent at the same dose as before, and all patients previously treated with placebo started ustekinumab. Changes in PASDAS and AEs were reported.[30]

Of the 180 patients who completed part A, 173 (96%) were included in part B. Of the 118 patients initially randomized to deucravacitinib, 25% (n=29) achieved MDA at week 16 and continued at the same dose. All other patients switched to ustekinumab in part B, 100% (n=55) from the placebo group, 78% (47/60 patients) from the deucravacitinib 6 mg group and 72% (42/58 patients) from the deucravacitinib 12 mg group.[30]

Decrease in mean PASDAS score observed at week 16 was maintained at week 52 in patients who continued deucravacitinib. Improvements in other outcomes, namely ACR responses, PASI, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and DAPSA, were also sustained at week 52.[30]

Patients who had not achieved MDA on deucravacitinib at week 16 showed a decrease in mean PASDAS score at week 52 after switching to ustekinumab.

The safety profile of deucravacitinib was similar in both parts A and B. All AEs were mild or moderate, except two AEs in one patient who reported psoriatic arthropathy and peripheral neuropathy that occurred concurrently whilst the patient was hospitalized. No thrombotic events, opportunistic infections, herpes zoster, malignancy or death were reported in patients treated with long-term deucravacitinib.[30]

Phase III studies are currently in the recruiting phase (NCT04908202 and NCT04908189).

Deucravacitinib for psoriasis and other immune-mediated diseases

Deucravacitinib is being studied in a wide spectrum of immune-mediated diseases, including psoriasis, lupus and inflammatory bowel disease (Table 2).

In the phase II trial of psoriasis, patients treated with deucravacitinib at doses of 3 mg daily and higher for 12 weeks achieved significantly greater PASI75 rates than patients in the placebo group (39% with deucravacitinib 3 mg daily, 60% with deucravacitinib 3 mg twice daily or higher; p<0.001).[31]

Furthermore, improvement in quality of life (assessed by the Dermatology Life Quality Index Questionnaire; DLQI) was observed in the groups receiving 3 mg of deucravacitinib twice daily, 6 mg twice daily and 12 mg once daily (42%, 60% and 64%, respectively, *versus* 4% in the placebo group).[31]

Regarding safety data, 55–80% of patients reported AEs in the groups treated with different doses of deucravacitinib and 51% of patients reported AEs in the placebo group. The most common AEs were nasopharyngitis, headache and diarrhoea. Only four patients, from the placebo group and deucravacitinib 3 mg groups, reported serious AEs. As in the PsA trial, no cases of herpes zoster infection, tuberculosis, opportunistic infections or cardiovascular events were reported.[31]

In both phase III trials (POETYK PSO-1 and POETYK PSO-2), deucravacitinib 6 mg once daily showed a superior efficacy *versus* apremilast 30 mg twice daily (active control) and placebo, at week 16, regarding PASI75 and physician global assessment (PGA) 0/1 (p<0.0001).[32,33] Efficacy improved beyond week 16 and was maintained until week 52.[32,33] The superiority of deucravacitinib over apremilast was even greater at week 24 (p<0.0001).[32,33] Deucravacitinib also demonstrated a greater impact on quality of life in both trials, with a significantly greater DLQI 0/1 response rate at week 16 (37.6–41.0%), *versus* patients who received placebo (p<0.0001) or apremilast (p<0.0088).[32,33]

In both phase III trials, deucravacitinib proved to be well tolerated and safe. At week 16, patients treated with deucravacitinib had a slightly lower percentage of AEs than patients treated with apremilast or placebo. The most frequent AEs were upper respiratory tract infection, which are in line with the results in the previous trial. Headache, diarrhoea and nausea were also reported, with a similar frequency in patients treated with deucravacitinib and placebo and a higher frequency in patients treated with apremilast. No cases of opportunistic infections, tuberculosis or significant changes in cholesterol levels and blood cell counts were reported.[32,33]

Discussion

Fortunately, in the past decade, the pathogenesis of PsA has been better understood, leading to the

Table 2. Ongoing clinical trials of deucravacitinib in patients with psoriasis, psoriatic arthritis and other inflammatory diseases.

Clinical trials of deucravacitinib				
Disease	**NCT number**	**Phase**	**Recruitment status**	**Estimated study completion date**
Psoriasis				
Paediatric population	NCT04772079	Phase III	Recruiting	September, 2031
Scalp psoriasis	NCT05478499	Phase III	Recruiting	October, 2024
Nail psoriasis	NCT05124080	Phase I	Not yet recruiting	April 2025
Psoriatic arthritis	NCT04908189	Phase III	Recruiting	August, 2026
	NCT04908202	Phase III	Recruiting	May, 2027
Ulcerative colitis	NCT04613518	Phase II	Recruiting	March, 2024
	NCT03934216	Phase II	Active, not recruiting	April, 2023
Crohn's disease	NCT03599622	Phase II	Active, not recruiting	September, 2024
Ulcerative colitis and Crohn's disease	NCT04877990	Phase II	Recruiting	June, 2027
Systemic lupus erythematosus	NCT03920267	Phase II	Active, not recruiting	November, 2023
	NCT05617677	Phase III	Recruiting	December, 2027
	NCT05620407	Phase III	Not yet recruiting	December, 2027
Discoid and/or subacute cutaneous lupus erythematosus	NCT04857034	Phase II	Recruiting	October, 2024
Alopecia areata	NCT05556265	Phase II	Not yet recruiting	December, 2024

development of several new therapies such as anti-TNF, anti-IL-12/23, anti-IL-17 and anti-IL-23 agents and JAK inhibitors.[9] These new drugs allowed a better disease control, lesser joint damage and an improvement in quality of life of patients with PsA. However, not all patients with PsA responded favourably to the approved therapies.[12] Additional drugs are under investigation and will likely lead to better disease control in patients with multirefractory PsA.

Deucravacitinib, a novel oral selective TYK2 inhibitor, has shown promising results in PsA and psoriasis treatment as well as a good safety profile. In a phase II clinical trial including patients with active PsA, deucravacitinib, given at 6 mg or 12 mg daily, showed higher efficacy in several domains of PsA, namely arthritis, enthesitis and dactylitis.[29,30] Furthermore, an improvement in multiple patient-reported outcomes, including physical function (assessed by HAQ) and quality of life (assessed by SF-36 PCS), was observed as early as week 4 of treatment.[29] On the psoriasis development programme, deucravacitinib showed a higher efficacy *versus* apremilast.[32,33]

A phase II study in patients with moderate-to-severe plaque psoriasis showed that a daily dose of at least 3 mg of deucravacitinib was necessary to be effective for skin lesions.[31] In phase II trials of PsA, both 6 mg and 12 mg daily doses were used and AEs were similar in the two groups.[29] In general, deucravacitinib was well tolerated and safe, and the most frequently reported AEs were nasopharyngitis, headache, diarrhoea and nausea.[29–33] This favourable safety profile may be explained by the mechanism of action of deucravacitinib and its high selectivity for TYK2 because no relevant adverse effects associated with JAK1–3 inhibition occurred in previous studies. Unlike other JAK inhibitors, the FDA did not issue deucravacitinib a black box warning on psoriasis approval. The narrow spectrum of activity of deucravacitinib is less likely to be associated with some side-effects related to JAK inhibitors such as malignancies, cardiovascular disease and thromboembolic events. Therefore, although deucravacitinib is, technically, a JAK inhibitor because TYK2 is part of the JAK family, it may behave as a distinct class of signalling kinase inhibitor and not be associated with the side-effects of other JAK inhibitors.

Conclusion

Deucravacitinib is a promising therapeutic agent, with a unique mechanism of action, different from all DMARDs approved for the treatment of PsA. Deucravacitinib seems to be a safe, effective and well-tolerated treatment for patients with PsA. The results from the phase III programme and studies evaluating long-term response and head-to-head comparisons with other targeted agents will be important to establishing the position of deucravacitinib in the management of PsA.

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