

Review Article

# Current role and future scope of upadacitinib in dermatology

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## ABSTRACT

Upadacitinib, a selective Janus Kinase 1 (JAK1) inhibitor, has rapidly emerged as an important therapeutic option for a wide range of immune-mediated inflammatory conditions. Upadacitinib efficiently targets important pathways causing chronic inflammation by selectively blocking JAK1-dependent cytokine signaling. Clinical trials have demonstrated efficacy in atopic dermatitis (AD), hidradenitis suppurativa (HS), and psoriasis in cases of psoriatic arthritis. Real-world data reinforce these findings, and also in other dermatologic conditions such as vitiligo, lichen planus (LP), and alopecia areata (AA). Future scope includes biomarker-driven personalization, data comparison with next-generation biologics, long-term safety monitoring, and dose selection optimization to balance tolerability and efficacy across a range of patient populations.

**Keywords:** Atopic dermatitis, Hidradenitis suppurativa, Janus Kinase inhibitor, Psoriasis, Upadacitinib

## INTRODUCTION

Janus kinase (JAK) inhibitors constitute an important group of oral immunomodulators expanding the therapeutic possibilities for immune-mediated dermatoses. Upadacitinib (ABT494) is a selective JAK1 inhibitor, approved by the Food and Drug Administration (FDA) for moderate-to-severe atopic dermatitis (AD). It is under investigation for several other chronic dermatoses such as hidradenitis suppurativa (HS), alopecia areata (AA), lichen planus (LP), vitiligo, and psoriasis.

**Objective and review framework:** This narrative review compiles the currently available evidence with emphasis on clinical positioning, the hierarchy of evidence (randomized controlled trials (RCTs) > open-label cohorts > case series > case reports), safety data, and potential future directions of upadacitinib in dermatology.

## METHODS

A literature search was conducted in PubMed/MEDLINE and ClinicalTrials.gov. Using the keywords “upadacitinib” AND (“atopic dermatitis” OR “hidradenitis suppurativa” OR “psoriasis” OR “vitiligo” OR “lichen planus” OR “alopecia areata”), along with synonyms and Medical Subject Headings terms where appropriate, clinical trials, observational studies, case series, and dermatology case reports were found in the publications. There was no formal meta-analysis; instead, the evidence was summarized narratively. Off-label indications

were clearly marked as such, and studies were interpreted in accordance with the hierarchy of evidence.

## REGULATORY MILESTONES AND CURRENT STATUS IN DERMATOLOGY

In the United States, upadacitinib received FDA approval for moderate-to-severe AD on January 14, 2022, for adults and adolescents  $\geq 12$  years whose disease remains inadequately controlled with other systemic agents. It was earlier approved on December 14, 2021, for adults with active psoriatic arthritis (PsA) who had an inadequate response or intolerance to at least one tumor necrosis factor (TNF) inhibitor. In the European Union, the European Commission authorized upadacitinib for systemic treatment of moderate-to-severe AD in adults and adolescents  $\geq 12$  years on August 24, 2021, and subsequently approved its use, either as monotherapy or combined with methotrexate, for active PsA in adults with insufficient response or intolerance to conventional DMARDs on January 25, 2021.<sup>[1,2]</sup>

## PHARMACOLOGY

Upadacitinib is rapidly absorbed following oral administration, reaching peak plasma concentrations within 2-4 hours, with steady-state levels achieved by day 4 and minimal drug accumulation. The compound exhibits up to 52% plasma protein binding and undergoes extensive hepatic metabolism predominantly through CYP3A4, with

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a minor contribution from CYP2D6. Its principal metabolic pathway involves oxidative conversion to a carboxylic acid intermediate followed by glucuronidation, yielding metabolite M4, which accounts for about 13% of circulating drug-related material; unchanged upadacitinib constitutes roughly 79%, while other metabolites are negligible and pharmacologically inactive. Elimination occurs mainly as the unchanged drug, with 24% excreted in urine and 38% in feces, and the terminal half-life ranges between 9 and 14 hours.<sup>[1,2]</sup>

Pharmacodynamically, upadacitinib modulates cytokine-driven intracellular signaling dependent on the JAK-signal transducer and activator of transcription (JAK-STAT) pathway. Ligand engagement of cytokine receptors induces receptor dimerization, JAK juxtaposition, and reciprocal phosphorylation, followed by phosphorylation of receptor intracellular domains that serve as docking sites for STAT proteins. Activated STAT dimers translocate to the nucleus to regulate gene transcription. Upadacitinib is a second-generation JAK inhibitor with preferential selectivity for JAK1, demonstrating substantially lower activity against JAK2, JAK3, and TYK2 (74-fold, 58-fold, and comparable differentials, respectively) [Figure 1].<sup>[3-5]</sup>

#### Formulations available

Upadacitinib is available as oral tablets in 15 mg, 30 mg, and 45 mg strengths for adult/adolescent use. Pediatric-specific formulations are oral solutions with 1 mg/mL strength. In India, 15 mg is the only strength available at present for dermatological use.

### MONITORING GUIDELINES FOR UPADACITINIB

A comprehensive blood count, along with evaluations for renal function, liver function, a fasting lipid profile, viral markers to rule out active hepatitis B, hepatitis C, and HIV, and an interferon gamma (IFN- $\gamma$ ) release assay to rule out tuberculosis, should be conducted at baseline. The complete blood count, renal function tests, liver function tests, and fasting lipid profile should be retested after 1 month and subsequently every 3 months. The IFN- $\gamma$  release assay should be repeated annually. Before therapy, vaccinations should be updated (live vaccines should be avoided during treatment) [Figure 2].<sup>[1,2,6]</sup>

#### Pregnancy and lactation

Upadacitinib is contraindicated during pregnancy owing to potential teratogenic risk (Category D); women of reproductive potential should employ effective contraception throughout therapy and for at least 4 weeks following the final dose. Breastfeeding is generally not recommended during treatment due to limited safety data and potential risk to the infant. Pregnancy status should be checked at baseline and every month where indicated.<sup>[1,6]</sup>

#### Special populations and polypharmacy

The lowest effective dose should be used in elderly patients and those with cardiovascular or thrombotic risk factors,

and the ongoing benefit-to-risk ratio should be periodically reevaluated. Clinicians should check concurrent medications (e.g., CYP3A4 inhibitors and inducers) for possible interactions. According to approved prescribing information and local regulatory guidelines, dose modifications or avoidance may be necessary in cases of severe hepatic or renal impairment.<sup>[1,2,6]</sup>

#### Serious adverse events requiring urgent interruption/cessation

In cases of suspected serious infection/sepsis, disseminated herpes zoster, clinically significant cytopenias, severe hepatitis/transaminitis, suspected thrombosis (deep vein thrombosis (DVT)/pulmonary embolism (PE)/arterial event), or symptoms suggestive of myocardial infarction or stroke, upadacitinib should be immediately stopped and the patient assessed.<sup>[1,6]</sup>

### CONTRAINDICATIONS

Upadacitinib is contraindicated in patients with active serious infections, including tuberculosis and other opportunistic infections, malignancies and lymphoproliferative disorders, known hypersensitivity to the drug or its components, severe hepatic impairment (Child-Pugh C), and during pregnancy due to potential fetal risk. The treatment should not be initiated in patients with neutropenia (absolute neutrophil count  $<1,000$  cells/mm<sup>3</sup>), lymphopenia (absolute lymphocyte count  $<500$  cells/mm<sup>3</sup>), or severe anemia (hemoglobin  $<8$  g/dL). Relative contraindications include recent major cardiovascular events, thrombosis, and those who are at risk for gastrointestinal perforation.<sup>[1-5]</sup>

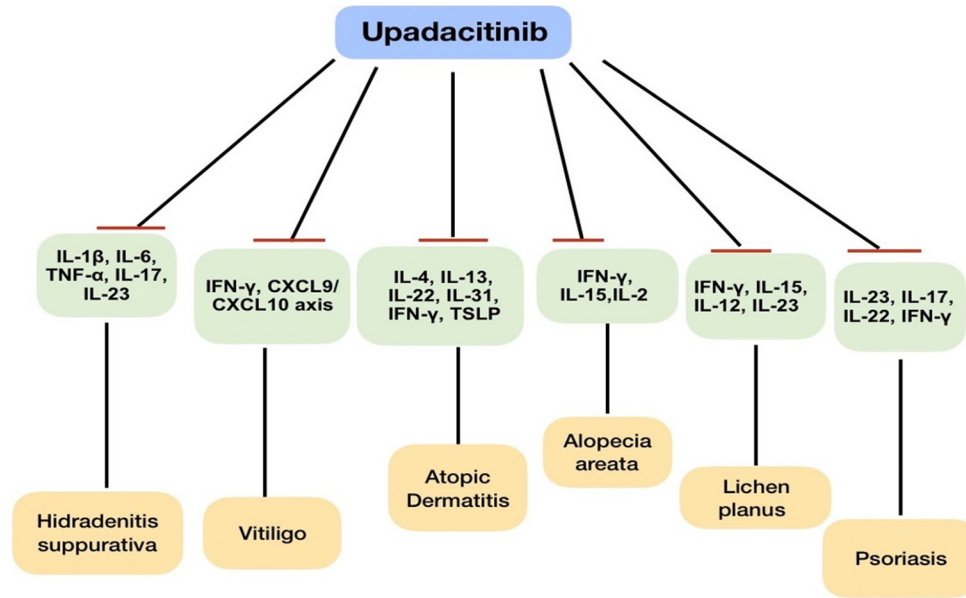
### DRUG INTERACTIONS

Upadacitinib undergoes primary metabolism through CYP3A4, necessitating caution when co-administered with agents that modulate this pathway. Strong CYP3A4 inhibitors, such as grapefruit products, ketoconazole, and clarithromycin, may elevate systemic drug levels and increase the risk of adverse effects, whereas potent inducers such as rifampin substantially reduce drug exposure and compromise therapeutic efficacy; concomitant use with such inducers is therefore not recommended.<sup>[6,7]</sup>

### APPRAISAL OF CURRENT ROLE OF UPADACITINIB

#### AD

AD is a chronic, recurrent inflammatory skin condition caused by a dysregulated immune response that includes dysfunction of the epidermal barrier and Th2, Th22, Th1, and Th17 cytokine activity. Important mediators, including Interleukin (IL)-4, IL-13, IL-31, IL-22, and IFN- $\gamma$ , communicate through the JAK-STAT pathways, specifically JAK1 [Figure 3].<sup>[8]</sup> A selective JAK1 inhibitor, upadacitinib,



**Figure 1:** Immunological pathways targeted by upadacitinib across key dermatologic diseases. This schematic depicts cytokine and chemokine pathways modulated by upadacitinib, a selective Janus Kinase 1 (JAK1) inhibitor, across immune-mediated dermatoses. By inhibiting interferon gamma (IFN- $\gamma$ ), interleukin (IL)-, and tumor necrosis factor (TNF)- $\alpha$ -driven signaling, upadacitinib attenuates downstream JAK– signal transducer and activator of transcription (STAT) activation. Key targets include IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IL-17, and IL-23 in hidradenitis suppurativa; IFN- $\gamma$ -CXCL9/CXCL10 in vitiligo; IL-4, IL-13, IL-22, IL-31, IFN- $\gamma$ , and thymic stromal lymphopoietin in atopic dermatitis; IFN- $\gamma$ , IL-15, and IL-2 in alopecia areata; IFN- $\gamma$ , IL-15, IL-12, and IL-23 in lichen planus; and the IL-23/IL-17/IL-22 axis with IFN- $\gamma$  in psoriasis. Overall, the figure highlights the broad immunomodulatory scope of JAK1 inhibition across inflammatory dermatoses.

inhibits signaling downstream of several cytokines linked to the pathophysiology of AD. In doing so, it suppresses IL-31-induced pruritus, lowers IL-4/IL-13-driven Th2 inflammation, and modifies Th1/Th17 cytokines that maintain chronic lesions. Rapid itching suppression, decreased inflammation, and enhanced skin-barrier repair are the outcomes of the ensuing immunomodulation.<sup>[9]</sup>

#### Current clinical evidence

Multiple Phase 3 RCTs and long-term extension studies have consistently demonstrated the efficacy and durability of upadacitinib in moderate-to-severe AD, with rapid improvement in skin clearance, itch, sleep, and quality of life maintained through at least 1 year. Head-to-head and confirmatory trials further show that upadacitinib provides faster and greater clinical responses than dupilumab across body regions, including in adult and adolescent populations [Table 1].<sup>[9-17]</sup>

#### Future scope

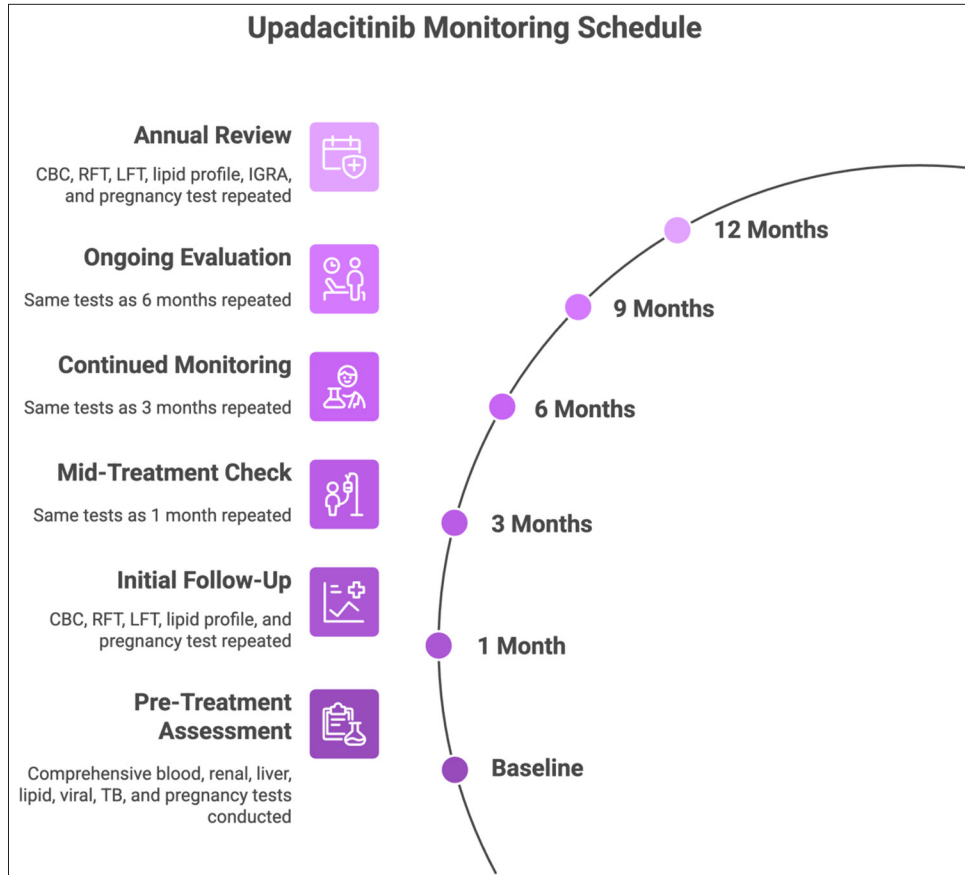
Important knowledge gaps remain in the role and use of upadacitinib in AD. Longer-term real-world data beyond current trial durations are needed to better define safety, as well as to refine long-term risk-benefit assessment.

Comparative and combination studies with newer biologics will be crucial to guide management protocols, patient selection, and cost-effectiveness, especially in resource-limited settings. Emerging research into biomarker-based stratification and extension of studies into younger pediatric populations and combination regimens may further enable individualized therapy and improve the durability of response.

#### HS

HS is a chronic inflammatory, relapsing dermatosis characterized by follicular occlusion, draining sinuses, and recurrent abscesses. There is a dysregulation of the innate and adaptive immune system with overexpression of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-17, IL-23, and IFN- $\gamma$ . These cytokines promote T-cell activation, neutrophil chemotaxis, and keratinocyte hyperproliferation; many of these processes are signaled by JAK1-dependent STAT pathways.

Upadacitinib's selective JAK1 inhibition affects several inflammatory pathways that are involved in the pathophysiology of HS.<sup>[18]</sup> Upadacitinib limits the recruitment and infiltration of activated T cells into lesional skin by inhibiting the IFN- $\gamma$ /JAK1/STAT1 axis, which in turn lowers the expression of chemokines such as CXCL9 and CXCL10.



**Figure 2:** Recommended monitoring schedule for patients receiving upadacitinib. CBC: Complete blood count, RFT: Renal function test, LFT: Liver function test, IGRA: Interferon-gamma release assay, TB: Tuberculosis.

A key factor in maintaining chronic inflammation in HS is Th17 differentiation and IL-17 production, which are both attenuated by inhibition of the IL-6 and IL-23/JAK1/STAT3 signaling pathway. Furthermore, keratinocyte proliferation and tissue remodeling are normalized through the modulation of the IL-22/JAK1/STAT3 pathway, which aids in the resolution of inflammatory nodules and enhances epithelial repair. Upadacitinib therapy rapidly decreases IFN- $\gamma$ -associated and B-cell-linked chemokines in clinical responders, according to translational biomarker research, indicating a mechanistic role for JAK1 blockade in reducing inflammation linked to HS.<sup>[19]</sup>

**Current clinical evidence**

Upadacitinib 30 mg once daily was compared to a placebo in the STEP-UP HS phase 2 randomized, double-blind trial for moderate-to-severe HS.<sup>[20]</sup> Patients with refractory HS who are not responsive to TNF- $\alpha$  or IL-17 blockade have shown significant clinical improvement, according to numerous case reports, case series, and small observational cohorts. A retrospective cohort documented

early real-world efficacy and tolerability.<sup>[21]</sup> Quick remission was reported in a case report, even after biologic failure.<sup>[22]</sup> In severe cases, a synergistic improvement was achieved by combining upadacitinib with either secukinumab or adalimumab [Table 2].<sup>[23-25]</sup>

**PSORIASIS**

Psoriasis is a T-cell-driven inflammatory disease with the IL-17/IL-23 axis playing a key role in keratinocyte activation and epidermal hyperproliferation. Other cytokines, such as IFN- $\gamma$ , IL-6, and IL-22, also contribute to inflammation and tissue remodeling. JAK1 is a crucial node for several upstream mediators that intensify cutaneous inflammation and pruritus, and many psoriasis-relevant cytokines communicate through JAK-STAT pathways.<sup>[26]</sup> Therefore, selective inhibition of JAK1 with upadacitinib attenuates multiple converging cytokine signals, including keratinocyte activation, Th17-driven responses, and IFN- $\gamma$ -driven chemokine production. This provides a mechanistic rationale for efficacy in a variety of psoriatic phenotypes and related manifestations, including nail disease and pustular forms.

**Current clinical evidence**

**Table 1:** Summary of evidence of upadacitinib in atopic dermatitis.

Study/Year	Design	Population/Intervention	Key outcomes
Guttman-Yassky <i>et al.</i> , 2021 <sup>[9,10]</sup>	Phase 3 RCT (Measure up 1 and 2)	Adults/adolescents, upadacitinib 15 mg or 30 mg versus placebo	EASI 75 at week 16: 70-80% (upadacitinib 30 mg), rapid itch relief within week 1; sustained at week 52
Reich <i>et al.</i> , 2021 <sup>[11,12]</sup>	Phase 3 RCT (AD Up)	Adults/adolescents, upadacitinib 15mg or 30 mg+TCS versus placebo+TCS	EASI 75 up to 84% at week 16; maintained at week 52
Paller <i>et al.</i> , 2023 <sup>[13]</sup>	Pooled phase 3 adolescent analysis	Adolescents 12-17 years	EASI 75 63-84%
Paller <i>et al.</i> , 2024 <sup>[14]</sup>	76-week extension	Adolescents 12-17 years	Sustained EASI 90; no new Aes
Blauvelt <i>et al.</i> , 2022 (Heads Up) <sup>[15]</sup>	Phase 3b RCT	Upadacitinib 30 mg QD versus Dupilumab 300 mg every 2 weeks	Faster and greater EASI 75/90 and itch reduction with upadacitinib by week 2; sustained 40 weeks
Blauvelt <i>et al.</i> , 2024 (Heads Up) <sup>[16]</sup>	Open-label extension	Dupilumab to upadacitinib switch versus continuous upadacitinib	Patients switched from Dupilumab achieved additional improvement within 4 weeks; safety consistent with prior trials
Silverberg <i>et al.</i> , 2024 (Level Up) <sup>[17]</sup>	Phase IIIb/IV open-label RCT	Upadacitinib 15 dose escalation to 30 mg versus Dupilumab	Upadacitinib achieved higher EASI 90/100 rates and earlier clearance (week 1-4) across all body regions

EASI: Eczema area and severity index, TCS: Topical corticosteroids, RCT: Randomized controlled trial

**Table 2:** Summary of evidence of upadacitinib in hidradenitis suppurativa.

Study/Year	Design	Intervention	Key outcomes
Ackerman, <i>et al.</i> , 2025 <sup>[20]</sup>	Randomized, double-blind, placebo-controlled	30 mg once daily vs. placebo	HiSCR50 response significantly higher than historical placebo; sustained to week 40; safety consistent with prior dermatology trials
Kozera, <i>et al.</i> , 2022 <sup>[21]</sup>	Retrospective cohort	15-30 mg once daily	Real-world improvement in lesion count and pain; safety consistent with known profile
Takei, <i>et al.</i> , 2025 <sup>[22]</sup>	Case report	15-30 mg once daily in refractory HS after TNF/IL-17 failure	Clinical remission within 3 months; well tolerated
Islam, <i>et al.</i> , 2024 <sup>[23]</sup>	Case series-combination adalimumab+upadacitinib	Adalimumab+Upadacitinib (dose varied)	Improved drainage and pain in refractory HS
Melgosa Ramos, <i>et al.</i> , 2026 <sup>[24]</sup>	Case series-combination secukinumab+upadacitinib	Secukinumab+15-30 mg upadacitinib	Dual therapy is effective in HS with comorbid immune-mediated inflammatory diseases (SLE and psoriasis)
Ok, <i>et al.</i> , 2025 <sup>[25]</sup>	Pediatric case-HS+ulcerative colitis	Pediatric dosing	Dual improvement in HS and UC

HS: Hidradenitis suppurativa, TNF: Tumor necrosis factor, IL: Interleukin, UC: Ulcerative colitis, SLE: Systemic lupus erythematosus

The current body of evidence supporting upadacitinib in psoriasis mainly includes case reports, small series, preclinical research, and data from RCTs in PsA that included cutaneous outcomes as secondary endpoints. No specific large-scale randomized trial has been published for psoriasis alone, although there are strong RCTs for PsA (select- PsA 1 and 2) that showed notable improvements in both joint and skin manifestations.<sup>[27]</sup> As a result, small observational studies and actual clinical experience account for the majority of the psoriasis-specific data currently available.<sup>[28-35]</sup> The ability of upadacitinib to modulate shared inflammatory pathways involving IL-4/IL-13, IL-23, and IFN- $\gamma$  signaling is further demonstrated by cases where psoriasis and AD

coexist, and both conditions improved simultaneously on the medication [Table 3].<sup>[36]</sup>

The phenotypic switch phenomenon, in which patients receiving upadacitinib for AD developed psoriasiform lesions while undergoing treatment, is a noteworthy finding in the literature.<sup>[37]</sup> This highlights the intricate immunological interactions between Th2- and Th17-skewed pathways, indicating that in susceptible individuals, selective JAK1 inhibition may occasionally reveal or change underlying immune predispositions toward a psoriatic phenotype. On the other hand, other reports show that AD and psoriasis can be controlled simultaneously or alternately in the same patient, which reflects the drug's complex effects on

overlapping cytokine networks.

However, it should be noted that specific randomized trials for psoriasis are still needed to determine its effectiveness, durability, and relative role among the available systemic options. Upadacitinib can produce significant clinical improvement across a variety of psoriatic variants in real-world settings.

## VITILIGO

Autoreactive CD8<sup>+</sup> cytotoxic T cells detect and destroy melanocytes in the epidermis in vitiligo, an autoimmune depigmenting condition. These T cells produce IFN- $\gamma$ , a key upstream driver that activates keratinocytes through the JAK1/JAK2 $\rightarrow$ STAT1 pathway to produce chemokines (most notably CXCL9/CXCL10) that attract and hold onto more cytotoxic T cells at lesional sites.<sup>[38]</sup> Pathogenic memory T cells are maintained by IL-15 and related cytokines, whereas melanocyte loss and local tissue stress are intensified by other inflammatory mediators. A self-sustaining cytotoxic loop that stops melanocyte recovery is produced by these coordinated signals.

Upadacitinib, by inhibiting JAK1-dependent signaling, reduces IL-15-mediated T-cell survival signals and interferes with the IFN- $\gamma$   $\rightarrow$  STAT1  $\rightarrow$  CXCL9/CXCL10 chemokine axis.<sup>[39]</sup> Attenuation of local inflammatory mediators, decreased recruitment/activation of autoreactive CD8<sup>+</sup> T cells, and a tissue environment that supports melanocyte survival and repopulation, particularly when paired with pro-pigmentary stimuli like phototherapy, are the overall results.

### Current clinical evidence

Oral upadacitinib (6, 11, and 22 mg once daily) was compared to a placebo in adults with extensive non-segmental vitiligo in a multicenter, double-blind, dose-ranging phase 2 RCTs ( $n = 185$ ).<sup>[40]</sup> Clinical improvement was noted in a case of vitiligo treated with a combination of upadacitinib and 308nm excimer laser.<sup>[41]</sup>

Combination therapy of upadacitinib and 308 excimer laser was found superior to other monotherapies in a comparative study.<sup>[42]</sup> Upadacitinib along with NB - UVB showed notable repigmentation in refractory vitiligo patients.<sup>[43]</sup> Significant repigmentation was documented with upadacitinib in a case of paediatric vitiligo.<sup>[44]</sup> In a case of coexistent vitiligo and atopic dermatitis, upadacitinib showed complete remission of both AD and vitiligo,<sup>[45]</sup> whereas in another case, AD improved but there was worsening of vitiligo.<sup>[46]</sup> Upadacitinib at a dose of 15 mg/day showed repigmentation in a case series.<sup>[47]</sup>

In a comparative case series, upadacitinib demonstrated more favourable repigmentation in steroid resistant vitiligo as compared to tofacitinib and baricitinib.<sup>[48]</sup>

In another case series, upadacitinib at a dose of 30mg/ day showed clinical improvement.<sup>[49]</sup> A paediatric case report demonstrated improvement in coexistent vitiligo and

alopecia areata.<sup>[50]</sup> An another case series showed significant repigmentation and tolerability with upadacitinib in recalcitrant vitiligo.<sup>[51]</sup>

In comparison to placebo, the 11 and 22 mg doses resulted in statistically significant improvements in facial vitiligo area scoring index (F-VASI) and total VASI (T-VASI) at Week 24 (LS-mean differences for F-VASI: -21.3 for 11 mg and -19.6 for 22 mg; T-VASI improvements were also significant), and repigmentation persisted through Week 52. To date, these findings offer the most compelling randomized evidence in favor of upadacitinib in vitiligo [Table 4].

Single-patient case reports and small case series from various centers around the world make up the majority of published real-world data. Upadacitinib 15 mg once daily was administered to the majority of patients; in some cases, it was also combined with topical JAK inhibitors or Narrowband Ultraviolet B/308-nm excimer. Early and more noticeable repigmentation is seen at the facial and truncal sites; numerous reports note noticeable repigmentation by 8-16 weeks and ongoing improvement through 24-52 weeks.

## LP

LP is a chronic inflammatory dermatosis involving T-cell-mediated destruction of basal keratinocytes. IFN- $\gamma$  and Th1/Th17 cytokines trigger autoreactive CD8<sup>+</sup> cytotoxic T cells, which are the main mediators of the condition. Through the JAK1/JAK3-STAT1/STAT3 pathways, these cytokines stimulate keratinocytes, leading to overexpression of CXCL9, CXCL10, and CXCL11, which draws more CD8<sup>+</sup> cells to the skin and mucosa of lesions.<sup>[52]</sup> In addition, IL-15/JAK1/STAT5 signaling promotes resident memory T-cell persistence, which adds to the chronicity and recurrence of the disease.

By blocking IFN- $\gamma$  and IL-15-driven signaling, upadacitinib lowers keratinocyte apoptosis, cytotoxic T-cell recruitment, and downstream chemokine release. It is especially helpful for erosive, mucosal, nail, or hypertrophic LP variants that are resistant to traditional treatments because of its mechanistic targeting.

### Current clinical evidence

Upadacitinib in LP has not been the subject of any published RCTs as of late 2025. Nonetheless, a growing amount of empirical evidence, such as case reports and small case series, shows clinical efficacy in erosive, cutaneous, oral, nail, and esophageal variants [Table 4].

Early mechanistic support was highlighted in the earliest reports that described the resolution of erosive oral and esophageal LP.<sup>[52,53]</sup> Responses in hypertrophic and generalized cutaneous LP that were not responsive to acitretin, cyclosporine, or steroids were confirmed by later series.<sup>[54,55]</sup>

With upadacitinib 15-30 mg daily, oral and nail LP forms have also demonstrated long-lasting improvement, frequently accompanied by notable declines in severity indices such as the nail LP severity index.<sup>[56,57]</sup>

Clinical improvement was reported within 4-12 weeks,

and adverse events were mild. No new safety concerns were observed beyond the known JAK1 inhibitor profile. Currently, upadacitinib in LP is not being specifically evaluated in any registered Phase 2 or Phase 3 RCTs. The objectives of future studies include relapse prevention, dose optimization, and comparative effectiveness with other JAK inhibitors [Table 5].

## AA

Autoreactive CD8<sup>+</sup> cytotoxic T cells specifically destroy anagen hair follicles in AA. These lymphocytes interfere with hair-follicle immune privilege by secreting proinflammatory cytokines such as IFN- $\gamma$ . In follicular keratinocytes, IFN- $\gamma$  signals through the JAK1/JAK2  $\rightarrow$  STAT1 pathway, triggering the expression of the chemokines CXCL9 and CXCL10, which attract more cytotoxic T cells and maintain follicular inflammation.<sup>[57]</sup> IL-15 contributes to the persistence of disease via JAK1/JAK3  $\rightarrow$  STAT5 signaling, which promotes the survival of pathogenic tissue-resident memory T cells. Upadacitinib breaks the inflammatory loop and restores an environment that promotes hair regrowth by attenuating both IL-15-dependent T-cell survival and IFN- $\gamma$ -driven chemokine production.<sup>[58]</sup> This mechanism reflects results from clinical data and translational models that demonstrate reversal of IFN- $\gamma$  signatures after JAK inhibition.

## Current clinical evidence

According to real-world data, upadacitinib significantly increases hair growth in AA patients of all ages, including those who are resistant to other JAK inhibitors.<sup>[59-62]</sup> The majority of reports showed clinically significant hair growth in 3-6 months, frequently with eyelash and eyebrow regrowth as well. Early response onset (within 1-2 months) was observed in several adolescent case series. Interestingly, some patients who had previously failed conventional therapies showed improvement with upadacitinib. Although there are no RCTs, the consistency of positive clinical outcomes across several centers offers compelling empirical support for its therapeutic role [Table 6].

## SAFETY PROFILE

JAK inhibitor class-wide risks and boxed warnings: Upadacitinib has class-wide warnings for major adverse cardiovascular events, thrombosis (DVT/PE/arterial thrombosis), cancer, serious infections (including opportunistic infections and tuberculosis), and increased mortality in high-risk populations.<sup>[1]</sup> Careful patient selection, baseline infectious screening (including Tuberculosis), counseling, and routine monitoring are necessary due to these risks. Since there are still fewer long-term safety data in dermatology than in rheumatology, risk mitigation and collaborative decision-making are crucial, especially for elderly patients and those with cardiovascular risk factors or a history of thromboembolic events.

Upadacitinib has generally shown a positive and predictable safety profile in the published literature, which is consistent

with what has previously been seen in other rheumatologic and dermatological indications. Common treatment-emergent adverse events included acne (10–15%), upper respiratory infections, and transient laboratory abnormalities (elevation of creatine phosphokinase, mild increases in lipid or liver enzymes), which generally were self-limiting.<sup>[6]</sup> Rates of non-melanoma skin cancer (<1/patient-years) and herpes zoster (1.6-3.6/100 patient-years) were low and comparable to other JAK inhibitors in the pooled safety analysis of 2693 AD patients.<sup>[63]</sup> Up to 76 weeks of continuous treatment, no additional safety concerns were found.

Crucially, the available literature did not consistently identify any signal for cytopenias, malignancy, major cardiovascular events, or thromboembolic events. One case of upadacitinib in HS reported a serious adverse event, a varicella zoster infection complicated by hemophagocytic lymphohistiocytosis, highlighting the necessity of infection risk assessment and close monitoring during treatment.<sup>[64]</sup> A single adolescent case documented transient leukopenia at weeks 4 and 8 that resolved spontaneously.<sup>[65]</sup> There were no consistent reports of opportunistic infection, cancer, major cardiovascular events, or thromboembolism. Although causality is still unknown, one unusual case of drug-induced AA following a year of upadacitinib for AD was reported.<sup>[66]</sup> A patient with inflammatory arthritis and plaque psoriasis who experienced generalized pustular psoriasis (GPP) right after stopping upadacitinib abruptly is of particular clinical interest.<sup>[67]</sup> Shortly after discontinuing upadacitinib, the patient developed fever, diffuse erythema, and sterile pustules. Laboratory results revealed systemic inflammation (high CRP, leukocytosis). After immunosuppressive treatment was resumed, symptoms subsided. The authors stressed that abruptly stopping JAK1 inhibition may cause paradoxical hyperinflammation and ascribed this reaction to rebound hyperactivation of inflammatory cytokine pathways, particularly IL-36, IL-17, and TNF- $\alpha$ . In order to avoid severe rebound phenomena like GPP, this case emphasizes the necessity of tapering off upadacitinib gradually or switching to another immunomodulator.

There have also been reports of phenotypic switching from AD to psoriasis while receiving continuous upadacitinib therapy.<sup>[37]</sup> This highlights how intricately Th2- and Th17-dominant pathways interact, and it implies that selective JAK1 blockade may occasionally reveal latent psoriatic predisposition. Although this growing body of evidence is positive, long-term safety data and RCTs are required to prove conclusive efficacy and the best course of treatment.

## ROLE OF UPADACITINIB IN THE INDIAN CONTEXT

In India, upadacitinib represents an important therapeutic option for patients with moderate-to-severe AD and psoriasis who fail to respond adequately to conventional immunosuppressants or biologics. Its broad anti-inflammatory

**Table 3:** Summary of evidence of upadacitinib in psoriasis.

Study/Year	Psoriasis subtype	Dose and duration	Key outcome (s)
Antolini <i>et al.</i> , 2025 <sup>[28]</sup>	Chronic plaque psoriasis+PsA (refractory)	Upadacitinib 15 mg daily+guselkumab (combination)× 12 months	Combination controlled both skin and joint disease
Choi <i>et al.</i> , 2025 <sup>[29]</sup>	Palmoplantar plaque psoriasis (2 cases, refractory)	Upadacitinib 15 mg daily×3 months	Complete response at 3 months
Yatsuzuka <i>et al.</i> , 2025 <sup>[30]</sup>	Eczematized psoriasis	Upadacitinib	Clinical resolution of eczematous transformation of psoriasis
Woodbury <i>et al.</i> , 2024 <sup>[31]</sup>	TNF inhibitor-induced psoriasis	Upadacitinib (dose variable; case-level)	Complete resolution of paradoxical TNF-inhibitor-induced psoriasis
Hu <i>et al.</i> , 2024 <sup>[32]</sup>	Scalp psoriasis and palmoplantar pustulosis	Upadacitinib (dose per case)	Symptomatic control in secukinumab/adalimumab/ ustekinumab-failed patients
Wang <i>et al.</i> , 2024 <sup>[33]</sup>	Generalized pustular psoriasis (refractory)	Upadacitinib	Clinical improvement reported
Wang <i>et al.</i> , 2023 <sup>[34]</sup>	Nail psoriasis	Upadacitinib 15 mg daily×5 months	Improved nail disease; authors review JAK involvement in nail pathology
Martinez-Molina <i>et al.</i> , 2023 <sup>[35]</sup>	Palmoplantar psoriasis	Upadacitinib	Positive clinical response

JAK: Janus Kinase, TNF: Tumor necrosis factor

**Table 4:** Summary of evidence of upadacitinib in vitiligo.

Study/Year	Study design	Intervention	Key findings
Passeron <i>et al.</i> , 2024 <sup>[40]</sup>	Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study	Upadacitinib 6, 11, or 22 mg once daily vs. placebo for 24-52 weeks	Significant F-VASI and T-VASI improvement at 24-52 weeks with upadacitinib11 and upadacitinib22; continuous repigmentation
Yuan <i>et al.</i> , 2025 <sup>[41]</sup>	Retrospective clinical observation (n=10)	Upadacitinib±308 nm excimer laser	78% of lesions showed ≥25% pigmentation at 16 weeks
Zhang <i>et al.</i> , 2025 <sup>[42]</sup>	Retrospective comparative study	upadacitinib+308 nm excimer vs. monotherapies	Combination therapy superior to monotherapy in VASI and DLQI improvement at 20 weeks
Yue <i>et al.</i> , 2025 <sup>[43]</sup>	Case series (progressive vitiligo)	Oral upadacitinib+NB-UVB	Notable repigmentation in refractory vitiligo
Wang <i>et al.</i> , 2025 <sup>[44]</sup>	Pediatric case report	Oral upadacitinib in a child with vitiligo	Significant repigmentation and lesion stabilization; safe in pediatric use
Magnanimiti <i>et al.</i> , 2025 <sup>[45]</sup>	Case report	Oral upadacitinib 15 mg/day	Complete remission of AD and concurrent vitiligo by week 28
Wang <i>et al.</i> , 2025 <sup>[46]</sup>	Case report	Upadacitinib for an AD patient with stable vitiligo	AD improved, vitiligo worsened; improved after switch to abrocitinib
Zhu <i>et al.</i> , 2024 <sup>[47]</sup>	Retrospective case series (n=5)	Oral upadacitinib 15 mg/day for 4 months	All patients achieved repigmentation
Zhu <i>et al.</i> , 2025 <sup>[48]</sup>	Prospective case series	Oral tofacitinib, baricitinib, and upadacitinib	Upadacitinib demonstrated favorable repigmentation in steroid-resistant vitiligo
Magdaleno-Tapiál <i>et al.</i> , 2024 <sup>[49]</sup>	Case series	Oral upadacitinib 30mg	Clinical improvement; discussed therapeutic potential in vitiligo
Mu <i>et al.</i> , 2024 <sup>[50]</sup>	Case report	Upadacitinib+NB-UVB in a child with vitiligo and AA	Improvement in both vitiligo and AA
Su <i>et al.</i> , 2023 <sup>[51]</sup>	Case series	Upadacitinib monotherapy	Significant repigmentation and good tolerability in recalcitrant vitiligo

NB-UVB: Narrowband ultraviolet B, VASI: Vitiligo area scoring index, F-VASI: Facial vitiligo area scoring index, T-VASI: Total vitiligo area scoring index, AD: Atopic dermatitis, AA: Alopecia areata, DLQI: Dermatology life quality index, OD: Once daily

**Table 5:** Summary of evidence of upadacitinib in lichen planus.

Study/Year	LP Subtype	Dose and duration	Key outcome (s)
Kooybaran <i>et al.</i> , 2021 <sup>[53]</sup>	Oral+esophageal erosive LP	15 mg daily×12 weeks	Complete mucosal healing with endoscopic resolution; well tolerated
Balestri <i>et al.</i> , 2022 <sup>[52]</sup>	Oral erosive LP	15 mg daily×12 weeks	Rapid symptomatic improvement and sustained remission
Zundell <i>et al.</i> , 2023 <sup>[54]</sup>	Cutaneous (generalized) LP	15 mg daily×8 weeks	70–80% lesion clearance by week 8
McNamara <i>et al.</i> , 2025 <sup>[55]</sup>	Cutaneous and mucosal LP variants	15-30 mg daily×12 weeks	>75% lesion reduction in 80% patients
Zhao <i>et al.</i> , 2025 <sup>[56]</sup>	Nail LP	15 mg daily×6 months	NALSI score 146-37

LP: Lichen planus, NALSI: Nail Lichen Planus Severity Index

**Table 6:** Summary of evidence of upadacitinib in alopecia areata.

Study/Year	Alopecia areata subtype	Dose and duration	Key outcome (s)
Gao <i>et al.</i> , 2025 <sup>[59]</sup>	Severe alopecia areata (case series of 3 adolescents)	15 mg/day once daily for 6 months	Mean SALT score reduced 58%; eyebrow and scalp regrowth within 2-4 months
Chambres <i>et al.</i> , 2026 <sup>[60]</sup>	Refractory AA (case series of 22 patients)	15–30 mg once daily	Significant regrowth, including baricitinib-refractory cases; well-tolerated
Battilotti <i>et al.</i> , 2025 <sup>[61]</sup>	AA in patients with AD (case series of 3 patients)	15 mg once daily for 12 months	SALT score improved from baseline (100,100, 51.5) to 21.8,15,45 at 6 months and 14,1.8,0, respectively, by 12 months
Wang <i>et al.</i> , 2025 <sup>[62]</sup>	Refractory AA	15–30 mg once daily×≥3 months	Substantial scalp regrowth

AA: Alopecia areata, SALT: Severity of alopecia tool, AD: Atopic dermatitis

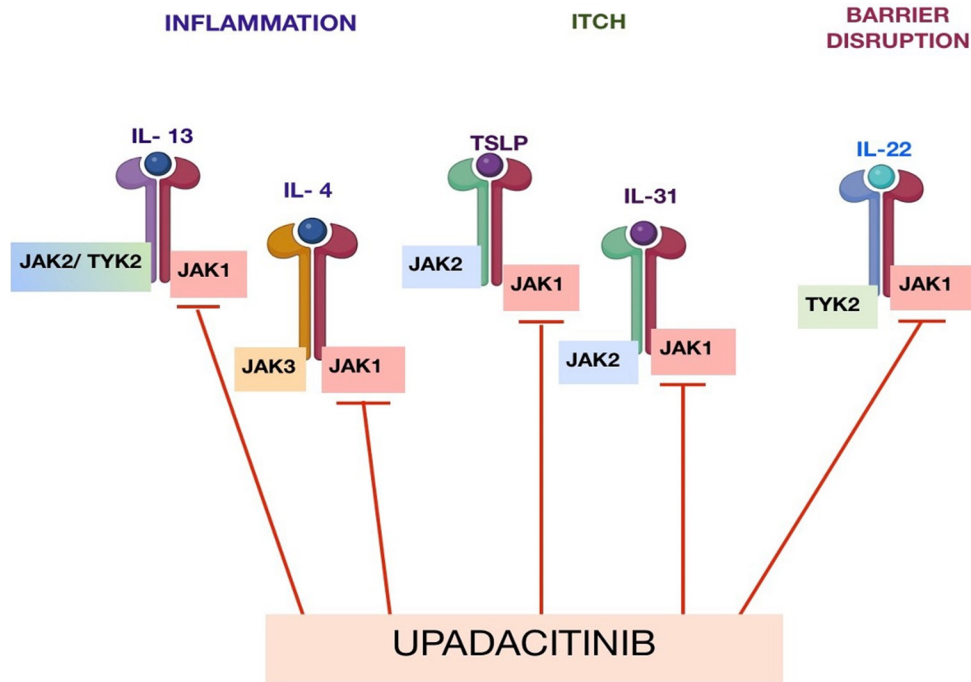
**Table 7:** Upadacitinib in dermatology: Dose, duration, and level of evidence.

Indication	Dose used in studies/reports	Suggested duration	Level of evidence
Atopic dermatitis	15 or 30 mg OD	RCT evidence supports maintenance through 52 weeks; LTE suggests durability up to~140 weeks; may continue long-term in responders with monitoring	Level 1 (Phase 3 RCTs+LTE)
Hidradenitis suppurativa	15-30 mg OD (limited reports)	Individualized; prolonged therapy may be required in responders	Level 3-4 (case series/reports)
Psoriasis	15-30 mg OD (limited dermatology data)	Individualized; consider in refractory cases only	Level 23 (limited trials/observational)
Psoriatic arthritis	15 mg OD (trial dose)	Long-term maintenance supported by rheumatology trials	Level 1 (RCTs in PsA)
Psoriatic erythroderma	15-30 mg OD (case-based)	Individualized; limited evidence	Level 4 (case reports)
Vitiligo (mainly non-segmental)	15-30 mg OD (case reports/series)	Treat 3–6 months to assess response (evidence limited)	Level 4 (case reports/series)
Lichen planus	15-30 mg OD (case reports/series)	Individualized; may require prolonged therapy	Level 4 (case reports/series)
Alopecia areata	15-30 mg OD (case reports/series)	Individualized; long-term therapy often required	Level 3-4 (case series/reports)

RCT: Randomized controlled trials, PsA: Psoriatic arthritis, LET: Long-term extension, OD: Once daily

activity, rapid onset of action, and oral formulation make it particularly valuable in settings where biologics are inaccessible, unaffordable, or contraindicated. Given the high national burden of hepatitis B and latent tuberculosis,

comprehensive infection screening and appropriate prophylaxis are essential before initiation. Notably, rifampin, commonly used in tuberculosis treatment, induces CYP3A4 and can markedly reduce upadacitinib exposure, necessitating



**Figure 3:** Key Janus Kinase 1 (JAK1)–signal transducer and activator of transcription (STAT) signaling pathways modulated by upadacitinib in atopic dermatitis. This schematic illustrates cytokine-driven JAK–STAT pathways central to inflammation, pruritus, and barrier dysfunction in atopic dermatitis and their modulation by upadacitinib, a selective JAK1 inhibitor. Upadacitinib inhibits JAK1-dependent signaling downstream of interleukin (IL)-4 and IL-13, reducing type 2 inflammation; blocks TSLP- and IL-31-mediated pathways involved in neuronal activation and itch; and attenuates IL-22-driven epidermal hyperplasia and barrier impairment. Collectively, the figure highlights the central role of JAK1 across key pathogenic axes in atopic dermatitis and the broad therapeutic impact of its selective inhibition. Key: IL: Interleukin, JAK: Janus kinase, TSLP: Thymic stromal lymphopoietin, TYK: Tyrosine kinase.

avoidance or tailored management. Pre-treatment vaccination review, particularly for hepatitis and varicella, together with routine laboratory monitoring of lipids, hepatic enzymes, and hematologic parameters, remains integral to safe use.

Upadacitinib is approved and available in India, with cost-effective formulations introduced by domestic manufacturers from October 2025 onward for autoimmune diseases such as rheumatoid arthritis, PsA, Crohn's disease, and AD, following regulatory clearance by the CDSCO and expert committee recommendations.<sup>[68]</sup>

As utilization expands, future Indian studies should evaluate its cost-effectiveness, long-term safety, and potential roles in combination strategies or treatment sequencing with biologics. Real-world evidence from diverse practice settings, together with post-marketing surveillance through multicentric registries, will be critical to defining its optimal integration into national dermatologic treatment pathways.

### Limitations

The review has several limitations. The quality of the evidence varies significantly among dermatologic indications; AD is the only indication with strong randomized data, while the majority of other indications rely on small cohorts, case series, or case

reports, which may have publication bias and inconsistent outcome measures. Long-term safety results in dermatology might not be entirely extrapolated from other immune-mediated disease cohorts. For the majority of conditions, optimal duration, discontinuation strategies, and relapse rates are still unknown, and there are few head-to-head comparisons with biologics. For the majority of conditions, optimal duration, discontinuation strategies, and relapse rates are still unknown, and there are few head-to-head comparisons with biologics [Table 7].

### CONCLUSION

Upadacitinib is an effective and rapid-acting selective JAK1 inhibitor with strong evidence in the treatment of moderate-to-severe atopic dermatitis and rising clinical evidence for other inflammatory skin conditions such as hidradenitis suppurativa, psoriasis, vitiligo, lichen planus, and alopecia areata. Its oral formulation, extensive immunomodulatory effects, and swift symptom management makes it a significant treatment choice, especially for resistant conditions. Careful patient selection, initial screening and work-up and regular monitoring are crucial. Upcoming randomized trials, extended safety studies, and real-world evidence will further clarify its ideal role in dermatologic practice.

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