Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2023, Volume 3, Page No: 1-8

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Pharmacological Insights into Janus Kinase Inhibition for the Treatment of Autoimmune Skin Diseases: A Literature Review

Mohammed Al Abadie[1], Zinah Sharara[2], Patrick A Ball[3], Hana Morrissey[3*]

[1]North Cumbria integrated care NHS Foundation Trust, Clinical Director & Consultant Dermatologist.
[2]National Health Service (NHS), Community Dermatology Clinics (Health Harmonie), United Kingdom.
[3] School of Pharmacy, University of Wolverhampton, United Kingdom.

***E-mail** ✉ Hana.morrissey@cdu.edu.au

Received: 09 November 2022; **Revised:** 18 January 2023; **Accepted:** 20 January 2023

ABSTRACT

The Janus kinase (JAK) family and signal transducer and activator of transcription (STAT) proteins play a central role in intracellular signaling pathways and mediate the effects of more than 50 cytokines and growth factors. JAK inhibitors act by selectively targeting receptor-associated kinases, thereby suppressing the transduction of pro-inflammatory signals. With increasing evidence supporting the therapeutic potential of targeted agents, both systemic and topical JAK inhibitors have been investigated for the management of atopic dermatitis and have demonstrated diverse mechanisms of action, variable efficacy, and distinct safety profiles. This review evaluates the clinical utility and safety of JAK inhibitors in the treatment of inflammatory and atopic dermatoses. While these agents have shown promising therapeutic outcomes in many patients, there remains considerable variability in response rates and a risk of severe and sometimes life-threatening adverse effects. Ongoing research is essential to further elucidate the complex signaling mechanisms involved, optimize therapeutic efficacy, and reduce the incidence of adverse effects.

Keywords: Janus kinase, Atopic dermatitis, Inflammatory pathways, Topical therapy, JAK inhibitors

How to Cite This Article: Al Abadie M, Sharara Z, A Ball P, Morrissey H. Pharmacological Insights into Janus Kinase Inhibition for the Treatment of Autoimmune Skin Diseases: A Literature Review. Ann Pharm Pract Pharmacother. 2023;3:1-8. https://doi.org/10.51847/lhABjfuIwh

Introduction

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway plays a pivotal role in regulating numerous intracellular processes, modulating the activity of more than 50 cytokines and growth factors, including interleukins (ILs), interferons (IFNs), colony-stimulating factors (CSFs), and various hormones [1]. This pathway influences a broad spectrum of cellular functions, including immune modulation, inflammatory response, hematopoiesis, tissue regeneration, adipogenesis, and apoptosis. Dysregulation or disruption within the JAK/STAT pathway is associated with the pathogenesis of several human diseases. Mechanistically, JAKs associate non-covalently with cytokine receptors, facilitating receptor phosphorylation upon cytokine engagement. This, in turn, recruits STAT proteins, which become phosphorylated, dimerize, and translocate to the nucleus to modulate gene expression. These STAT dimers can exert both specific and overlapping biological effects [1].

Advancements in the understanding of the JAK/STAT cascade have transformed therapeutic approaches for several complex and treatment-resistant conditions. JAK inhibitors have demonstrated significant promise across a diverse range of diseases, although interindividual variability in efficacy and adverse effect profiles, including severe reactions, remains a challenge [2].

The JAK family comprises four receptor-associated tyrosine kinases—JAK1, JAK2, JAK3, and TYK2. While JAK1, JAK2, and TYK2 are ubiquitously expressed in various tissues, JAK3 expression is more restricted, primarily to hematopoietic cells, lymphoid tissues, vascular smooth muscle, and endothelium. The concept of

kinase inhibition in therapeutics began with the introduction of imatinib for chronic myelogenous leukemia [3], and by 2014, the U.S. Food and Drug Administration (FDA) had approved over 30 kinase inhibitors, primarily for oncologic indications [4, 5].

Schwartz has elucidated the complex interplay among cytokine receptors and their associated JAK enzymes, emphasizing that many receptors share JAK components, leading to overlapping biological responses [2]. He highlighted that a deeper mechanistic understanding may ultimately enhance therapeutic precision. Although numerous JAK inhibitors have been developed—many via computational drug design—to improve selectivity for specific kinases, Virtanen noted that enhanced selectivity does not always correlate with improved therapeutic outcomes or reduced adverse effects, as demonstrated in some early clinical trials [6].

As JAK inhibitors are increasingly employed for long-term management of chronic inflammatory diseases, their pharmacokinetic properties, particularly metabolism and elimination, become crucial. These agents are frequently prescribed to patients with complex comorbidities who are concurrently using multiple medications, thus raising concerns regarding drug–drug interactions, particularly via the cytochrome P450 (CYP450) system. Agents such as baricitinib and filgotinib, which are not substantially metabolized via CYP enzymes, may offer clinical advantages in such settings.

Within dermatology, JAK inhibitors have been explored in autoimmune and inflammatory conditions, including psoriasis and atopic dermatitis (AD). These diseases are characterized by cytokine-driven pathogenesis, involving TNF, IL-17, IL-12/23, and IL-23 in psoriasis, and IL-4, IL-5, and IL-13 in AD [2, 7]. Given the established role of JAK-mediated signaling in these cytokine pathways, inhibitors such as tofacitinib have undergone clinical evaluation in various dermatologic trials. This review aims to comprehensively examine the clinical efficacy and safety of JAK inhibitors investigated for the treatment of autoimmune dermatologic conditions.

Materials and Methods

This review was conducted using a manual search strategy to identify recent and relevant literature about all Janus kinase (JAK) and tyrosine kinase 2 (TYK2) inhibitors currently approved or under investigation for autoimmune dermatological disorders. Emphasis was placed on identifying studies involving atopic dermatitis (AD) and psoriasis, with a focus on topical and systemic therapeutic approaches. The review adopts a narrative format, aiming to synthesize emerging evidence regarding the pharmacological profiles, clinical efficacy, and safety of these targeted therapies.

Results and Discussion

Narrative Review

Topical Ruxolitinib

Ruxolitinib is a selective inhibitor of JAK1 and JAK2, recently approved by the U.S. Food and Drug Administration in a topical cream formulation for the treatment of mild-to-moderate atopic dermatitis in immunocompetent individuals aged 12 years and older who have not responded adequately to conventional topical treatments. Two pivotal randomized clinical trials enrolled 2,631 and 618 participants, respectively. Treatment success, as assessed by the Investigator's Global Assessment (IGA), was significantly greater in patients receiving 0.75% and 1.5% ruxolitinib cream compared to placebo at week 8 ($P < 0.0001$). A notable reduction in pruritus was reported within 12 hours of initial application, and local adverse effects at the application site were infrequent and generally mild (< 1%) [8].

Application of 1.5% ruxolitinib cream twice daily yielded the most significant improvements in the Eczema Area and Severity Index (EASI), surpassing outcomes from a comparator medium-potency topical corticosteroid, although no comparison was made with higher-potency corticosteroids. Adverse effects, such as localized pruritus and burning, were less frequent in the treatment group than in the placebo arm. Pharmacokinetic assessments indicated that topical application across 20% of the body surface area did not result in detectable systemic plasma concentrations of ruxolitinib [8].

Topical Delgocitinib

Delgocitinib, a pan-JAK inhibitor that also targets TYK2, has been approved in Japan as a 0.5% ointment for the management of atopic dermatitis. Early-phase studies demonstrated a rapid reduction in pruritus, potentially mediated by inhibition of IL-31 signaling. The proportion of patients achieving modified EASI-50 and EASI-75 responses increased progressively during treatment. In a phase 3 study involving 158 patients aged ≥ 16 years with moderate-to-severe AD, delgocitinib 0.5% ointment produced a 44.3% reduction in mean EASI score at week 4, compared to 1.7% in the placebo group, with clinical benefit sustained through week 24 [8].

Mild adverse events were reported in 4.7% of treated patients versus 1.9% in the placebo group. The most frequent adverse events included nasopharyngitis, acne, and Kaposi's varicelliform eruption. Pediatric efficacy was also observed in a randomized trial involving Japanese children (aged 2–15 years), where participants received 0.25% or 0.5% delgocitinib ointment or placebo for 4 weeks, followed by extended treatment for up to 56 weeks. EASI scores improved significantly in both delgocitinib groups compared to placebo, with mild, unrelated adverse events predominating.

Topical Tofacitinib

Topical tofacitinib 2% ointment demonstrated significant therapeutic benefit in patients with atopic dermatitis, with marked improvements in EASI, Physician's Global Assessment (PGA), and percentage of body surface area (BSA) involvement by the first week of treatment. Pruritus relief was noted as early as day 2 [9-11]. At week 4, the mean EASI score improved by 81.7% in the tofacitinib group, compared to a 29.9% decline in the control group ($P < 0.001$). Statistically significant improvements across all clinical endpoints were observed in the treatment arm relative to placebo ($P < 0.001$), with additional benefit noted in pruritus reduction.

Topical tofacitinib was well tolerated, with fewer adverse events reported in the active treatment group compared to placebo. Pharmacokinetic modeling indicated that for patients with BSA involvement ≤ 50%, systemic exposure to 2% tofacitinib ointment remained below 10% of the plasma concentrations typically observed with oral tofacitinib (5 mg twice daily) used in plaque psoriasis treatment [12].

Oral Tofacitinib

Tofacitinib is a potent inhibitor of JAK1, JAK2, JAK3, and TYK2 [11]. Oral tofacitinib was administered in a dose of 5 mg once or twice daily in 6 patients in an open-label study. Their SCORAD decreased significantly by 66.6% from 36.5 to 12.2 across 8 to 29 weeks of treatment, with no significant side effects, but the number of patients was limited, and the study had no control group [11]. Tofacitinib is metabolized by CYP3A4 and CYP2C19, so it has the potential for a wide range of drug interactions [2].

Oral Tofacitinib

Tofacitinib is a potent small-molecule inhibitor targeting JAK1, JAK2, JAK3, and TYK2 [11]. In an open-label clinical trial, six patients received oral tofacitinib at a dose of 5 mg once or twice daily. Over a treatment period ranging from 8 to 29 weeks, the SCORAD (scoring atopic dermatitis) index showed a significant mean reduction of 66.6%, declining from 36.5 to 12.2. Although no major adverse events were reported, the study was limited by a small sample size and the absence of a control group [11]. Tofacitinib undergoes hepatic metabolism predominantly via CYP3A4 and CYP2C19, indicating a potential for various drug-drug interactions [2].

Oral Gusacitinib

Gusacitinib is an investigational oral agent that simultaneously inhibits both JAK and SYK signaling pathways. In a phase 1b clinical trial involving 36 participants, doses of 20, 40, and 80 mg were evaluated. The proportion of patients achieving an EASI-50 response was 20% at 20 mg, 100% at 40 mg, and 83% at 80 mg, all exceeding the 22% response rate observed in the placebo group. Most patients also reported a reduction in pruritus by week 4 of treatment. Additionally, EASI-75 responses were observed in 63% and 50% of the 40 mg and 80 mg groups, respectively, compared to 22% in the placebo group [13]. Clinical improvement correlated with reductions in inflammatory biomarkers (TH2, TH17, TH22) and skin barrier-related markers such as filaggrin (FLG) and CLDN23 [14].

Oral Baricitinib

Baricitinib selectively inhibits JAK1 and JAK2, with reduced activity against JAK3. It became the first oral JAK inhibitor approved for adults with moderate to severe atopic dermatitis (AD) [15]. In a phase II study, baricitinib

was administered alongside topical corticosteroids. After 16 weeks, 61% of patients receiving 4 mg daily achieved EASI-50, compared to 37% in the placebo group [16].

Further evaluation in the BREEZE-AD1 and BREEZE-AD2 randomized controlled trials examined baricitinib at doses of 1 mg, 2 mg, and 4 mg versus placebo over 16 weeks, using the Investigator's Global Assessment (IGA) as the primary endpoint. In BREEZE-AD1, 16.8% of patients receiving 4 mg responded, compared to 4.8% in the placebo group. In BREEZE-AD2, 13.8% of those on 2 mg responded versus 4.5% on placebo. Secondary outcomes, including EASI-75/90, pruritus, sleep quality, pain, and quality of life, also improved significantly with the 4 mg dose [17].

A 2021 meta-analysis of eight studies confirmed the efficacy and favorable safety profile of baricitinib, particularly at the 4 mg dose, either as monotherapy or in combination with topical corticosteroids. Common side effects included nasopharyngitis, upper respiratory tract infections, elevated creatine phosphokinase (CPK) levels, and headaches [18]. With its oral bioavailability, rapid onset of action, and limited drug interactions due to CYP-independent clearance, baricitinib represents a promising therapeutic option for AD management.

Oral Abrocitinib

Abrocitinib is a selective inhibitor of Janus kinase 1 (JAK1) [19]. In a phase 3 randomized, double-blind clinical trial, the efficacy and safety of once-daily abrocitinib at doses of 100 mg and 200 mg were assessed in adults with moderate-to-severe atopic dermatitis (AD). The study compared outcomes with the monoclonal antibody dupilumab and placebo. By week 12, both doses of abrocitinib, as well as dupilumab, significantly reduced AD signs and symptoms relative to placebo. The proportion of patients achieving an IGA response at week 12 was 48.4% for the 200 mg abrocitinib group, 36.6% for the 100 mg group, and 36.5% for dupilumab, compared to 14.0% with placebo. EASI-75 was attained in 70.3% (200 mg), 58.7% (100 mg), and 58.1% (dupilumab) of patients, versus 27.1% in the placebo group. Notably, the 200 mg abrocitinib group showed a more rapid reduction in pruritus by week 2 compared to all other groups. Nausea and acne were the most frequently reported side effects, and all participants continued concurrent topical therapies [20].

A recent systematic review confirmed that both the 100 mg and 200 mg doses of abrocitinib were superior to placebo in achieving higher IGA responses and greater proportions of EASI-50, EASI-75, and EASI-90. The 200 mg dose demonstrated a more robust effect compared to 100 mg. Improvements were also seen in patient-reported outcomes, including the numerical rating scale (NRS) for itch, the Dermatology Life Quality Index (DLQI), and the Children's Dermatology Life Quality Index (CDLQI), with no significant difference between the two doses. Both doses were associated with greater reductions in SCORAD, percentage of body surface area affected, pruritus and symptom assessment (PSAAD), and Patient-Oriented Eczema Measure (POEM) relative to placebo [21].

The incidence of adverse events was higher with the 200 mg dose, particularly nausea and headache. In this group, additional side effects included thrombocytopenia (n = 5), herpes zoster (n = 2), and decreased platelet counts (n = 2). In the 100 mg group, cases of eczema herpeticum (n = 2), herpangina (n = 1), and pneumonia (n = 1) were noted.

A parallel-group, randomized, double-blind, placebo-controlled trial administering either 100 mg or 200 mg of abrocitinib daily for 12 weeks further demonstrated its clinical efficacy. Improvement in IGA scores was observed in 44.5% and 27.8% of patients on 200 mg and 100 mg, respectively, compared to 6.3% in the placebo arm. Corresponding reductions in EASI were 82.6%, 59.0%, and 35.2%, respectively [19].

Oral Upadacitinib

Upadacitinib is a JAK1-selective inhibitor approved for the treatment of rheumatoid arthritis [22] and is under investigation for use in moderate-to-severe AD. In a phase 2b study involving 167 participants, patients were randomized to receive upadacitinib at daily doses of 7.5 mg, 15 mg, or 30 mg, or a placebo. After 16 weeks, all upadacitinib groups showed superior EASI score reductions compared to placebo: 39% (7.5 mg), 62% (15 mg), and 74% (30 mg), compared to 23% in the placebo group. An EASI-100 response was observed in 24% of patients in the 30 mg group, an outcome not achieved by any placebo recipient [23].

The Measure Up 1 and Measure Up 2 trials further evaluated upadacitinib in adults with moderate-to-severe AD. In Measure Up 1, EASI-75 was achieved by 70% (15 mg) and 80% (30 mg) of patients at 16 weeks, while Measure Up 2 reported corresponding rates of 60% and 73%. In comparison, placebo groups in the respective trials had EASI-75 rates of 16% and 13%. Regarding IGA 0/1 responses, outcomes for the 15 mg and 30 mg groups were 48% and 62% in Measure Up 1, and 39% and 52% in Measure Up 2, respectively. Placebo response rates were

8% and 5%. Pruritus relief was rapid and sustained through week 16. Common adverse events included nasopharyngitis, upper respiratory tract infections, headache, and acne. These findings support the use of upadacitinib monotherapy as a safe and efficacious option for patients with moderate-to-severe AD [24].

Upadacitinib: Combination Therapy and Comparative Efficacy

When used in conjunction with topical corticosteroids, both 15 mg and 30 mg doses of upadacitinib demonstrated superior efficacy compared to topical corticosteroids alone, while maintaining a favorable safety profile [25]. Furthermore, in a large-scale, randomized, double-blind trial involving 692 patients with moderate-to-severe atopic dermatitis (AD), upadacitinib was compared directly to dupilumab. At week 16, 71.0% of patients receiving upadacitinib achieved EASI-75, significantly surpassing the 61.1% observed in the dupilumab cohort. Upadacitinib also achieved statistically significant improvements in several secondary endpoints, including reductions in worst pruritus numerical rating scale (NRS) by week 1 ($P < .001$), EASI-75 by week 2 ($P < .001$), and EASI-100 at week 16 ($P < .001$) [26]. Despite its clinical advantages, upadacitinib was associated with a higher incidence of herpes zoster, eczema herpeticum, and serious bacterial infections, while dupilumab treatment was more frequently linked with injection site reactions and conjunctivitis.

JAK Inhibitors in Other Dermatologic Conditions

Tofacitinib has shown efficacy in psoriasis, as measured by the Psoriasis Area and Severity Index (PASI), with significant improvement observed at oral doses of 5 mg and 10 mg administered twice daily [27, 28]. Notably, only the 10 mg twice-daily dose demonstrated non-inferiority to etanercept, the established standard of care at the time [29]. Baricitinib has also proven effective in psoriasis management at higher doses (8–10 mg daily) [30]. However, the broad spectrum of potential drug interactions—particularly with tofacitinib, which undergoes hepatic metabolism via CYP3A4 and CYP2C19—has led to increasing interest in topical formulations. In contrast, baricitinib is metabolized independently of the cytochrome P450 system and is primarily renally excreted, potentially limiting pharmacokinetic interactions [2].

In dermatology, topical JAK inhibitors offer the potential to minimize systemic exposure and associated adverse events. Trials involving the topical application of tofacitinib and ruxolitinib have shown promising results in psoriasis, with improvements surpassing those of several approved treatments. However, these effects were not maintained after treatment cessation, and systemic absorption was minimal with no significant systemic adverse events reported [31, 32].

Topical tofacitinib demonstrated notable efficacy, with up to 80% improvement in EASI scores after four weeks of treatment [11]. JAK inhibition has also shown particular promise in reducing pruritus and scratching behavior, which are hallmark symptoms in many inflammatory skin conditions [33].

JAK Inhibition in Alopecia and Other Immune-Mediated Skin Diseases

The therapeutic potential of JAK inhibitors extends beyond AD. In alopecia areata—a condition characterized by immune-mediated hair follicle destruction—JAK inhibition has gained substantial attention. Overexpression of pro-inflammatory cytokines, particularly those signaling through interferon-gamma (IFN-γ), which utilizes the JAK1 and JAK2 pathways, contributes to disease pathogenesis [34]. Agents such as baricitinib, ruxolitinib, and tofacitinib have demonstrated efficacy in promoting hair regrowth in alopecia areata, although treatment cessation frequently results in disease relapse, and the long-term effectiveness of tofacitinib appears to decline over time [34–38]. Topical ruxolitinib has also shown benefit in cases of alopecia universalis [39], and the ability of JAK inhibitors to stimulate hair regrowth remains an area of particular interest [40].

Beyond alopecia, tofacitinib has been associated with clinical improvement in other immune-mediated skin disorders, including vitiligo [41], palmoplantar pustulosis [42], and idiopathic erythema multiforme [43].

Conclusion

This review consolidates current evidence regarding the efficacy and safety of JAK inhibitors in the treatment of AD and other dermatologic conditions. Oral agents including abrocitinib, baricitinib, gusacitinib, and upadacitinib, as well as topical formulations such as delgocitinib, ruxolitinib, and tofacitinib, have demonstrated substantial improvements in clinical signs and symptoms compared to placebo. These improvements extend to pruritus, sleep quality, and overall quality of life.

While the safety profiles of JAK inhibitors in short-term AD trials appear largely acceptable, data from long-term use in other inflammatory conditions such as rheumatoid arthritis have raised concerns regarding serious adverse events, including herpes zoster reactivation, malignancies, thromboembolic events, and cardiovascular complications [44–46]. These findings underscore the need for long-term, prospective studies, particularly in pediatric populations, and cost-effectiveness analyses to inform clinical practice and guideline development.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021;6(1):402.
2. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov. 2017;16(12):843-62.
3. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031-7.
4. Rask-Andersen M, Zhang J, Fabbro D, Schiöth HB. Advances in kinase targeting: current clinical use and clinical trials. Trends Pharmacol Sci. 2014;35(11):604-20.
5. Herrera AF, Jacobsen ED. Ibrutinib for the treatment of mantle cell lymphoma. Clin Cancer Res. 2014;20(1):5365-71.
6. T Virtanen A, Haikarainen T, Raivola J, Silvennoinen O. Selective JAKinibs: prospects in inflammatory and autoimmune diseases. BioDrugs. 2019;33(1):15-32.
7. Neis MM, Peters B, Dreuw A, Wenzel J, Bieber T, Mauch C, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. J Allergy Clin Immunol. 2006;118(4):930-7.
8. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol. 2021;85(4):863-72.
9. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol. 2020;145(2):572-82.
10. Gong X, Chen X, Kuligowski ME, Liu X, Liu X, Cimino E, et al. Pharmacokinetics of ruxolitinib in patients with atopic dermatitis treated with ruxolitinib cream: data from phase II and III studies. Am J Clin Dermatol. 2021;22(4):555-66.
11. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol. 2016;175(5):902-11.
12. Purohit VS, Ports WC, Wang C, Riley S. Systemic tofacitinib concentrations in adult patients with atopic dermatitis treated with 2% tofacitinib ointment and application to pediatric study planning. J Clin Pharmacol. 2019;59(6):811-20.
13. Bissonnette R, Maari C, Forman S, Bhatia N, Lee M, Fowler J, et al. The oral Janus kinase/spleen tyrosine kinase inhibitor ASN002 demonstrates efficacy and improves associated systemic inflammation in patients with moderate-to-severe atopic dermatitis: results from a randomized double-blind placebo-controlled study. Br J Dermatol. 2019;181(4):733-42.
14. Pavel AB, Song T, Kim HJ, Del Duca E, Krueger JG, Dubin C, et al. Oral Janus kinase/SYK inhibition (ASN002) suppresses inflammation and improves epidermal barrier markers in patients with atopic dermatitis. J Allergy Clin Immunol. 2019;144(4):1011-24.

15. Radi G, Simonetti O, Rizzetto G, Diotallevi F, Molinelli E, Offidani A. Baricitinib: The first Jak inhibitor approved in Europe for the treatment of moderate to severe atopic dermatitis in adult patients. Healthcare (Basel). 2021;9(11):1575.
16. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol. 2019;80(4):913-21.
17. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol. 2020;183(2):242-55.
18. Bieber T, Thyssen JP, Reich K, Simpson EL, Katoh N, Torrelo A, et al. Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials. J Eur Acad Dermatol Venereol. 2021;35(2):476-85.
19. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. Efficacy and safety of oral Janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial. JAMA Dermatol. 2019;155(12):1371-9.
20. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. N Engl J Med. 2021;384(12):1101-12.
21. Fadlalmola HA, Albadrani MS, Elhusein AM, Mohamedsalih WE, Swamy VDS, Mamanao DM. Effectiveness and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a systematic review and meta-analysis of randomized clinical trials. Dermatol Res Pract. 2021;2021:8382761.
22. Duggan S, Keam SJ. Upadacitinib: First Approval. Drugs. 2019;79(16):1819-28.
23. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020;145(3):877-84.
24. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomized controlled phase 3 trials. Lancet. 2021;397(10290):2151-68.
25. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2021;397(10290):2169-81.
26. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol. 2021;157(9):1047-55.
27. Bissonnette R, Iversen L, Sofen H, Griffiths CE, Foley P, Romiti R, et al. Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. Br J Dermatol. 2015;172(5):1395-406.
28. Chiricozzi A, Faleri S, Saraceno R, Bianchi L, Buonomo O, Chimenti S, et al. Tofacitinib for the treatment of moderate-to-severe psoriasis. Expert Rev Clin Immunol. 2015;11(4):443-55.
29. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomized non-inferiority trial. Lancet. 2015;386(9993):552-61.
30. Papp KA, Menter MA, Raman M, Disch D, Schlichting DE, Gaich C, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol. 2016;174(6):1266-76.
31. Punwani N, Scherle P, Flores R, Shi J, Liang J, Yeleswaram S, et al. Preliminary clinical activity of a topical JAK1/2 inhibitor in the treatment of psoriasis. J Am Acad Dermatol. 2012;67(4):658-64.
32. Punwani N, Burn T, Scherle P, Flores R, Shi J, Collier P, et al. Downmodulation of key inflammatory cell markers with a topical Janus kinase 1/2 inhibitor. Br J Dermatol. 2015;173(4):989-97.
33. Meng J, Steinhoff M. Molecular mechanisms of pruritus. Curr Res Transl Med. 2016;64(4):203-6.
34. Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014;20(9):1043-9.

35. Liu LY, Craiglow BG, Dai F, King BA. Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients. J Am Acad Dermatol. 2017;76(1):22-8.
36. Scheinberg M, Ferreira SB. Reversal of alopecia universalis by tofacitinib: a case report. Ann Intern Med. 2016;165(10):750-1.
37. Kennedy Crispin M, Ko JM, Craiglow BG, Li S, Shankar G, Urban JR, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI Insight. 2016;1(15):e89776.
38. Pieri L, Guglielmelli P, Vannucchi AM. Ruxolitinib-induced reversal of alopecia universalis in a patient with essential thrombocythemia. Am J Hematol. 2015;90(1):82-3.
39. Craiglow BG, Tavares D, King BA. Topical ruxolitinib for the treatment of alopecia universalis. JAMA Dermatol. 2016;152(4):490-1.
40. Craiglow BG, Liu LY, King BA. Tofacitinib for the treatment of alopecia areata and variants in adolescents. J Am Acad Dermatol. 2017;76(1):29-32.
41. Craiglow BG, King BA. Tofacitinib citrate for the treatment of vitiligo: a pathogenesis-directed therapy. JAMA Dermatol. 2015;151(10):1110-2.
42. Koga T, Sato T, Umeda M, Fukui S, Horai Y, Kawashiri SY, et al. Successful treatment of palmoplantar pustulosis with rheumatoid arthritis, with tofacitinib: Impact of this JAK inhibitor on T-cell differentiation. Clin Immunol. 2016;173:147-8.
43. Damsky W, King BA. Idiopathic erythema multiforme: Evidence of underlying Janus kinase-signal transducer and activator of transcription activation and successful treatment with tofacitinib. JAAD Case Rep. 2016;2(6):502-4.
44. He H, Guttman-Yassky E. JAK inhibitors for atopic dermatitis: an update. Am J Clin Dermatol. 2019;20(2):181-92.
45. Agboola F, Atlas SJ, Brouwer E, Carlson JJ, Hansen RN, Herron-Smith S, et al. JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value. J Manag Care Spec Pharm. 2022;28(1):108-14.
46. FDA. FDA requires warnings about the increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. Washington DC, USA: United States Food and Drug Administration; 2021. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death#:~:text=FDA%20is%20requiring%20new%20and,treat%20certain%20serious%20inflammatory%20conditions.