Review

How Janus kinase selectivity impacts efficacy and safety of abrocitinib for atopic dermatitis: an expert consensus panel

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Keywords: abrocitinib, adverse events, atopic dermatitis, biologic, JAK inhibitor

Dermatology Online Journal

Vol. 31, Issue 4, 2025

Abstract

Atopic dermatitis is a chronic, itch-inducing inflammatory skin condition that significantly affects quality of life. Abrocitinib, an oral medication that selectively inhibits Janus kinase 1, targets inflammatory pathways involved in the disease. All Janus kinase inhibitors approved by the United States Food and Drug Administration for inflammatory conditions carry boxed warnings for serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis. A panel of eight dermatologists met to evaluate the safety of abrocitinib and the impact of Janus kinase selectivity on side effects. A literature search of PubMed, Scopus, and Google Scholar identified 246 English-language studies, of which 36 met inclusion. These were reviewed by the panel prior to a roundtable discussion. Using a modified Delphi method, the panel developed 10 consensus statements and assigned a strength of recommendation to each: seven statements were rated "A," one "B," and two "C." Abrocitinib provides rapid itch relief for people with moderate-to-severe atopic dermatitis. It shows greater selectivity for Janus kinase 1 than other treatments and higher efficacy than biologic therapies. Its safety profile is similar to other Janus kinase 1 inhibitors, with low risk of serious infections and a rate of cardiovascular events and thrombosis comparable to placebo.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by intense itching, which profoundly affects quality of life by causing physical discomfort, emotional distress, and interruptions to daily activities.[1, 2] Prevalence of adult AD ranges from 2.1% in Japan to 4.9% in the United States.[3] Various treatment options are available, including topical medications, phototherapy, and systemic therapy. Dilute bleach baths, dietary avoidance, and allergen immunotherapy may sometimes be used as adjunctive therapies in specific clinical scenarios.[4] Biologics, targeting interleukin (IL)-4, IL-13, IL-31, and Janus kinase (JAK) inhibitors have shown to be efficacious in treating AD. However, JAK inhibitors that are approved by the US Food and Drug Administration (FDA) for inflammatory conditions carry a boxed warning for serious risks.[5] Given the boxed warning, significant concern related to the safety of JAK inhibitors exists.

The JAK-signal transducer of activators of transcription (STAT) pathway plays a critical role in AD by mediating the signaling of key cytokines (IL-4, IL-5, IL-13, IL-31, and thymic stromal lymphopoietin) involved in the inflamma-

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tory processes that drive chronic inflammation and pruritus.[6] JAK inhibitors FDA-approved for AD include both oral (upadacitinib and abrocitinib) and topical (ruxolitinib) therapies. Oral JAK inhibitors have been shown to improve skin symptoms quickly.[7] These therapies differ in their JAK binding site selectivity, which impacts downstream cytokine signaling and causes specific adverse events.

Abrocitinib, the most selective JAK inhibitor for AD, primarily targets JAK1 to modulate inflammatory pathways involved in the disease's pathogenesis, demonstrating efficacy in alleviating itch and skin inflammation.[8-11] Currently, there are limited guidelines addressing the safety profile of abrocitinib for AD and how it differs from other JAK inhibitors. This study aimed to convene a panel of AD experts to review existing literature and develop consensus statements on the safety of abrocitinib and the role of JAK inhibitor selectivity in influencing adverse events.

Methods

Literature search and study selection

A comprehensive literature search was performed across PubMed, Scopus, and Google Scholar on December 2, 2024, using the keywords "atopic dermatitis," "abrocitinib," "JAK inhibitor," and "selectivity," in combination with the Boolean operator "AND." The search was restricted to English-language original research articles, systematic reviews, and meta-analyses. This study did not require institutional review board approval. Retrieved articles were screened for relevance to the safety and efficacy of abrocitinib in the treatment of AD and adverse effects based on JAK selectivity.

The articles meeting the inclusion criteria were distributed to the panelists, who independently reviewed the selected studies and assigned a level of evidence using the Strength of Recommendation Taxonomy (SORT) criteria.[12] These levels are defined as follows: level 1 (high-quality patient-oriented evidence), level 2 (moderate-quality patient-oriented evidence), and level 3 (evidence from consensus guidelines, routine practice, expert opinion, or disease-oriented studies).[12] Notably, retrospective studies or basic science articles focused on disease states are appropriately categorized as level 2 or 3, which does not necessarily indicate a study's inadequacy.

Development of consensus statements

The panel was composed of 8 dermatologists specializing in the treatment of AD. Panel members included Andrew Alexis MD MPH, Natasha Atanaskova-Mesinkovska MD PhD, Alexandra Golant MD, Mark Lebwohl MD, Tejesh Patel MD, Todd Schlesinger MD, Bruce Strober MD PhD, and Lisa Swanson MD.

They congregated on December 13, 2024, to grade the studies and develop consensus statements regarding the safety and efficacy of abrocitinib in AD. A modified Delphi process was employed to achieve consensus on each statement.[13] This method, commonly used in dermatology to develop expert recommendations, involves multiple rounds of real-time voting and requires supermajority approval for a recommendation to be adopted.[14-16] All panel members, who are also coauthors of this manuscript, were fully informed of the study's objectives and unanimously support its submission to a peer-reviewed journal.

Results

Literature search and study selection

A total of 246 articles were identified through the literature search as meeting the initial criteria. After careful screening, 36 articles were determined to be directly relevant to the research questions and were provided to the panelists for review prior to the roundtable discussion. For the 36 articles that were evaluated, the panel assigned level 1 evidence to 13 articles, level 2 evidence to 11 articles, and level 3 evidence to 12 articles (Table 1).

Consensus statements

The panel established 10 consensus statements on the safety of abrocitinib in AD and the role of JAK selectivity in adverse events. All 10 statements received unanimous approval (8/8 vote) for adoption. The SORT criteria were applied to determine the strength of recommendation for each statement (Table 2).

Statement 1: JAK inhibitors have proven to be highly effective in blocking downstream signaling of inflammatory mediators responsible for AD including T-helper (Th)-2 cytokines [IL-4, IL-5, IL-13, IL-31], Th22 cytokines (IL-22), interferon-gamma, and thymic stromal lymphopoietin (TSLP). (SORT level C)

The immune response driven by Th-2 cytokines (IL-4, IL-5, IL-13, IL-31), TSLP, and Th22 cytokines (IL-22) are central to the immunopathogenesis of AD, particularly during the acute phase. In the chronic stage, these responses are accompanied by varying levels of Th1 (interferon-γ, tumor necrosis factor [TNF], and Th17 [IL-17]) activation.[42] Many of these inflammatory cytokines rely on the JAK/STAT pathway for downstream signaling.

The JAK family consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), whereas the STAT family comprises STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6. JAKs are activated when a ligand binds to cytokine transmembrane receptors, and in turn, they phosphorylate and activate STATs, which then translocate to the cell nucleus to regulate transcription of target genes.[49] JAK1 inhibitors are effective treatments as they prevent the binding and activation of the STAT pathway that signals for the Th2 cytokines primarily responsible for AD.[6] JAK inhibitors approved in the US for the treatment of AD inhibit the

Table 1. *SORT Criteria Level of Evidence for Articles Pertaining to Selectivity, Safety, and Efficacy of JAK Inhibitors.*

Article Title	Author, Year	Level of Evidence
Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis	Bieber T et al, 2021[17]	1
Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial	Blauvelt A et al, 2022[18]	1
Pharmacodynamics of Janus kinase inhibitors for the treatment of atopic dermatitis	Calabrese L et al, 2022[19]	3
Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance	Charles-Schoeman C et al, 2023[20]	2
Association of Risk of Incident Venous Thromboembolism With Atopic Dermatitis and Treatment With Janus Kinase Inhibitors: A Systematic Review and Meta-analysis	Chen TL et al, 2022[21]	2
Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: results from the open-label, randomised controlled ORAL Surveillance trial	Curtis JR et al, 2023[22]	2
Efficacy and Safety of Abrocitinib in Combination With Topical Therapy in Adolescents With Moderate-to-Severe Atopic Dermatitis: The JADE TEEN Randomized Clinical Trial	Eichenfield LF, 2021[23]	1
Major adverse cardiovascular events in patients with atopic dermatitis treated with oral Janus kinase inhibitors: a systematic review and meta-analysis	Ertus C et al, 2023[24]	2
Selective JAK1 Inhibitors for the Treatment of Atopic Dermatitis: Focus on Upadacitinib and Abrocitinib	Ferreira S et al, 2020[25]	3
Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial	Gooderham MJ et al, 2019[26]	1
JAK-STAT signaling pathway in the pathogenesis of atopic dermatitis: An updated review	Huang IH et al, 2022[6]	3
Cardiovascular and Venous Thromboembolic Risk With JAK Inhibitors in Immune-Mediated Inflammatory Skin Diseases: A Systematic Review and Meta-Analysis	Ingrassia JP et al, 2024[27]	1
Short-Term Cardiovascular Complications in Dermatology Patients Receiving JAK-STAT Inhibitors: A Meta-Analysis of Randomized Clinical Trials	Ireland PA et al, 2024[28]	2
Systematic Review on the Efficacy and Safety of Oral Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis	Le M et al, 2021[29]	3
Efficacy and Safety of Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis: A Systematic Review and Meta-Analysis	Li C et al, 2022[30]	2
Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden	Molander V et al, 2021[31]	2
Real-world effectiveness of abrocitinib treatment in patients with difficult-to-treat atopic dermatitis	Olydam JI et al, 2023[32]	3
In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494)	Parmentier JM et al, 2018[9]	3
Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial	Reich K et al, 2022[33]	1
JAK inhibitors and the risk of malignancy: a meta-analysis across disease indications	Russell MD et al, 2023[34]	2
Efficacy and safety of the Janus kinase 1 inhibitor PF-04965842 in patients with moderate-to-severe psoriasis: phase II, randomized, double-blind, placebo-controlled study	Schmieder GJ et al, 2018[10]	1
Risk of Thromboembolic Events and Associated Risk Factors, Including Treatments, in Patients with	Setyawan J	2

Immune-mediated Diseases	et al, 2021[35]	
Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND)	Shi VY et al, 2022[36]	1
Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial	Silverberg JI et al, 2020[37]	1
Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysis	Silverberg JI et al, 2022[38]	2
Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial	Simpson EL et al, 2020[39]	1
Integrated Safety Analysis of Abrocitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis From the Phase II and Phase III Clinical Trial Program	Simpson EL et al, 2021[40]	1
Integrated Safety Update of Abrocitinib in 3802 Patients with Moderate-to-Severe Atopic Dermatitis: Data from More than 5200 Patient-Years with Up to 4 Years of Exposure	Simpson EL et al, 2024[41]	1
The JAK/STAT Pathway and Its Selective Inhibition in the Treatment of Atopic Dermatitis: A Systematic Review	Tsiogka A et al, 2022[42]	3
Venous Thromboembolism Risk With JAK Inhibitors: A Meta-Analysis	Yates M et al, 2021[43]	2
Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis	Ytterberg SR et al, 2022[44]	1
Janus kinase inhibitors for the treatment of rheumatoid arthritis demonstrate similar profiles of in vitro cytokine receptor inhibition	Dowty ME et al, 2019[11]	3
The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers	Shi JG et al, 2014[45]	3
Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data	Bally M et al, 2017[46]	3
Selectivity, efficacy and safety of JAKinibs: new evidence for a still evolving story	Bonelli M et al, 2024[47]	3
JAK inhibition as a therapeutic strategy for immune and inflammatory diseases	Schwartz DM et al, 2017[48]	3

JAK1 pathway and include topical ruxolotinib and the oral medications, abrocitinib, and upadacitinib.

Statement 2: The boxed warnings for JAK inhibitors derive from data on tofacitinib for the treatment of rheumatoid arthritis and include cardiovascular events, malignancy, thromboembolic events, serious infection, and mortality. (SORT level A)

The FDA employs boxed warnings to highlight critical scientific information for health care providers. In 2021, a boxed warning was issued for the entire JAK inhibitor class based on findings from the ORAL Surveillance trial,[22,44] which identified an increased risk of cardiovascular events, malignancies, thromboembolic events, serious infections, and mortality associated with tofacitinib.[50] The ORAL Surveillance trial specifically evaluated the safety profile of tofacitinib in comparison to TNF inhibitors in patients with rheumatoid arthritis.[22,44] Safety was further evaluated in a post-hoc analysis of the ORAL Surveillance trial that found, in rheumatoid arthritis patients with a history of atherosclerotic cardiovascular disease (all of whom were also receiving methotrexate), the incidence of major adverse cardiovascular events (MACE) was higher with tofacitinib at 5mg twice a day (8.3%) and 10mg twice a day (7.7%) compared to TNF inhibitors (4.2%).[20] Of note, various registries have shown that TNF inhibitors lower the risk of cardiovascular disease, so that comparing cardiac risks of JAK inhibitors to risk in the general public may have different results.[51-53]

A meta-analysis assessing the risk of venous thromboembolism (VTE) associated with JAK inhibitors in patients with inflammatory arthropathies, psoriasis, and inflammatory bowel disease found no evidence in the pooled incidence rate ratios for tofacitinib, baricitinib, upadacitinib, or filgotinib to substantiate the current VTE risk warnings for these medications.[43] In a separate meta-analysis of JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib, peficitinib) in adults with rheumatoid arthritis, PsA, PsO, axial spondyloarthritis, inflam-

Table 2. *Consensus Statements for the Safety and Efficacy of abrocitinib for Atopic Dermatitis.*

Consensus Statement/Recommendation	Strength of Recommendation	Consensus Vote
JAK inhibitors have proven to be highly effective in blocking downstream signaling of inflammatory mediators responsible for AD including T-helper (Th)-2 cytokines [IL-4, IL-5, IL-13, IL-31], Th22 cytokines (IL-22), IFN gamma, and TSLP.	C	8/8
The boxed warnings for JAK inhibitors derive from data on tofacitinib for the treatment of rheumatoid arthritis and include cardiovascular events, malignancy, thromboembolic events, serious infection, and mortality.	A	8/8
Tofacitinib is the least selective JAK inhibitor, blocking JAK 1, JAK 2, and JAK 3. Of the oral and topical JAK inhibitors approved for AD, abrocitinib is the most selective, predominantly inhibiting JAK 1.	C	8/8
The selectivity and specificity of JAK inhibition may contribute to specific adverse events.	A	8/8
The ORAL Surveillance study, which prompted the boxed warning for JAK inhibitors, enrolled patients with rheumatoid arthritis (RA) who were all over 50 years old, had at least one cardiovascular risk factor, were on methotrexate, and most were on prednisone. This study population differs from patients with AD. These factors could influence the risk of major adverse cardiovascular events (MACE), malignancy, serious infection, venous thromboembolism (VTE), and mortality.	A	8/8
Rheumatoid arthritis patients have increased risk of thromboembolic events compared to healthy controls.	A	8/8
Published data do not show an increased incidence of MACE or thromboembolic events for patients with AD treated with JAK inhibitors compared to healthy controls.	A	8/8
JAK 1 inhibitors are effective treatments with rapid onset for AD.	A	8/8
Abrocitinib can be effective in treating AD patients who have failed other JAK inhibitors and biologics.	B	8/8
Available data in studies of JAK inhibitors for AD suggest an increased risk for serious and opportunistic infections, including herpes zoster, and nonmelanoma skin cancer.	A	8/8

Abbreviations: AD, atopic dermatitus; JAK, Janus kinase; Th, T-helper.

matory bowel disease (IBD), or AD, findings revealed a higher incidence of malignancy (Incidence rate ratio 1.50; 95% CI 1.16–1.94) compared to TNF inhibitors.[34]

Statement 3: Tofacitinib is the least selective JAK inhibitor, blocking JAK 1, JAK 2, and JAK 3. Of the oral and topical JAK inhibitors approved for AD, abrocitinib is the most selective, predominantly inhibiting JAK 1. (SORT level C)

Selectivity of JAK inhibitors can be determined by measuring their inhibitory activity for each JAK isoform (JAK1,2,3, or TYK2) through in vitro or ex vivo measures of cytokine release and/or phosphorylated STAT (pSTAT) activation.[25] A lower half-maximal inhibitory concentration (IC50) indicates greater inhibitory activity. Additionally, when the IC50 values for different isoforms are similar, the JAK inhibitor is considered less selective.

A study evaluating JAK-dependent cytokine receptor inhibition profiles using in vitro whole blood cytokine inhibition potencies and plasma pharmacokinetics found that tofacitinib was less selective than baricitinib, upadacitinib, and filgotinib.[11] Tofacitinib's IC50 values were 15nmol/L for JAK1, 71nmol/L for JAK2, 45nmol/L for JAK3, and 472nmol/L for T.[11] Baricitinib was slightly more selective than tofacitinib, with IC50 values of 0.78nmol/L for JAK1, 2nmol/L for JAK2, 253nmol/L for JAK3, and 14nmol/L for TYK2.[11] In a randomized controlled trial of baricitinib versus placebo, ex vivo whole blood was stimulated with IL-6 or thrombopoietin to activate the JAK/STAT pathway.[45]

After lysis of the blood cells, total cell extracts were examined for pSTAT3 levels using a specific enzyme-linked immunosorbent assay.[45] The study showed that baricitinib had an IC50 of 90nmol/L for inhibiting pSTAT3 (JAK2).[45] Another study of baricitinib selectivity showed baricitinib potently inhibits JAK1 and JAK2 with IC50 values of 5.9 and 5.7nmol/L, respectively, whereas it had an IC50 of 560nmol/L for JAK3.[8] Upadacitinib had an IC50 of 0.76nmol/L for JAK1, 19nmol/L for JAK2, 224nmol/L for JAK3, and 118nmol/L for TYK2.[11] Although filgotinib had an IC50 of 45nmol/L for JAK1, 357nmol/L for JAK2, 9097nmol/L for JAK3, and 397nmol/L for TYK2.[11] These findings suggest that tofacitinib is less selective than baricitinib, upadacitinib, and filgotinib.

Research on abrocitinib indicates higher selectivity with higher IC50 values for JAK2 and JAK3 compared to upadacitinib, baricitinib, and tofacitinib. Specifically, abrocitinib demonstrated IC50 values of 29nmol/L for JAK1, 803nmol/L for JAK2, >10,000nmol/L for JAK3, and 1250nmol/L for TYK2.[10] In a study using active recombinant human catalytic domains of engineered cells, upadacitinib showed an IC50 of 47nmol/L for JAK1 and inhibited JAK2 to a lesser extent (IC50 = 120nmol/L), while exhibiting lower potency for JAK3 (IC50 = 2304nmol/L) and TYK2 (IC50 = 4690nmol/L).[9] As upadacitinib has lower IC50 values for JAK2 and JAK3 compared to abrocitinib, it inhibits JAK2 and JAK3 at lower concentrations and suggests abrocitinib is the most selective JAK inhibitor for AD. This conclusion must be tempered because IC50 assays can differ when performed in different labs at different times.

Statement 4: The selectivity and specificity of JAK inhibition may contribute to specific adverse events. (SORT level A)

Key cytokines involved in AD primarily signal through JAK1, and minimizing concurrent inhibition of JAK2 and JAK3 pathways may help reduce potential safety risks.[19] Understanding the pathways affected by downstream cytokines may help explain adverse events profiles. Inhibition of JAK2 by less selective JAK inhibitors (eg, tofacitinib, baricitinib, ruxolitinib, and oclacitinib) can affect myeloid and lymphoid differentiation, T cell proliferation, lymphocyte function, hematopoiesis, growth, and metabolic processes.[48] This relates to the key role of JAK2 in the signal transduction of the IL-3 receptor family (IL-3R, IL-5R, and GM-CSF receptor) as well as single-chain receptors, including the erythropoietin receptor, growth hormone receptor, prolactin receptor, and thrombopoietin receptor.[54] The most frequently reported treatment-emergent adverse events in baricitinib (JAK1,2) studies include respiratory symptoms, headaches, skin infections, gastrointestinal symptoms, and elevated blood creatine phosphokinase levels.[29]

Selective inhibition of JAK3 (ie, with decernotinib or PF-06651600) impacts T cell proliferation, survival, and memory, T regulatory cell function, and B cell activity.[48] Janus kinase 3 is predominantly expressed in medullary and lymphoid tissues, with high expression levels observed in activated T cells, B cells, and monocytes.[55] Natural killer cells, essential for antiviral defense, rely on JAK3-dependent cytokines for their development and function.[55] Tofacitinib causes a dose-dependent reduction in natural killer cell counts, although this effect may be transient.[48] Studies show upadacitinib's increased selectivity for JAK1 led to less impact on reticulocyte production and natural killer cell depletion, demonstrating improved efficacy and safety compared to tofacitinib.[9] These effects suggest that adverse events, particularly those related to hematologic and immunologic systems, are mainly caused by inhibition of JAK2 and JAK3.

Statement 5: The ORAL Surveillance study, which prompted the boxed warning for JAK inhibitors, enrolled patients with rheumatoid arthritis (RA) who were all over 50 years old, had at least one cardiovascular risk factor, were on methotrexate, and most were on prednisone. This study population differs from patients with AD. These factors could influence the risk of MACE, malignancy, serious infection, VTE, and mortality. (SORT level A)

The ORAL Surveillance study included patients who were all over age 50 with RA and at least one cardiovascular risk factor.[44] Patients with RA are often more overweight, engage in less physical activity, have lower cardiorespiratory fitness, and exhibit reduced muscle strength compared to age- and sex-matched individuals without RA.[56] Patients with baseline cardiovascular risk factors and low fitness levels are shown to have an independent risk for MACE.[57] Similarly, findings suggest a potential link between methotrexate dosage and bacterial infections in patients with RA undergoing biologic treatment combined with glucocorticoids.[58] Given that these patients have increased risk of adverse events from independent risk factors, the ORAL Surveillance trial findings are not representative of AD patients receiving JAK inhibitor therapy.

There are several clinical trials assessing the safety of abrocitinib for AD patients. In the JADE MONO-1 safety trial adverse events were reported in 69% of patients in the abrocitinib 100mg group, 78% in the abrocitinib 200mg group, and 57% in the placebo group, with similar percentages of serious adverse events between groups.[39] Another randomized controlled trial assessing safety of abrocitinib for AD recorded three MACE in the abrocitinib cohort; these were two events of myocardial infarction (MI) and one event of sudden death, with a MACE incidence ratio (95% Confidence Interval [CI] of 0.18/100 person-years [0.04–0.52]).[40] For comparison, a patient-level meta-analysis assessing the risks of acute MI associated with oral nonsteroidal anti-inflammatory drugs (NSAIDs) revealed an increased risk of MI with higher NSAID doses.[46] Among the evaluated NSAIDs, rofecoxib demonstrated the highest odds of MI, OR (95% CI: 1.58 [1.07 to 2.17]).[46] Nonsteroidal anti-inflammatory drugs are frequently prescribed for pain relief even for people with underlying cardiovascular risks despite the boxed warning for serious cardiovascular and gastrointestinal side effects.[59] No trials compare the risk of MI in patients taking NSAIDs versus JAK inhibitors.

Statement 6: Rheumatoid arthritis patients have increased risk of thromboembolic events compared to healthy controls. (SORT level A)

When assessing clinical trial safety data, it is important to understand the study population's baseline risks, as independent variables may inflate the risk of adverse events. Studies comparing RA patients to healthy con-

trols have demonstrated RA may independently increase the risk of adverse events.[31] A retrospective cohort study specifically assessed the incidence of VTE in RA patients compared to those without RA.[31] The findings showed a risk ratio of 1.88 (95% CI: 1.65-2.15), with the risk increasing as RA disease activity intensified.[31] These findings suggest that RA is linked to a markedly higher risk of thromboembolic events when compared to the general population, with the risk increasing with higher disease activity. This is particularly relevant in the context of the ORAL Surveillance trial, which evaluated the safety profile of tofacitinib against TNF inhibitors in RA patients, who are already at an elevated risk for VTE.[44]

Statement 7: Published data do not show an increased incidence of MACE or thromboembolic events for patients with AD treated with JAK inhibitors compared to healthy controls. (SORT level A)

The safety of JAK inhibitors in patients with AD has been evaluated in multiple studies. A meta-analysis investigated the association between AD and the risk of VTE in patients treated with JAK inhibitors.[21] The results indicated no increased risk of VTE associated with AD or treatment with JAK inhibitors, including abrocitinib, baricitinib, upadacitinib, and SHR0302.[21]

A pooled safety meta-analysis assessed the cardiovascular risk of AD patients using JAK inhibitors (baricitinib, upadacitinib, abrocitinib, ivarmacitinib). The odds ratio (OR) for MACE in patients treated with JAK inhibitors compared to placebo or dupilumab was 1.35 (95% CI: 0.15-12.21), suggesting little to no impact of JAK inhibitors on MACE occurrence.[24] Similarly, the randomized controlled trial analyzing the safety of abrocitinib versus placebo in AD reported a MACE incidence rate of 0.18 per 100 person-years (95% CI: 0.04–0.52).[40]

Another meta-analysis reported no significant differences in the incidence of composite MACE and all-cause mortality (OR: 0.83; 95% CI: 0.44-1.57), or VTE (OR: 0.52; 95% CI: 0.26-1.04) between patients receiving JAK inhibitors and those on placebo or active comparators for immune-mediated inflammatory skin diseases.[27] Similarly, a study evaluating the safety of systemic JAK-STAT inhibitors versus placebo in patients with alopecia areata, psoriasis, vitiligo, AD, lichen planus, or hidradenitis suppurativa found no significant increase in MACE (relative risk: 0.47; 95% CI: 0.28-0.80) or VTE (relative risk: 0.46; 95% CI: 0.26-0.80).[28]

In contrast, a retrospective cohort study of patients with immune-mediated diseases, including ankylosing spondylitis, AD, inflammatory bowel disease, multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus, observed that JAK inhibitors (unspecified) were associated with an increased incidence of pulmonary embolism (incidence rate ratio=2.52; P<0.05).[35] However, the diseases treated have their own relative risks of thrombotic events, and as stated earlier, some JAK inhibitors are less selective and may therefore have different side effect profiles. Further safety trials of abrocitinib, a highly selective JAK1 inhibitor, for AD show the most reported adverse events are nasopharyngitis, upper respiratory tract infections, headache, nausea, and diarrhea.[26,29,30] Data from the JADE REGIMEN showed abrocitinib had a dose response in terms of AE occurrence in AD.[18]

Another abrocitinib safety trial including patients over age 12 years with moderate-to-severe AD showed decreases in platelet count of 26% in the 200mg group, 19% in the 100mg group, and less than 1% in the placebo group.[37] Although studies in AD patients have not demonstrated an increased risk of serious adverse events, the selection of patients for JAK inhibitor therapy should carefully consider factors such as cardiovascular comorbidities, susceptibility to opportunistic infections, and a history of malignancy.

Statement 8: JAK 1 inhibitors are effective treatments with rapid onset for AD. (SORT level A)

AD involves numerous pathways driving immune response. Its pathogenesis is characterized by the downstream activation of cytokines such as IL-4, IL-5, IL-13, IL-31, TSLP, IL-22, interferon-γ, TNF, and IL-17.[42] Treatments FDA-approved for moderate-to-severe AD include injectable therapies like dupilumab (an IL-4 and IL-13 inhibitor) lebrikizumab and tralokinumab (IL-13 inhibitors), and nemolizumab (an IL-31 inhibitor) as well as oral options such as abrocitinib and upadacitinib, both of which are JAK1 inhibitors. Inhibitors of JAK1 effectively block the activation of the STAT pathway, which mediates Th2 cytokines (IL-4, IL-13, and IL-31) that play a key role in AD pathogenesis.[6]

A clinical trial comparing abrocitinib with dupilumab revealed that a 200mg dose of abrocitinib outperformed dupilumab in itch reduction by week two.[17] Another phase 3 trial assessed efficacy and safety of abrocitinib versus dupilumab in AD patients using concomitant topical corticosteroids, topical calcineurin inhibitors, or a topical phosphodiesterase 4 inhibitor.[33] Data showed abrocitinib 200mg per day was more efficacious than dupilumab in adults with moderate-to-severe AD on background topical therapy in inducing early reductions of itch and AD disease signs by week two (P<0.0001).[33]

Level Up was a phase 3b/4 global randomized open-label efficacy assessor-blinded study evaluating upadacitinib versus dupilumab in adolescents and adults with moderate-to-severe AD who had an inadequate response to systemic therapy or when use was inadvisable.[60] Superior efficacy in achieving simultaneous eczema area and severity index (EASI)-90 and worst pruritus numerical rating scale (WP-NRS) 0/1 response at week 16 was demonstrated with upadacitinib versus dupilumab (19.9% versus 8.9%, respectively; P<0.001).[60] Post hoc analyses showed higher itch response rates as early as day two in upadacitinib treated patients.[60] These findings suggest that JAK1 inhibitors provide faster itch relief than dupilumab, resulting in quicker symptom improvement.

The efficacy of biologics and JAK inhibitors for AD is commonly evaluated using measures such as EASI-75, EASI-90, investigator global assessment (IGA) scores, and patient-reported outcomes. In the JADE TEEN trial, patients aged 12 to 17 years treated with abrocitinib (200mg or 100mg) versus placebo achieved significant improvements at week 12, including an IGA response of 0 or 1 (46.2% and 41.6% versus 24.5%; P<0.05 for both), EASI-75 (72.0% and 68.5% versus 41.5%; P<0.05 for both), and peak pruritus numerical rating scale 4 (55.4% and 52.6% versus 29.8%; P<0.01) for 200mg and 100mg versus placebo, respectively.[23] A meta-analysis evaluated the efficacy of upadacitinib, IL-4 and IL-13 inhibitors, and JAK inhibitors compared to placebo or active treatments for AD.[38] The findings suggest that upadacitinib (30mg and 15mg daily) and abrocitinib (200mg daily) are among the most effective targeted systemic therapies for AD over 12 to 16 weeks of treatment.[38]

Statement 9: Abrocitinib can be effective in treating AD patients who have failed other JAK inhibitors and biologics. (SORT level B)

Studies show that abrocitinib is an effective treatment for AD refractory to other JAK inhibitors and biologics.[32,36] In a prospective observational single-center study in patients who had previously failed other JAK inhibitors and biologics, abrocitinib treatment resulted in a significant decrease in disease severity during a median follow-up period of 25 weeks (IQR 16-34).[32] Median EASI score decreased significantly from 14.7 (IQR 10.4-25.4) at baseline to 4.0 (IQR 1.6-11.4) at the final review (P<0.001).[32] In the JADE EXTEND phase 3 extension trial, patients with moderate-to-severe AD who previously received dupilumab during the double-blind, placebo-controlled phase 3 JADE COMPARE study were treated with abrocitinib at doses of 200mg or 100mg once daily.[36] Among patients who did not respond to dupilumab, over 75% improvement in EASI scores was achieved in 80% of those receiving abrocitinib 200mg and 67.7% of those receiving abrocitinib 100mg for 12 weeks.[36]

Statement 10: Available data in studies of JAK inhibitors for AD suggest an increased risk for serious and opportunistic infections, including herpes zoster and nonmelanoma skin cancer. (SORT level A)

When considering oral JAK inhibitors for AD, it is wise to consider each patient's past medical history, current medications, smoking history, and family planning goals. Integrated safety data was analyzed from the phase 2 monotherapy study and the phase 3 trials, including JADE MONO-1, JADE MONO-2, JADE TEEN, JADE COMPARE, JADE DARE (200mg only), JADE REGIMEN, and JADE EXTEND to assess abrocitinib safety in AD.[41] The most commonly reported serious infections with consistent-dose abrocitinib at 200mg and 100mg included herpes zoster (0.5% and 0.2%, respectively), pneumonia (0.2% for both doses), and herpes simplex virus (0.1% for both doses).[41]

Similarly, data from in vivo studies and clinical trials comparing the side effects of pan versus selective JAK inhibitors indicate distinct safety profiles.[47] Tofacitinib (JAK1-3) demonstrated a significantly increased risk of herpes zoster and a slightly elevated risk of malignancies, thrombosis, elevated liver function tests, upper respiratory tract infections, disruptions in lymphocyte and platelet hematopoiesis, and hyperlipidemia compared to placebo.[47] Baricitinib (JAK1,2) was associated with a significantly increased risk of herpes zoster and a slightly higher risk of thrombosis, elevated liver function tests, URIs, platelet hematopoiesis effects, and hyperlipidemia.[47] Upadacitinib (JAK1,2) showed a significantly elevated risk of herpes zoster and a slightly increased risk of upper respiratory tract infections, elevated liver function tests, and hyperlipidemia.[47] It must be noted that in the absence of head-to-head trials, safety or efficacy profiles cannot be easily differentiated. Nonetheless, given the risk of serious and opportunistic infections, patients with a positive purified protein derivative not previously treated with prophylaxis should be treated with prophylaxis if using JAK inhibitors and that includes JAK1 inhibitors.

Strengths and limitations

The Delphi process offers both advantages and challenges. A common limitation is its reliance on clinical opinions rather than strictly evidence-based data to formulate consensus statements. However, this study leveraged high-quality published clinical research to guide the development of its recommendations. In this context, the Delphi process proved to be a structured and effective approach for creating evidence-informed clinical guidelines.

Conclusion

A deeper understanding of the data behind the boxed warning for JAK inhibitors remains essential. Current evidence indicates that the selectivity of JAK inhibitors significantly influences their specific safety profiles. Although much of the evidence supporting the boxed warning stems from tofacitinib studies in rheumatoid arthritis patients, it is critical to consider the baseline independent risk factors for MACE, VTE, and serious infections in this population. Data on abrocitinib demonstrate that selective JAK1 inhibition offers a safe and effective strategy for reducing symptom burden in AD, with a favorable risk profile. Following a thorough review of the literature, these 10 consensus statements on the safety and efficacy of abrocitinib aim to guide clinical management of AD. Head-to-head comparisons reveal that abrocitinib exhibits a rapid onset of action and high efficacy, even in patients refractory to other systemic agents or biologics. This expert panel concluded that abrocitinib's safety profile aligns with other JAK1 inhibitors, with a higher incidence of serious and opportunistic infections, including herpes zoster, but an extremely low risk of MACE or VTE.

We recommend future studies to compare efficacy and safety of JAK inhibitors for atopic dermatitis.

Potential conflicts of interest

The authors declare the following potential conflicts: Dr. Alexis is a consultant or speaker for Abbvie, Aerolase, Allergan, Almirall, Alphyn, Amgen, Apogee, Arcutis, Avita Medical, Bausch health, Beiersdorf, BMS, Boehringer Ingelheim, Canfield, Cara, Castle, Cutera, Dermavant, Eli Lilly, EPI, Galderma, Genentech, Genzyme, Incyte, Janssen, J&J, Leo, L'Oreal, Ortho, Pfizer, Sanofi-Regeneron, Swiss American, UCB, and VisualDx, and has received grants or royalties from Abbvie, Amgen, Arcutis, Castle, Dermavant, Elsevier, Galderma, Incyte, Leo, Springer, Wiley-Blackwell, and Wolters Kluwer Health, and equipment from Aerolase. Dr. Golant is a consultant, speaker, and/or investigator for Abbvie, Amgen, Apogee Therapeutics, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Galderma, Incyte, Janssen, LEO Pharma, Lilly, Pfizer, Regeneron, Sanofi, and Takeda Pharmaceuticals. Dr. Schlesinger has served as a consultant, speaker and/or investigator for AbbVie, Almirall, Amgen, Apogee, Arcutis, Boehringer-Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Dermsquared, Eli Lilly and Company, Galderma, Incyte, Janssen, Novartis, Pfizer Inc., Regeneron, Sanofi, SiSaf, Sun Pharma, Takeda, Pfizer Inc., RBC Consultants, Verrica, and UCB. Dr. Strober has received consulting fees and/or honoraria from AbbVie, Alamar, Almirall, Alumis, Amgen, Arcutis, Arena, Aristea, Asana, Boehringer Ingelheim, Bristol Myers Squibb, Capital One, Connect Biopharma, CorEvitas, Dermavant, Eli Lilly, Evelo Biosciences, Immunic Therapeutics, Incyte, Janssen, Kangpu Pharmaceuticals, Leo Pharma, Maruho, Meiji Seika Pharma, Mindera Health, Nimbus, Novartis, Pfizer, Protagonist, Regeneron, Sanofi Genzyme, Sun Pharma, UCB, UNION therapeutics, Ventyxbio, and vTv Therapeutics; is a shareholder in Connect Biopharma and Mindera Health; serves as scientific codirector of CorEvitas Psoriasis Registry; and serves as editor-in-chief of the Journal of Psoriasis and Psoriatic Arthritis. Dr. Swanson is or has been a consultant or speaker for AbbVie, Alphyn, Arcutis, Boehringer Ingelheim, Castle, Dermavant, Galderma, Incyte, Janssen, LEO Pharma, Lilly, Novan, Pfizer, Sanofi-Regeneron, and Verrica. Dr. Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte,Inozyme, Janssen, Pfizer, Sanofi-Regeneron, and UCB, and is a consultant for Almirall, AltruBio Inc., Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer-Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Evommune, Inc., Facilitation of International Dermatology Education,Forte biosciences, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals Pfizer,Sanofi-Regeneron, Seanergy, Strata, Takeda,Trevi, and Verrica. Dr. Rosenberg, Zakria, DeBusk, Burshtein, Shah, Atanaskova-Mesinkovska, Patel, and Rigel have no conflicts to disclose.

References

1. Koszorú K, Borza J, Gulácsi L, Sárdy M. Quality of life in patients with atopic dermatitis. *Cutis*. 2019;104(3):174-177. PMID:31675393

2. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. *Ann Allergy Asthma Immunol*. 2018;121(3):340-347. doi:10.1016/j.anai.2018.07.006. PMID:30025911

3. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy*. 2018;73(6):1284-1293. doi:10.1111/all.13401. PMID:29319189

4. AAAAI/ACAAI JTF Atopic Dermatitis Guideline Panel, Chu DK, Schneider L, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. *Ann Allergy Asthma Immunol*. 2024;132(3):274-312. doi:10.1016/j.anai.2023.11.009. PMID:38108679

5. Kim RW, Lam M, Abuabara K, Simpson EL, Drucker AM. Targeted systemic therapies for adults with atopic dermatitis: selecting from biologics and JAK inhibitors. *Am J Clin Dermatol*. 2024;25(2):179-193. doi:10.1007/s40257-023-00837-w. PMID:38216802

6. Huang IH, Chung WH, Wu PC, Chen CB. JAK-STAT signaling pathway in the pathogenesis of atopic dermatitis: An updated review. *Front Immunol*. 2022;13:1068260. doi:10.3389/fimmu.2022.1068260. PMID:36569854

7. Nakashima C, Yanagihara S, Otsuka A. Innovation in the treatment of atopic dermatitis: Emerging topical and oral Janus kinase inhibitors. *Allergol Int*. 2022;71(1):40-46. doi:10.1016/j.alit.2021.10.004. PMID:34815171

8. Fridman JS, Scherle PA, Collins R, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: Preclinical characterization of INCB028050. *J Immunol*. 2010;184(9):5298-5307. doi:10.4049/jimmunol.0902819. PMID:20363976

9. Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatol*. 2018;2:23. doi:10.1186/s41927-018-0031-x. PMID:30886973

10. Schmieder GJ, Draelos ZD, Pariser DM, et al. Efficacy and safety of the Janus kinase 1 inhibitor PF-04965842 in patients with moderate-to-severe psoriasis: Phase II, randomized, double-blind, placebo-controlled study. *Br J Dermatol*. 2018;179(1):54-62. doi:10.1111/bjd.16004. PMID:28949012

11. Dowty ME, Lin TH, Jesson MI, et al. Janus kinase inhibitors for the treatment of rheumatoid arthritis demonstrate similar profiles of in vitro cytokine receptor inhibition. *Pharmacol Res Perspect*. 2019;7(6):e00537. doi:10.1002/prp2.537. PMID:31832202

12. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract*. 2004;17(1):59-67. doi:10.3122/jabfm.17.1.59. PMID:15014055

13. Hsu CCSB. The Delphi Technique: Making Sense of Consensus. *Practical Assessment, Research, and Evaluation*. 2007;12(1). doi:10.7275/pdz9-th90

14. Berman BCR, Cockerell C, et al. Appropriate use criteria for the integration of diagnostic and prognostic gene expression profile assays into the management of cutaneous malignant melanoma: An expert panel consensus-based modified Delphi process assessment. *SKIN J Cutan Med*. 2019;3(5):291-306. doi:10.25251/skin.3.5.1

15. Burshtein J, Zakria D, Shah M, et al. Advances in technology for melanoma diagnosis and prognosis: An expert consensus panel. *J Drugs Dermatol*. 2024;23(9):774-781. doi:10.36849/JDD.8365. PMID:39231082

16. Zakria DBN, Berman B, et al. Incorporating prognostic gene expression profile assays into the management of cutaneous melanoma: an expert consensus panel. *SKIN J Cutan Med*. 2023;7(1):556-569. doi:10.25251/skin.7.1.1

17. Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384(12):1101-1112. doi:10.1056/NEJMoa2019380. PMID:33761207

18. Blauvelt A, Silverberg JI, Lynde CW, et al. Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial. *J Am Acad Dermatol*. 2022;86(1):104-112. doi:10.1016/j.jaad.2021.05.075. PMID:34416294

19. Calabrese L, Chiricozzi A, De Simone C, Fossati B, D'Amore A, Peris K. Pharmacodynamics of Janus kinase inhibitors for the treatment of atopic dermatitis. *Expert Opin Drug Metab Toxicol*. 2022;18(5):347-355. doi:10.1080/17425255.2022.2099835. PMID:35796377

20. Charles-Schoeman C, Buch MH, Dougados M, et al. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: A post hoc analysis from ORAL Surveillance. *Ann Rheum Dis*. 2023;82(1):119-129. doi:10.1136/ard-2022-222259. PMID:36137735

21. Chen TL, Lee LL, Huang HK, Chen LY, Loh CH, Chi CC. Association of risk of incident venous thromboembolism with atopic dermatitis and treatment with Janus kinase inhibitors: A systematic review and meta-analysis. *JAMA Dermatol*. 2022;158(11):1254-1261. doi:10.1001/jamadermatol.2022.3516. PMID:36001310

22. Curtis JR, Yamaoka K, Chen YH, et al. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: Results from the open-label, randomised controlled ORAL Surveillance trial. *Ann Rheum Dis*. 2023;82(3):331-343. doi:10.1136/ard-2022-222543. PMID:36600185

23. Eichenfield LF, Flohr C, Sidbury R, et al. Efficacy and safety of abrocitinib in combination with topical therapy in adolescents with moderate-to-severe atopic dermatitis: The JADE TEEN Randomized Clinical Trial. *JAMA Dermatol*. 2021;157(10):1165-1173. doi:10.1001/jamadermatol.2021.2830. PMID:34406366

24. Ertus C, Scailteux LM, Lescoat A, et al. Major adverse cardiovascular events in patients with atopic dermatitis treated with oral Janus kinase inhibitors: A systematic review and meta-analysis. *Br J Dermatol*. 2023;189(4):368-380. doi:10.1093/bjd/ljad229. PMID:37410552

25. Ferreira S, Guttman-Yassky E, Torres T. Selective JAK1 inhibitors for the treatment of atopic dermatitis: Focus on upadacitinib and abrocitinib. *Am J Clin Dermatol*. 2020;21(6):783-798. doi:10.1007/s40257-020-00548-6. PMID:32776305

26. Gooderham MJ, Forman SB, Bissonnette R, 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):1371-1379. doi:10.1001/jamadermatol.2019.2855. PMID:31577341

27. Ingrassia JP, Maqsood MH, Gelfand JM, et al. Cardiovascular and venous thromboembolic risk with JAK inhibitors in immune-mediated inflammatory skin diseases: A systematic review and meta-analysis. *JAMA Dermatol*. 2024;160(1):28-36. doi:10.1001/jamadermatol.2023.4090. PMID:37910098

28. Ireland PA, Jansson N, Spencer SKR, Braden J, Sebaratnam D. Short-term cardiovascular complications in dermatology patients receiving JAK-STAT inhibitors: A meta-analysis of randomized clinical trials. *JAMA Dermatol*. 2024;160(3):281-289. doi:10.1001/jamadermatol.2023.5509. PMID:38294793

29. Le M, Berman-Rosa M, Ghazawi FM, et al. Systematic review on the efficacy and safety of oral Janus kinase inhibitors for the treatment of atopic dermatitis. *Front Med (Lausanne)*. 2021;8:682547. doi:10.3389/fmed.2021.682547. PMID:34540860

30. Li C, Sun X, Zhao K, et al. Efficacy and safety of Janus kinase inhibitors for the treatment of atopic dermatitis: A systematic review and meta-analysis. *Dermatology*. 2022;238(4):725-735. doi:10.1159/000518541. PMID:34455413

31. Molander V, Bower H, Frisell T, Askling J. Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: A nationwide cohort study from Sweden. *Ann Rheum Dis*. 2021;80(2):169-175. doi:10.1136/annrheumdis-2020-218419. PMID:33032998

32. Olydam JI, Schlösser AR, Custurone P, Nijsten TEC, Hijnen D. Real-world effectiveness of abrocitinib treatment in patients with difficult-to-treat atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2023;37(12):2537-2542. doi:10.1111/jdv.19378. PMID:37478296

33. Reich K, Thyssen JP, Blauvelt A, et al. Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: A randomised, double-blind, multicentre phase 3 trial. *Lancet*. 2022;400(10348):273-282. doi:10.1016/S0140-6736(22)01199-0. PMID:35871814

34. Russell MD, Stovin C, Alveyn E, et al. JAK inhibitors and the risk of malignancy: A meta-analysis across disease indications. *Ann Rheum Dis*. 2023;82(8):1059-1067. doi:10.1136/ard-2023-224049. PMID:37247942

35. Setyawan J, Mu F, Yarur A, et al. Risk of thromboembolic events and associated risk factors, including treatments, in patients with immune-mediated diseases. *Clin Ther*. 2021;43(8):1392-1407.e1391. doi:10.1016/j.clinthera.2021.06.008. PMID:34238587

36. Shi VY, Bhutani T, Fonacier L, et al. Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND). *J Am Acad Dermatol*. 2022;87(2):351-358. doi:10.1016/j.jaad.2022.04.009. PMID:35439608

37. Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: A randomized clinical trial. *JAMA Dermatol*. 2020;156(8):863-873. doi:10.1001/jamadermatol.2020.1406. PMID:32492087

38. Silverberg JI, Hong HC, Thyssen JP, et al. Comparative efficacy of targeted systemic therapies for moderate to severe atopic dermatitis without topical corticosteroids: Systematic review and network meta-analysis. *Dermatol Ther (Heidelb)*. 2022;12(5):1181-1196. doi:10.1007/s13555-022-00721-1. PMID:35435637

39. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): A multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10246):255-266. doi:10.1016/S0140-6736(20)30732-7. PMID:32711801

40. Simpson EL, Silverberg JI, Nosbaum A, et al. Integrated safety analysis of abrocitinib for the treatment of moderate-to-severe atopic dermatitis from the phase II and phase III clinical trial program. *Am J Clin Dermatol*. 2021;22(5):693-707. doi:10.1007/s40257-021-00618-3. PMID:34406619

41. Simpson EL, Silverberg JI, Nosbaum A, et al. Integrated safety update of abrocitinib in 3802 patients with moderate-to-severe atopic dermatitis: Data from more than 5200 patient-years with up to 4 years of exposure. *Am J Clin Dermatol*. 2024;25(4):639-654. doi:10.1007/s40257-024-00869-w. PMID:38888681

42. Tsiogka A, Kyriazopoulou M, Kontochristopoulos G, et al. The JAK/STAT pathway and its selective inhibition in the treatment of atopic dermatitis: A systematic review. *J Clin Med*. 2022;11(15):4431. doi:10.3390/jcm11154431. PMID:35956047

43. Yates M, Mootoo A, Adas M, et al. Venous thromboembolism risk with JAK inhibitors: A meta-analysis. *Arthritis Rheumatol*. 2021;73(5):779-788. doi:10.1002/art.41580. PMID:33174384

44. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med*. 2022;386(4):316-326. doi:10.1056/NEJMoa2109927. PMID:35081280

45. Shi JG, Chen X, Lee F, et al. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J Clin Pharmacol*. 2014;54(12):1354-1361. doi:10.1002/jcph.354. PMID:24965573

46. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. *Bmj*. 2017;357:j1909. doi:10.1136/bmj.j1909. PMID:28487435

47. Bonelli M, Kerschbaumer A, Kastrati K, et al. Selectivity, efficacy and safety of JAKinibs: New evidence for a still evolving story. *Ann Rheum Dis*. 2024;83(2):139-160. doi:10.1136/ard-2023-223850. PMID:37923366

48. 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):843-862. doi:10.1038/nrd.2017.201. PMID:29104284

49. Guttman-Yassky E, Irvine AD, Brunner PM, et al. The role of Janus kinase signaling in the pathology of atopic dermatitis. *J Allergy Clin Immunol*. 2023;152(6):1394-1404. doi:10.1016/j.jaci.2023.07.010. PMID:37536511

50. Kragstrup TW, Glintborg B, Svensson AL, et al. Waiting for JAK inhibitor safety data. *RMD Open*. 2022;8(1):e002236. doi:10.1136/rmdopen-2022-002236. PMID:35197363

51. Lunt M, Watson KD, Dixon WG, et al. No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum*. 2010;62(11):3145-3153. doi:10.1002/art.27660. PMID:20662063

52. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis [published correction appears in Arch Dermatol. 2013 Feb;149(2):158]. *Arch Dermatol*. 2012;148(11):1244-1250. doi:10.1001/archdermatol.2012.2502. PMID:22911151

53. Yang ZS, Lin NN, Li L, Li Y. The effect of TNF inhibitors on cardiovascular events in psoriasis and psoriatic arthritis: An updated meta-analysis. *Clin Rev Allergy Immunol*. 2016;51(2):240-247. doi:10.1007/s12016-016-8560-9. PMID:27300248

54. Schindler C, Strehlow I. Cytokines and STAT signaling. *Adv Pharmacol*. 2000;47:113-174. doi:10.1016/S1054-3589(08)60111-8. PMID:10582086

55. Coricello A, Mesiti F, Lupia A, Maruca A, Alcaro S. Inside perspective of the synthetic and computational toolbox of JAK inhibitors: Recent updates. *Molecules*. 2020;25(15). doi:10.3390/molecules25153321. PMID:32707925

56. Azeez M, Clancy C, O'Dwyer T, Lahiff C, Wilson F, Cunnane G. Benefits of exercise in patients with rheumatoid arthritis: A randomized controlled trial of a patient-specific exercise programme. *Clin Rheumatol*. 2020;39(6):1783-1792. doi:10.1007/s10067-020-04937-4. PMID:32036584

57. Aker A, Saliba W, Bahouth F, Naoum I, Zafrir B. Cardiorespiratory fitness and risk of cardiovascular events and mortality in middle age patients without known cardiovascular disease. *J Clin Med*. 2023;12(22). doi:10.3390/jcm12227011. PMID:38002625

58. Ota R, Hata T, Hirata A, et al. Risk of infection from glucocorticoid and methotrexate interaction in patients with rheumatoid arthritis using biologics: A retrospective cohort study. *Br J Clin Pharmacol*. 2023;89(7):2168-2178. doi:10.1111/bcp.15687. PMID:36755477

59. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol*. 2020;17(9):574-584. doi:10.1038/s41569-020-0366-z. PMID:32322101

60. Silverberg JI, Bunick CG, Hong HC, et al. Efficacy and safety of upadacitinib versus dupilumab in adults and adolescents with moderate-to-severe atopic dermatitis: Week 16 results of an open-label randomized efficacy assessor-blinded head-to-head phase IIIb/IV study (Level Up). *Br J Dermatol*. 2024;192(1):36-45. doi:10.1093/bjd/ljae404. PMID:39438067