DERMIS

Review Article 2025; 5(3):41

Analysis of Janus Kinase Inhibitor Safety in Dermatology Patients with Multiple Cardiovascular Risk Factors

*Nicole Aust[1], Felicia Hung[2], Caitlyn Brown[3], Lynn Fadel[4], Carolyn Duong[5], Usiwat Abdul[6], Angelique Putris[7], Kelly Frasier[8]**

[1]Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Tampa, FL, USA

[2,4]California Health Sciences University College of Osteopathic Medicine, Clovis, CA, USA

[3]Philadelphia College of Osteopathic Medicine - Georgia Campus, Suwanee, GA, USA

[5]Kansas City University College of Osteopathic Medicine, Joplin, MO, USA

[6]State University of New York, Upstate Medical University, Syracuse, NY, USA

[7]A.T. Still University College of Osteopathic Medicine Arizona, Mesa, AZ, USA

[8]Department of Dermatology, Northwell Health, New Hyde Park, NY, USA

***Corresponding author:**

Kelly Frasier, DO, MS
Department of Dermatology, Northwell Health, New Hyde Park, NY, USA, Phone: 3105956882,
Email: kellymariefrasier@gmail.com

Received : June 14, 2025
Published : June 30, 2025

ABSTRACT

Analyzing the safety profile of Janus kinase (JAK) inhibitors in dermatology patients with multiple cardiovascular risk factors provides insight into the balance between therapeutic efficacy and potential adverse outcomes. JAK inhibitors, widely used for conditions such as atopic dermatitis, alopecia areata, and psoriasis, modulate pro-inflammatory signaling pathways, including JAK-STAT-dependent cytokines such as IL-6, IFN-γ, and TNF-α, which are also implicated in atherosclerosis and thrombogenesis. Emerging data indicate an increased risk of major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and venous thromboembolism, particularly in patients with preexisting risk factors such as hypertension, hyperlipidemia, obesity, and diabetes. Mechanistic insights suggest that JAK inhibition may alter endothelial function, disrupt lipid metabolism, and contribute to platelet aggregation, compounding cardiovascular risk in susceptible individuals. Large-scale post-marketing surveillance and real-world cohort studies have highlighted variable cardiovascular risk profiles across different JAK inhibitors, necessitating individualized risk assessments prior to treatment initiation. Regulatory agencies have responded by implementing boxed warnings and risk mitigation strategies, underscoring the need for vigilant patient selection and longitudinal cardiovascular monitoring. Integrating cardioprotective strategies, including lipid-lowering therapies,

DOI: https://doi.org/10.35702/Derm.10041

antiplatelet agents, and lifestyle modifications, may help optimize the safety of JAK inhibitors in dermatology patients with elevated cardiovascular risk while preserving therapeutic efficacy.

Keywords: Janus Kinase Inhibitor, JAK-STAT, Cardiovascular Risk Factors, Dermatology, MACE, VTE

INTRODUCTION

Janus kinase (JAK) inhibitors, also known as jakinibs, are a drug class that disrupt the JAK-STAT signaling pathway, mediating proinflammatory cytokine activity, dampening immune responses and reducing disease severity [1]. Jak inhibitors have emerged as an effective therapy for chronic inflammatory and autoimmune dermatologic conditions such as atopic dermatitis, alopecia areata, and psoriasis. These diseases involve immune system dysregulation, leading to chronic inflammation that drives disease progression. While JAK inhibitors have demonstrated remarkable efficacy, the U.S. Food and Drug Administration (FDA) has issued warnings about their increased risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), serious infections, malignant neoplasm, and death [2]. As JAK inhibitors alter immune pathways involved in both inflammation and vascular homeostasis, understanding their safety profile is essential for optimizing treatment outcomes in dermatologic populations with underlying cardiovascular comorbidities [2].

Following the ORAL Surveillance study, which compared tofacitinib with tumor necrosis factor-alpha (TNF-α) inhibitors in rheumatoid arthritis, the FDA issued warnings about the risks of MACE and VTE for all JAK inhibitors [2]. However, the currently approved JAK inhibitors vary in their preferential and dose-dependent selectivity for JAK enzymes, and the mechanisms underlying the reported adverse events remain poorly understood [3]. Moreover, pooled safety data suggest that the risk of MACE and VTE might be lower in patients using JAK inhibitors for dermatologic conditions compared to those observed in the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study. The risk reduction could be attributed to the younger age and generally better health of participants in trials focused on dermatologic indications [4].

Given this knowledge gap, a thorough evaluation of JAK inhibitors' mechanisms of action, epidemiological evidence of associated MACE and VTE risks, and regulatory and risk mitigation strategies are warranted. Through a comprehensive understanding of both the therapeutic benefits and potential risks of JAK inhibitors, physicians can make informed treatment decisions that prioritize patient cardiovascular safety while maintaining dermatologic disease control.

Mechanism of Action and Inflammatory Pathways

The Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway modulates gene expression in many inflammatory processes through its association with cytokine receptors. The signaling cascade is initiated by the binding of a cytokine to its receptor. Receptor activation triggers the phosphorylation of JAK proteins and their associated intracellular domains, and then STAT proteins are recruited to bind to the newly phosphorylated receptor. Once bound, the STATs are activated through phosphorylation, then they dimerize and translocate to the nucleus, where they act as a transcription factor to regulate gene expression [5]. Because of their involvement in cytokine-mediated inflammatory processes, there has been research into the use of a JAK inhibitor as a mechanism of action for anti-inflammatory drugs, with many currently on the market.

JAK inhibitors are currently used in the treatment of dermatological conditions, including atopic dermatitis, alopecia areata, plaque psoriasis, and vitiligo, due to the involvement of cytokines in the pathogenesis of these conditions [6]. There are multiple different members of the JAK and STAT protein families that provide the wide range of effects seen in the JAK-STAT pathway, but they all follow the same basic pattern [7]. Typically, a cytokine will bind to a specific receptor, which is associated with a specific JAK and a specific STAT that regulates the effects of the cytokine [8]. JAK inhibitors can use the specificity of cytokines related to specific conditions to provide targeted treatment. Currently, there are many different mechanisms of action used by JAKi to provide these results, but most focus on inhibiting adenosine triphosphate (ATP) binding to the JAK protein [9]. First-generation JAKi use competitive inhibition to prevent ATP from binding to its active site on the JAK protein. This provides non-selective inhibition due to the highly conserved structure of the ATP binding site across all four JAK proteins [1]. Second-generation JAK inhibitors are more selective due to using allosteric inhibition to prevent ATP binding and are targeted to specific JAK proteins [9]. Table 1 provides a breakdown of some of the current JAK inhibitors used for dermatological conditions and their selectivity.

Table 1. JAK inhibitors and their selectivity

Drug Name	Selectivity
Ruzolitinib, Baricitinib, Deuruxolitinib	JAK1/2
Upadacitinib, Abrocitinib	JAK1
Ritlecitinib	JAK3
Deucravacitinib	TYK2

The selectivity of dermatology related Janus kinase inhibitors and which of the four JAK proteins they selectively inhibit: JAK1, JAK2, JAK3, or TYK2 [10-14].

The use of JAK inhibitors in dermatology stems from the role of cytokines in the disease processes of many inflammatory skin conditions. Some of the key cytokines that play a role in these conditions are interleukin-6 (IL-6), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). Studies have shown that IL-6 is increased in patients with psoriasis, which is a cytokine that typically uses JAK1, JAK2, and TYK2 as its associated JAK proteins [7,15]. The pathogenesis of alopecia areata is attributed to many cytokines, with IFN-γ using JAK1 and JAK2 proteins and interleukin-15 (IL-15) and interleukin-2 (IL-2) using JAK1 and JAK3 [16]. TNF-α has been associated with atopic dermatitis and uses the JAK1 and TYK2 proteins [17,18]. As demonstrated, the JAK-STAT pathway is involved in many dermatological conditions. However, the complexity can lead to difficulties while treating with a JAK inhibitor. In addition to the examples provided, the JAK-STAT pathway and cytokines are important in regulating many aspects of homeostasis. The use of JAK inhibitors have demonstrated some cardiovascular side effects that have raised questions about their safety in patients with previous cardiovascular conditions.

In addition to the dermatological examples provided, the JAK-STAT pathway and cytokines are important in regulating many aspects of homeostasis, with studies linking cytokines to atherosclerosis and heart failure [19]. Currently, JAK inhibitors have a black-box warning from the Food and Drug Administration due to the number of adverse cardiovascular effects associated with their use, including venous thromboembolism, stroke, and tachyarrhythmias [20]. With the increasing research into the use of JAK inhibitors in the field of dermatology, questions are raised on the safety of their use, especially in patients with pre-existing cardiovascular conditions.

Epidemiological Evidence of Cardiovascular Risks Associated with JAK Inhibitors

With the ever-growing use of JAK inhibitors for inflammatory conditions, there is trepidation about a corresponding increase in the risk for a MACE. Numerous studies indicate that most, if not all, oral JAK inhibitors are associated with an increase in HDL and LDL cholesterol with an unfavorable LDL/HDL cholesterol ratio [21]. While dyslipidemia is not categorized as a MACE, it can put patients at risk for further complications. One retrospective study on upadacitinib for severe atopic dermatitis found that the most frequent adverse event occurring in 44.8% of patients was an increase in total cholesterol to levels greater than 200 mg/dl [22]. An increase in cholesterol levels on top of other comorbidities has the potential to advance patients into serious complications. In addition to hyperlipidemia, there has been reported incidence of both pulmonary embolism (PE) and deep vein thrombosis (DVT) while using JAK inhibitors. One review of the FDA's Adverse Event Reporting System (FAERS) identified adverse effects of PE and DVT in patients tofacitinib, ruxolitinb, and tofacitinib XR [23]. This data contributes to the evidence supporting concern for cardiovascular complications during treatment.

Due to the increasing incidence of hyperlipidemia, cancer, and MACE associated with JAK inhibitors, the ORAL Surveillance was conducted to evaluate the safety and efficacy of tofacitinib compared to a TNF inhibitor. Among the 4362 patients, the incidence of MACE was higher with the tofacitinib doses (3.4%, 98 patients) than with the TNF inhibitor (37 patients, 2.5%) after a median follow-up of 4.0 years. In addition, after 5.5 years, the estimated probability of MACE was greater with tofacitinib doses compared to the TNF inhibitor at 5.8% and 4.3%, respectively. Of note, the incidences of death and PE were high enough to intervene and adjust the dosing of patients using tofacitinib [24]. While there is an argument that

patients with rheumatoid arthritis are already at a higher risk for cardiovascular complications due to their inflammatory state, the results of the trial are not to be overlooked. Patients undergoing treatment with JAK inhibitors for dermatologic conditions such as psoriasis or atopic dermatitis are already at a higher risk for developing cardiovascular disease and venous thromboembolism [25,26]. In addition, with the growing prevalence of comorbidities in our society today, the risk of MACE will only continue to increase.

For patients who are already at higher risk for thromboembolic events due to conditions such as uncontrolled hypertension, hyperlipidemia, obesity, and diabetes, growing evidence implies that the potential for MACE should be carefully considered when starting JAK inhibitor therapy. In the ALLEGRO clinical trial program, which performed a safety analysis of ritlecitinib, an oral JAK3/TEC family kinase inhibitor for the treatment of alopecia areata, all patients who experienced CV adverse events had at least one CV risk factor [27]. In addition, the ORAL study included patients with at least one pre-existing cardiovascular risk factor. They found that the incidence rates of MACE were higher among patients 65 years of age or older and those living in North America [24]. These findings may add to the overall increased risk factors among patients residing in North America. Ultimately, while there is conflicting data on the correlation between JAK inhibitors and MACE, evidence supports that careful consideration should be taken when patients have CV comorbid conditions that may be exacerbated by treatment.

Mechanistic Insights into Cardiovascular Risk

The Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway plays a significant role in cardiac function by regulating processes involved in inflammation, remodeling, and stress responses in the heart. It is triggered by proinflammatory cytokines such as TNF-α. Physiological levels of TNF-α play a protective role in heart ischemia, tissue repair, and remodeling. TNF inhibitors are commonly used in autoimmune conditions like psoriasis and hidradenitis suppurativa for their inflammatory effects. However, an increased reduction in TNF-α levels may eliminate its protective effects in groups with a high predisposition to major cardiovascular effects [28]. This inhibition may contribute to an increased risk of heart failure hospitalization, as TNF-α is involved in ventricular remodeling, myocyte fibrosis, and cell survival [28]. These adverse effects suggest that TNF inhibitors may exacerbate heart failure or contribute to its development, particularly in patients with pre-existing heart conditions. These effects may translate into the use of JAK inhibitors due to their ability to suppress TNF-α.

Nitric oxide (NO) is a potent vasodilator that plays a crucial role in cardiovascular regulation by relaxing vascular smooth muscle, increasing blood flow, and reducing blood pressure. It is produced by nitric oxide synthase (NOS), with inducible NOS (iNOS) being upregulated during inflammation, particularly in response to IFN-γ [29]. The JAK-STAT pathway is a key regulator of IFN-γ-induced iNOS expression, and studies have shown that JAK2 inhibitor AG-490 and JAK3 inhibitor WHI-P154 suppress this process, reducing NO production and impacting inflammation-driven vascular damage [29]. This impact may lead to vascular stiffness, implying that patients may experience hypertension as a possible cardiovascular side effect. This is particularly relevant in rheumatoid arthritis patients treated with JAK inhibitors, as capillaroscopic analysis revealed significant microvascular alterations, including reduced venous limb diameter, apical width, and capillary length, along with increased capillary branching and overall abnormalities [30]. These findings suggest that JAK inhibition may disrupt normal vascular homeostasis, potentially leading to impaired endothelial function, altered blood flow, and pathological angiogenesis.

IL-6 is a powerful proinflammatory involved in transmitting activating signals to the JAK-STAT pathway. During inflammation, IL-6 influences lipid metabolism by enhancing lipid catabolism. When JAK inhibitors are used, they can suppress cytokines to mitigate inflammatory effects. However, medications like tofacitinib and baricitinib have exhibited the ability to increase both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels in a dose-dependent manner [21]. While HDL is generally considered cardioprotective, elevated LDL levels raise concerns, particularly for individuals predisposed to cardiovascular disease (CVD), as high LDL is a key contributor to atherosclerosis. Further evidence of this risk comes from an animal study in which researchers administered ruxolitinib, a JAK2 inhibitor, to apolipoprotein E-null (ApoE-null) mice on a high-cholesterol diet to model human CVD. The results demonstrated increased plaque formation in the aortic arch and descending aorta, suggesting that JAK inhibition may exacerbate atherosclerosis under higher doses [31]. These findings highlight a trade-off in Jakinib therapy where these drugs effectively manage inflammatory conditions, but

they may inadvertently increase CVD risk by altering lipid levels and promoting plaque formation. Given these concerns, careful patient selection and monitoring are essential when prescribing JAK inhibitors, particularly for individuals at high risk for cardiovascular complications.

Interferons (IFNs), specifically IFN-γ, play a key role in inflammation and thrombus formation due to their proinflammatory and prothrombotic properties. It has been hypothesized that JAK inhibitors may help reduce disease severity and promote thrombus resolution, potentially mimicking the effects of direct IFN inhibition by blocking IFN-γ signaling [32]. However, paradoxical events have shown the occurrence of VTE, a blood clot in a vein that may lodge in other parts of the body, in Jakinib users. Baricitinib has been linked to an increased risk of thromboembolic events, including deep vein thrombosis and pulmonary embolism, particularly in high-risk patients such as elderly individuals, those with CVD, or those on hormone therapy [33]. The proposed mechanism is that baricinib affects gene expression by upregulating IFN-γ and downregulating IL-6 [34]. Despite the reduction of IL-6, a proinflammatory and prothrombotic cytokine, it can be inferred that this effect does not suffice for the resolution of thrombi, making patients with autoimmune disease susceptible to cardiovascular adversities.

Clinical Evidence from Real-World and Post-Marketing Studies

In treating dermatological conditions, JAK inhibitors have been approved by the U.S. FDA to treat atopic dermatitis (oral abrocitinib, oral upadacitinib, topical ruxolitinib), alopecia areata (oral baricitinib), plaque psoriasis (oral deucravacitinib), and vitiligo (topical ruxolitinib) [10,35-37].

Table 2. FDA approved JAK inhibitors for dermatologic conditions

Atopic dermatitis/eczema	Ruxolitinib (Opzelura)
	Abrocitinib (Cibinqo)
	Upadacitinib (Rinvoq)
	Baricitinib (Olumiant)
Alopecia areata	Deuruxolitinib (Leqselvi)
	Ritlecitinib (Litfulo)
Plaque Psoriasis	Deucravacitinib (Sotyktu)
Vitiligo	Ruxolitinib (Opzelura)

In 2021, the FDA placed a black box warning on all approved JAK inhibitors due to an identified increased risk of VTE and MACE in patients taking JAK inhibitors [6]. MACE includes death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke [24]. The US FDA Adverse Events Reporting System (FAERS) collects adverse effect reports from sources such as drug manufacturers, hospitals, physicians, and individual consumers of FDA-approved drugs [23,38,39]. Using information from FAERS, we summarized the current post-surveillance clinical evidence of MACE and VTE for JAKi users.

Ruxolitinib

Ruxolitinib was approved by the FDA in 2021 for atopic dermatitis and in 2022 for vitiligo [36]. From January 1, 2011 to December 30, 2024, FAERS has reported the following MACEs and VTE events for ruxolitinib:

Table 3. Reported adverse effects of ruxolitinib from FAERS

Ruxolitinib Adverse Effect	Number of Cases	Percentage (Out of 63,997)
Thrombosis	458	0.72%
Pulmonary Embolism	313	0.49%
Myocardial Infarction	272	0.43%
Deep Vein Thrombosis	146	0.23%
Pulmonary Thrombosis	62	0.10%
Portal Vein Thrombosis	55	0.09%
Ischaemic Stroke	42	0.07%
Cardiac Death	4	0.01%
Haemorrhagic Stroke	7	0.01%
Embolic Stroke	4	0.01%
Middle Cerebral Artery Stroke	1	0.00%
Haemorrhagic Transformation Stroke	1	0.00%

Abrocitinib

In 2022, abrocitinib was approved by the FDA for atopic dermatitis [36]. From January 1, 2020, to December 30, 2024, FAERS has reported the following MACEs and VTE events for abrocitinib:

Table 4. Reported adverse effects of abrocitinib from FAERS

Abrocitinib Adverse Effect	Number of Cases	Percentage (Out of 2,456)
Thrombosis	11	0.45%
Deep Vein Thrombosis	11	0.45%
Myocardial Infarction	5	0.20%
Pulmonary Thrombosis	3	0.12%
Sudden Cardiac Death	2	0.08%
Cardiac Death	1	0.04%

Upadacitinib

Upadacitinib was approved for atopic dermatitis by the FDA in 2022 [36]. From January 1, 2015 to December 30, 2024, FAERS has reported the following MACEs and VTE events for upadacitinib:

Table 5. Reported adverse effects of upadacitinib from FAERS

Adverse Effect	Number of Cases	Percentage (Out of 53,545)
Myocardial Infarction	381	0.71%
Pulmonary Embolism	328	0.61%
Pulmonary Thrombosis	185	0.35%
Deep Vein Thrombosis	173	0.32%
Ischaemic Stroke	27	0.05%
Portal Vein Thrombosis	16	0.03%
Haemorrhagic Stroke	15	0.03%
Embolic Stroke	5	0.01%
Middle Cerebral Artery Stroke	5	0.01%
Sudden Cardiac Death	1	0.00%

Baricitnib

In 2022, baricitinib was approved by the FDA for alopecia areata [36]. From January 1, 2018, to December 30, 2024, FAERS has reported the following major adverse cardiovascular effects of baricitinib:

Table 6. Reported adverse effects of baricitinib from FAERS

Baricitinib Adverse Effect	Number of Cases	Percentage (Out of 7,443)
Pulmonary Embolism	278	3.74%
Myocardial Infarction	49	0.66%
Thrombosis	49	0.66%
Ischaemic Stroke	31	0.42%
Portal Vein Thrombosis	6	0.08%
Embolic Stroke	6	0.08%
Haemorrhagic Stroke	3	0.04%
Middle Cerebral Artery Stroke	2	0.03%

Deuruxolitinib

The FDA approved deuruxolitinib in 2024 for the treatment of alopecia areata [35]. From January 1, 2024, to December 30, 2024, FAERS reported no MACEs or VTE events for deuruxolitinib.

Ritlecitinib

In June 2023, ritlecitinib received approval from the FDA for the treatment of alopecia areata [10]. From January 1, 2022, to December 30, 2024, FAERS has reported the following major adverse cardiovascular effects for ritlectinib:

Table 7. Reported adverse effects of ritlecitinib from FAERS

Ritlecitinb Adverse Effect	Number of Cases	Percentage (Out of 59)
Myocardial Infarction	1	1.69%

Deucravacitinib

Deucravacitinib was approved for plaque psoriasis in 2022 by the FDA [36]. From January 1, 2020, to December 30, 2024, FAERS has reported the following major adverse cardiovascular effects of deucravacitinib:

Table 8. Reported adverse effects of deucravacitinib from FAERS

Deucravacitinb Adverse Effect	Number of Cases	Percentage (Out of 59)
Deep Vein Thrombosis	5	0.25%
Myocardial Infarction	4	0.20%
Pulmonary Embolism	1	0.05%

Characteristics of Patients with Adverse Events and the Need for Individualized Care

Characteristics of patients on JAK inhibitors who experienced a pulmonary embolism include a history of asthma, estrogen treatment, menopause, hypertension, hypercholesterolemia, first-degree atrioventricular heart block, morbid obesity, previous history of pulmonary embolism, COVID-19 [6,13]. Patients who experience myocardial infarction as an adverse effect of the drug had COVID-19, uncontrolled hypertension, obesity, hypercholesterolemia, tobacco use, and/or atrial fibrillation in their history [6]. For patients who experienced a deep vein thrombosis after starting a JAK inhibitor regimen,

a history of recent surgery, obesity, hypertension, and/or COVID-19 appeared in their history [13]. Incidence of MACE and VTE is noted particularly in adults older than 65 [6,39,40].

Each of the JAK inhibitor has been on the market for variable time frames, and with ruxolitinib being the first, it showcases the most adverse events. This makes it challenging to identify any single JAK inhibitor deemed safe for all patients. Given the variety of cardiovascular risk factors that may precipitate MACE or VTE in patients on JAK inhibitors, it is necessary to conduct individualized risk assessments and patient-specific treatment strategies, which include frequent lab monitoring.

Regulatory and Risk Mitigation Strategies

Several JAK inhibitor such as abrocitinib and upadacitinib (used in atopic dermatitis), baricitinib, deuruxolitinib, and ritlecitinib (used in alopecia areata), and ruxolitinib (used for vitiligo and atopic dermatitis), have been associated with serious cardiovascular risks, as noted in black box warnings issued by the U.S. Food and Drug Administration (FDA). On September 9, 2021, the FDA released a safety communication and revised boxed warnings for tofacitinib, baricitinib, and upadacitinib to include the risks of serious heart-related events, blood clots, cancer, and death [41]. These warnings indicate an increased incidence of MACE, including cardiovascular death, myocardial infarction, and stroke, as well as venous and arterial thrombotic events like deep vein thrombosis and pulmonary embolism. The FDA's decision was primarily informed by the ORAL Surveillance post-marketing trial, which found significantly higher rates of MACE and venous thromboembolism in rheumatoid arthritis patients treated with tofacitinib compared to TNF inhibitors [20]. Consequently, similar warnings were extended to upadacitinib and baricitinib due to their comparable mechanisms of action. In contrast, deucravacitinib, a selective TYK2 inhibitor approved for plaque psoriasis, does not carry a black box warning and has shown a milder adverse event profile [42]. However, as TYK2 belongs to the JAK family, its use in high-risk patients should still be approached with clinical caution.

Taking a detailed patient history evaluating factors such as age, hypertension, diabetes, obesity, and smoking status is important in assessing cardiovascular risk before initiating JAK inhibitor therapy. The FDA has specifically warned that patients who are current or former smokers may face an elevated risk of thrombosis when treated with oral JAK inhibitors, particularly those with rheumatoid arthritis over age 50 and at least one cardiovascular risk factor [43]. Traditionally, hyperlipidemia has also been considered a major contributor to MACE, reinforcing the importance of lipid screening prior to treatment [44]. In their clinical recommendations, Samuel et al. (2023) proposed a baseline assessment that includes blood pressure measurement, a complete blood count with differential, kidney and liver function tests, a lipid panel, and infectious disease screening including hepatitis B and C, tuberculosis, and human immunodeficiency virus (HIV). Using a comprehensive pre-treatment evaluation helps to identify at-risk patients early and supports a safer approach to managing chronic dermatologic conditions with JAK inhibitors.

In addition to baseline assessments, risk estimator tools can help with treatment decision-making. The Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator tool enables clinicians to calculate a patient's 10-year risk of having major cardiovascular events and modify their treatment approach accordingly [45]. This tool can be especially useful for dermatologists initiating treatment with JAK inhibitors, since cardiovascular risk may not be routinely assessed in dermatology. For dermatology patients screened with high cardiovascular risk, alternative therapies such as TNF inhibitors may be a safer option. Treatment decisions should be based on controlling symptoms related to both cardiovascular safety and individual patient history.

Patients using JAK inhibitors require continued monitoring throughout treatment and are advised to promptly report symptoms of thrombosis or cardiovascular events. For several JAK inhibitors, the FDA requires patients are informed of possible serious cardiovascular symptoms such as chest pain, shortness of breath, or leg swelling and advised to seek immediate medical attention if these occur [43]. Regular laboratory and symptom monitoring can help mitigate the risk of serious side effects associated with long-term use. This monitoring approach is important for dermatology patients who may not have viable alternatives, ensuring that the therapeutic benefits of JAK inhibitors are achieved with minimal harm. In this context, patient education and consistent follow-up are critical components of a well-rounded treatment regimen [46,47].

CONCLUSION AND FUTURE DIRECTIONS

The class-wide effect of JAK kinase inhibitors demonstrates elevated risk for MACE including tachyarrhythmias, ischemic

DOI: https://doi.org/10.35702/Derm.10041

heart disease, venous thromboembolism, atherosclerotic cardiovascular disease, and myocardial infarction. The main culprit is JAK inhibitors' ability to cause elevated serum LDL, total cholesterol/HDL ratio, and very-low-density lipoprotein (VLDL) cholesterol. A linear relationship exists between the age-adjusted risk of MACE with every 1 mmol/l increase in serum LDL, total cholesterol/HDL ratio, and VLDL cholesterol in both men and women. Before initiating JAK inhibitor therapy, a full assessment of the patient's age, smoking status, cardiovascular history, hormonal contraception and replacement therapy status, and venous thromboembolism risk should be performed. Prevention of MACE can be achieved using a multimodal approach with pharmacotherapy including statins and lifestyle modifications focused on a healthy diet and exercise. Future research on long-term safety data is needed to stratify the risk of JAK inhibitor therapy amongst adult vs pediatric populations and individuals receiving combination therapies. Limited data is available on the long-term adverse effects of biologics used in combination with JAK inhibitors for inflammatory conditions. Ultimately, a personalized approach for patients receiving JAK inhibitor therapy is essential for long-term safety and efficacy. Close follow-up and specific therapy dosing should be tailored to the severity and complexity of the disease being treated.

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

REFERENCES

1. Virtanen A, Haikarainen T, Raivola J, Silvennoinen O. (2019). Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. BioDrugs. 33(1):15-32.

2. Kragstrup TW, Glintborg B, Svensson AL, McMaster C, Robinson PC, Deleuran B, et al. (2022). Waiting for JAK inhibitor safety data. RMD Open. 8(1):e002236.

3. Nash P, Smolen JS. (2023). Response to: 'Correspondence on 'Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement" by Banday et al. Ann Rheum Dis. 82(5):e105.

4. Bieber T, Katoh N, Simpson EL, de Bruin-Weller M, Thaçi D, Torrelo A, et al. (2023). Safety of baricitinib for the treatment of atopic dermatitis over a median of 1.6 years and up to 3.9 years of treatment: an updated integrated analysis of eight clinical trials. J Dermatolog Treat. 34(1):2161812.

5. Samra S, Bergerson JRE, Freeman AF, Turvey SE. (2025). JAK-STAT signaling pathway, immunodeficiency, inflammation, immune dysregulation, and inborn errors of immunity. J Allergy Clin Immunol. 155(2):357-367.

6. Samuel C, Cornman H, Kambala A, Kwatra SG. (2023). A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring. Dermatol Ther (Heidelb). 13(3):729-749.

7. O'Shea JJ, Holland SM, Staudt LM. (2013). JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 368(2):161-170.

8. Morris R, Kershaw NJ, Babon JJ. (2018). The molecular details of cytokine signaling via the JAK/STAT pathway. Protein Sci. 27(12):1984-2009.

9. Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. (2022). A Comprehensive Overview of Globally Approved JAK Inhibitors. Pharmaceutics. 14(5):1001.

10. Blair HA. (2023). Ritlecitinib: First Approval. Drugs. 83(14):1315-1321.

11. Chimalakonda A, Burke J, Cheng L, Catlett I, Tagen M, Zhao Q, et al. (2021). Selectivity Profile of the Tyrosine Kinase 2 Inhibitor Deucravacitinib Compared with Janus Kinase 1/2/3 Inhibitors. Dermatol Ther (Heidelb). 11(5):1763-1776.

12. Damsky W, King BA. (2017). JAK inhibitors in dermatology: The promise of a new drug class. J Am Acad Dermatol. 76(4):736-744.

13. Iznardo H, Roé E, Serra-Baldrich E, Puig L. (2023). Efficacy and Safety of JAK1 Inhibitor Abrocitinib in Atopic Dermatitis. Pharmaceutics. 15(2):385.

14. King B, Senna MM, Mesinkovska NA, Lynde C, Zirwas M, Maari C, et al. (2024). Efficacy and safety of deuruxolitinib, an oral selective Janus kinase inhibitor, in adults with alopecia areata: Results from the Phase 3 randomized, controlled trial (THRIVE-AA1). J Am Acad Dermatol. 91(5):880-888.

15. Sobolev VV, Denisova EV, Chebysheva SN, Geppe NA, Korsunskaya IM. (2022). IL-6 Gene Expression as a Marker of Pathological State in Psoriasis and Psoriatic Arthritis. Bull Exp Biol Med. 173(1):77-80.

16. Fitzhugh MH, Hansen JG, Jabbari A, Berrebi KG. (2025). Pathophysiology of Alopecia Areata in the Pediatric Patient. Pediatr Dermatol. 42(Suppl 1):24-30.

17. Hon KL, Tsang KY, Kung JS, Leung TF, Lam CW, Wong CK. (2017). Clinical Signs, Staphylococcus and Atopic Eczema-Related Seromarkers. Molecules. 22(2):291.

18. Miscia S, Marchisio M, Grilli A, Di Valerio V, Centurione L, Sabatino G, et al. (2002). Tumor necrosis factor alpha (TNF-alpha) activates Jak1/Stat3-Stat5B signaling through TNFR-1 in human B cells. Cell Growth Differ. 13(1):13-18.

19. Mehra VC, Ramgolam VS, Bender JR. (2005). Cytokines and cardiovascular disease. J Leukoc Biol. 78(4):805-818.

20. Goldman A, Galper BL, Druyan A, Grossman C, Sharif K, Shechtman L, et al. (2024). Adverse cardiovascular events in rheumatoid arthritis patients treated with JAK inhibitors: An analysis of postmarketing spontaneous safety reports. Semin Arthritis Rheum. 67:152461.

21. Paolino G, Valenti M, Carugno A, Bianco M, Didona D, Di Nicola MR, et al. (2025). Serum Lipids Alterations in Patients Under Systemic JAK Inhibitors Treatments in Dermatology: Clinical Aspects and Management. Medicina (Kaunas). 61(1):54.

22. De Greef A, Ghislain PD, de Montjoye L, Baeck M. (2023). Real-Life Effectiveness and Tolerance of Upadacitinib for Severe Atopic Dermatitis in Adolescents and Adults. Adv Ther. 40(5):2509-2514.

23. Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. (2018). Analysis of Spontaneous Postmarket Case Reports Submitted to the FDA Regarding Thromboembolic Adverse Events and JAK Inhibitors. Drug Saf. 41(4):357-361.

24. Ytterberg SR, Bhatt DL, Connell CA. (2022). Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. Reply. N Engl J Med. 386(18):1768.

25. Garshick MS, Ward NL, Krueger JG, Berger JS. (2021). Cardiovascular Risk in Patients With Psoriasis: JACC Review Topic of the Week. J Am Coll Cardiol. 77(13):1670-1680.

26. Warren RB, Basey V, Lynam A, Curtis C, Ardern-Jones MR. (2023). The risk of venous thromboembolism in atopic dermatitis: a matched cohort analysis in UK primary care. Br J Dermatol. 189(4):427-436.

27. King B, Soung J, Tziotzios C, Rudnicka L, Joly P, Gooderham M, et al. (2024). Integrated Safety Analysis of Ritlecitinib, an Oral JAK3/TEC Family Kinase Inhibitor, for the Treatment of Alopecia Areata from the ALLEGRO Clinical Trial Program. Am J Clin Dermatol. 25(2):299-314.

28. Nair S, Singh Kahlon S, Sikandar R, Peddemul A, Tejovath S, Hassan D, et al. (2022). Tumor Necrosis Factor-Alpha Inhibitors and Cardiovascular Risk in Rheumatoid Arthritis: A Systematic Review. Cureus. 14(6):e26430.

29. Sareila O, Korhonen R, Karpanniemi O, Nieminen R, Kankaanranta H, Moilanen E. (2006). JAK inhibitors AG-490 and WHI-P154 decrease IFN-gamma-induced iNOS expression and NO production in macrophages. Mediators Inflamm. 2006(2):16161.

30. Anyfanti P, Angeloudi E, Dara A, Pagkopoulou E, Moysidou GS, Deuteraiou K, et al. (2024). Non-Invasive Assessment of Micro- and Macrovascular Function after Initiation of JAK Inhibitors in Patients with Rheumatoid Arthritis. Diagnostics (Basel). 14(8):834.

31. Dotan I, Yang J, Ikeda J, Roth Z, Pollock-Tahiri E, Desai H, et al. (2022). Macrophage Jak2 deficiency accelerates atherosclerosis through defects in cholesterol efflux. Commun Biol. 5(1):132.

32. Kotyla PJ, Engelmann M, Giemza-Stokłosa J, Wnuk B, Islam MA. (2021). Thromboembolic Adverse Drug Reactions in Janus Kinase (JAK) Inhibitors: Does the Inhibitor Specificity Play a Role? Int J Mol Sci. 22(5):2449.

33. Winthrop KL, Cohen SB. (2022). Oral surveillance and JAK inhibitor safety: the theory of relativity. Nat Rev Rheumatol. 18(5):301-304.

34. Dörner T, Tanaka Y, Petri MA, Smolen JS, Wallace DJ, Dow ER, et al. (2020). Baricitinib-associated changes in global gene expression during a 24-week phase II clinical systemic lupus erythematosus trial implicates a mechanism of action through multiple immune-related pathways. Lupus Sci Med. 7(1):e000424.

35. Deuruxolitinib. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

36. Huang MY, Armstrong AW. (2023). Janus-kinase inhibitors in dermatology: A review of their use in psoriasis, vitiligo, systemic lupus erythematosus, hidradenitis suppurativa, dermatomyositis, lichen planus, lichen planopilaris, sarcoidosis and graft-versus-host disease. Indian J Dermatol Venereol Leprol. 90(1):30-40.

37. Teixeira AJ, Duong JQ, Parraga SP, Feldman SR. (2025). Presenting JAK inhibitor safety information to dermatology patients. JEADV Clinical Practice. 4(1):12-20.

38. Dong Z, Ye X, Chen C, Wang R, Liu D, Xu X, et al. (2022). Thromboembolic events in Janus kinase inhibitors: A pharmacovigilance study from 2012 to 2021 based on the Food and Drug Administration's Adverse Event Reporting System. Br J Clin Pharmacol. 88(9):4180-4190.

39. Setyawan J, Azimi N, Strand V, Yarur A, Fridman M. (2021). Reporting of Thromboembolic Events with JAK Inhibitors: Analysis of the FAERS Database 2010-2019. Drug Saf. 44(8):889-897.

40. Cork MJ, Deleuran M, Geng B, Silverberg JI, Simpson EL, Stein Gold LF, et al. (2025). Long-Term Safety of Abrocitinib in Moderate-to-Severe Atopic Dermatitis: Integrated Analysis by Age. J Allergy Clin Immunol Pract. 13(5):1164-1175.e2.

41. Qian J, Xue X, Shannon J. (2022). Characteristics of adverse event reporting of Xeljanz/Xeljanz XR, Olumiant, and Rinvoq to the US Food and Drug Administration. J Manag Care Spec Pharm. 28(9):1046-1052.

42. Alexander M, Luo Y, Raimondi G, O'Shea JJ, Gadina M. (2021). Jakinibs of All Trades: Inhibiting Cytokine Signaling in Immune-Mediated Pathologies. Pharmaceuticals (Basel). 15(1):48.

43. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/.

44. Yang V, Kragstrup TW, McMaster C, Reid P, Singh N, Haysen SR, et al. (2023). Managing Cardiovascular and Cancer Risk Associated with JAK Inhibitors. Drug Saf. 46(11):1049-1071.

45. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al. (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 63(25 Pt B):2935-2959.

46. Li N, Gou ZP, Du SQ, Zhu XH, Lin H, Liang XF, et al. (2022). Effect of JAK inhibitors on high- and low-density lipoprotein in patients with rheumatoid arthritis: a systematic review and network meta-analysis. Clin Rheumatol. 41(3):677-688.

47. Liu M, Pei J, Zeng C, Xin Y, Zhang Y, Tang P, et al. (2025). Association of non-high-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio with cardiovascular outcomes in patients with type 2 diabetes mellitus: Evidence from the ACCORD cohort. Diabetes Obes Metab. 27(1):300-311.