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REVIEW

A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring

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ABSTRACT

Janus kinase (JAK) inhibitors are disease-modifying agents with efficacy in treating a spectrum of burdensome dermatologic conditions. The US Food and Drug Administration (FDA) recently placed a black box warning on this class of medications due to safety concerns based on data from studies investigating tofacitinib in patients with rheumatoid arthritis. Here we provide an overview of the timeline of FDA approval of JAK inhibitors in dermatology. We also discuss the available safety profiles of approved oral JAK1 inhibitors, namely abrocitinib and upadacitinib, oral baricitinib, a JAK1/2 inhibitor, deucravacitinib, a Tyk2 inhibitor, and the topical JAK1/2 inhibitor ruxolitinib in dermatology patients. Additionally, we offer suggestions for initial screening and laboratory monitoring for patients receiving JAK inhibitors. We found that the rates of venous thromboembolism reported in trials ranged from no events to 0.1–0.5% in dermatology-specific phase 3 clinical trials compared with no events in the placebo. The rates of cardiovascular events ranged from no events to 0.4–1.2% compared with no events to 0.5–1.2% in the placebo. The rates of serious infections were 0.4–4.8% compared with no events to 0.5–1.3% in the placebo. The rates of nonmelanoma skin cancer (NMSC) ranged from no event to 0.6–0.9% compared with no events in the placebo. The rates of non-NMSC ranged from no event to 0.2–0.7% compared with no event to 0.6% in the placebo. Most patients who developed these adverse events had risk factors for the specific event. The most common adverse events of oral JAK inhibitors included upper respiratory infections, nasopharyngitis, nausea, headache, and acne. Dermatologists should consider patients' baseline risk factors for developing serious complications when prescribing oral JAK inhibitors.

Keywords: Janus kinase; Alopecia areata; Atopic dermatitis; Chronic pruritus; Vitiligo; Psoriasis; Itch; Eczema

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Key Summary Points

Oral Janus kinase (JAK) inhibitors had low rates of venous thromboembolism, major adverse cardiovascular events, and malignancy compared with similarly low rates in the placebo in their use in clinical trials in dermatology.

Most patients who developed serious adverse events had risk factors specific to the event.

The most common treatment emergent adverse events observed in $\geq$ 5% of patients on oral JAK inhibitors included upper respiratory tract infection, nasopharyngitis, nausea, headache, and acne.

A comprehensive evaluation of a patient's baseline risk factors for complications and comorbid diseases is critical in assessing the net benefit of JAK inhibitors on a case-by-case basis.

INTRODUCTION

What are Janus Kinases and Their Pathophysiology?

Janus kinase proteins were historically named after the Greek god of gateways due to their intracellular association with membrane receptors. The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway serves a focal point in vital cellular processes with its rapid membrane-to-nucleus signaling paradigm. Its dysregulation is associated with inflammatory and autoimmune diseases. Numerous cytokines, including interleukins (ILs) and interferons (IFNs), growth factors, and colony-stimulating factors act as ligands to cytokine receptors associated with intracellular JAKs (Table 1) [1]. This process involves the activation of STAT proteins, which translocate to the nucleus, thereby inducing expression of key mediators of inflammation and cancer (Fig. 1). There is a considerable redundancy built in this system as there are over 50 cytokines and only four JAKs, namely JAK1, JAK2, JAK3, and Tyk2 (Table 1) [2]. The JAK-STAT pathway is, thereby, featured in several convergent immunologic mechanisms, which impacts its capacity for selectivity [3].

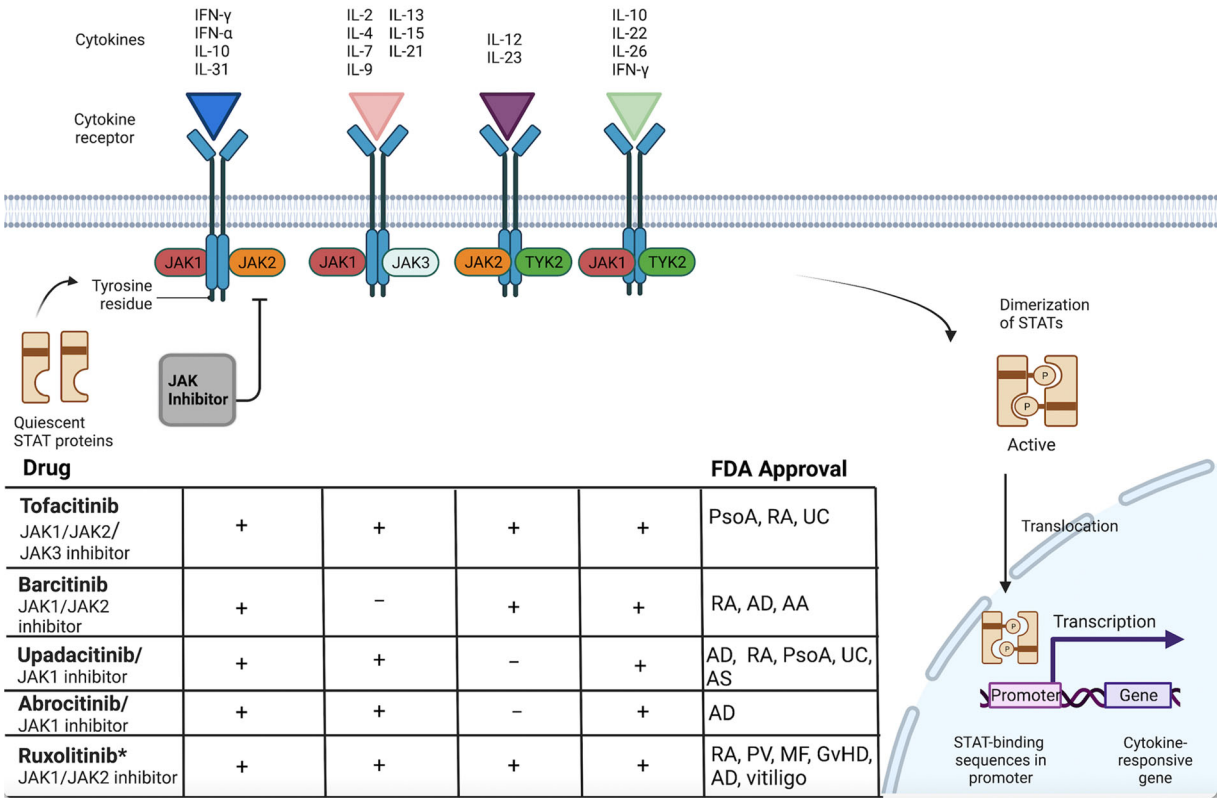
Mechanism of Action and Clinical Utility of JAK Inhibitors

Small-molecule therapies that inhibit JAK proteins have emerged as efficacious treatment options in rheumatic and dermatologic diseases (Fig. 1) [4]. JAK inhibitors exhibit anti-inflammatory effects through suppressing cytokine production involved in Th1, Th2, Th17, and Th22 immune pathways (Fig. 2) [5]. This mechanism contrasts with that of biological disease modifying antirheumatic drugs (bDMARDs), which are monoclonal antibodies targeted against only one or two specific

Table 1 JAK proteins and their cytokines

JAK protein	Cytokines
JAK1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-15, IL-19, IL-20, IL-21, IL-22, IL-27, LIF, OSM, IFN-alpha, IFN-beta, IFN-gamma
JAK2	IL-3, IL-5, IL-6, IL-11, IL-12, IL-23, IL-27, GM-CSF, LIF, OSM, erythropoietin, thrombopoietin, leptin, growth hormone
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
Tyk2	IL-6, IL-10, IL-11, IL-12, IL-19, IL-20, IL-21, IL-22, IL-23, IL-27, LIF, OSM, IFN-alpha, IFN-beta,

JAK Janus kinase, *IL* interleukin, *LIF* leukemia inhibitory factor, *OSM* oncostatin M *IFN* interferon, *EPO* erythropoietin, *G-CSF* granulocyte colony-stimulating factor, *GH* growth hormone, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *TPO* thrombopoietin, *Tyk2* tyrosine kinase 2



Drug					FDA Approval
Tofacitinib JAK1/JAK2/ JAK3 inhibitor	+	+	+	+	PsoA, RA, UC
Barcitinib JAK1/JAK2 inhibitor	+	–	+	+	RA, AD, AA
Upadacitinib/ JAK1 inhibitor	+	+	–	+	AD, RA, PsoA, UC, AS
Abrocitinib/ JAK1 inhibitor	+	+	–	+	AD
Ruxolitinib* JAK1/JAK2 inhibitor	+	+	+	+	RA, PV, MF, GvHD, AD, vitiligo

Fig. 1 Inhibition of the JAK-STAT pathway and selectivity of various JAK inhibitors. *PsoA* psoriatic arthritis, *RA* rheumatoid arthritis, *UC* ulcerative colitis, *AD* atopic dermatitis, *AA* alopecia areata, *AS* ankylosing spondylitis, *PV* polycythemia vera, *MF* myelofibrosis, *GvHD* graft-versus-host disease. *Topical ruxolitinib is FDA approved for AD and vitiligo only

cytokines, such as an IL-17 inhibitor. JAK inhibitors can work rapidly within hours in a topical formulation [6] and within days in oral formulation [7]. Some patients with dermatologic conditions, such as atopic dermatitis (AD), are either partially responsive or unresponsive to existing therapies, with only about 40% achieving clear or almost clear skin [8–10]. While some patients prefer non-injectable therapies, others may have multiple autoinflammatory comorbidities that can be concurrently managed by a JAK inhibitor. Some patients also prefer intermittent therapy, have unique disease endotypes or severe disease, or prefer more rapidly acting agents, which is more amenable to treatment with oral JAK inhibitors. Dermatologists can, therefore, leverage the versatility of JAK inhibitors to treat this gamut of dermatologic patients.

Use of JAK Inhibitors in Dermatology Over Time

Alopecia areata (AA)

Alopecia areata is a common autoimmune dermatosis characterized by immunologic attack of hair follicles. Preclinical evidence highlights the involvement of the JAK1/2 pathways in the inflammatory response around hair follicles [11]. Previous studies found that tofacitinib was effective in treating AA, but it did not have a durable response [12]. More recently, oral baricitinib, a JAK1/2 inhibitor, was approved by the FDA for the treatment of severe AA (Fig. 3a).

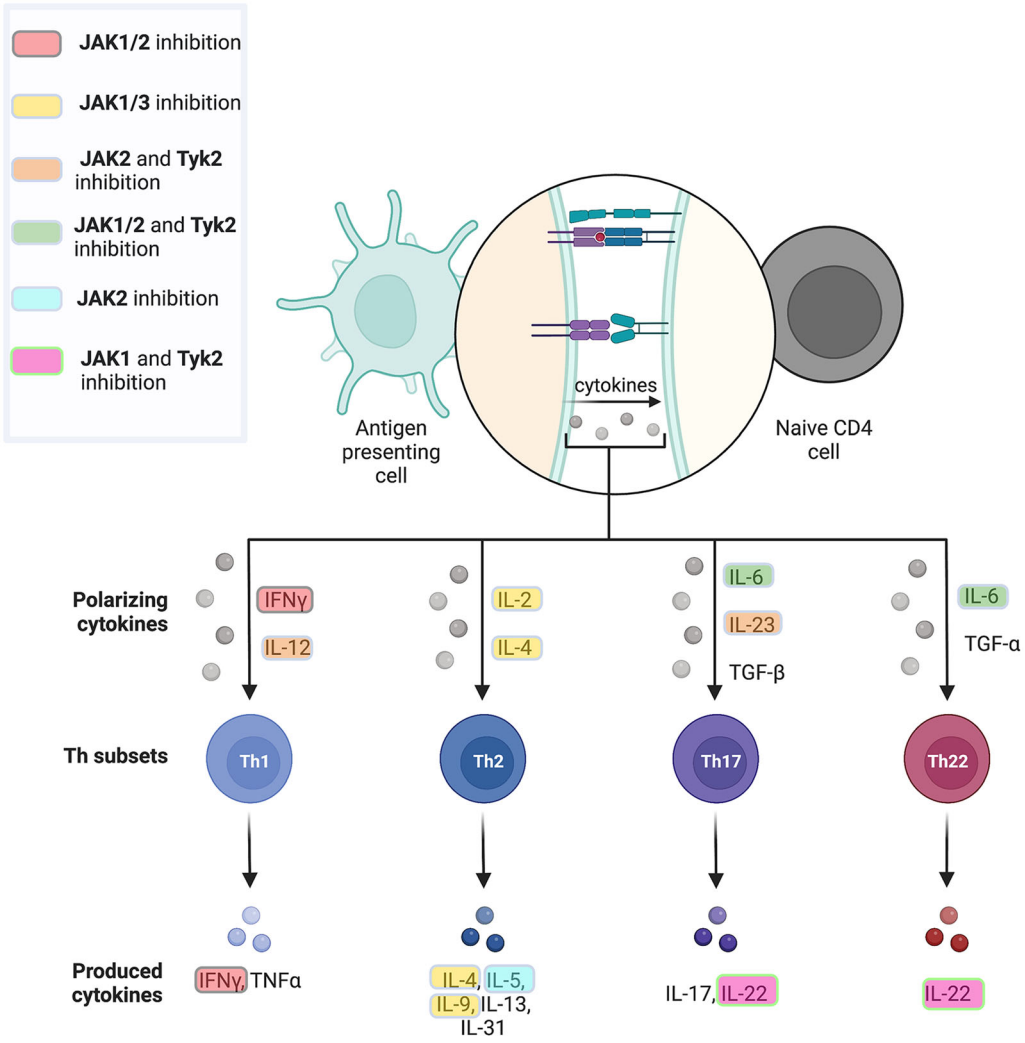


Fig. 2 JAK inhibitors targeting common immune pathways

Vitiligo

Vitiligo is an acquired, autoimmune disorder that causes patchy skin depigmentation. It involves JAK1/2 receptors in the interferon gamma chemokine pathway (Fig. 2) [13]. Topical ruxolitinib 1.5% cream was approved by the FDA for the treatment of vitiligo in 2022. Ongoing studies (NCT03715829) are examining the efficacy of ritlecitinib (PF-06651600), an inhibitor of JAK3 and tyrosine kinase expressed in the hepatocellular carcinoma (TEC) kinase family, in the treatment of vitiligo [14].

Psoriasis

Psoriasis is an autoimmune dermatosis characterized by epidermal hyperplasia [15, 16]. Although tofacitinib was approved by the FDA for psoriatic arthritis, it was not similarly approved for psoriasis because it requires relatively higher doses for achieving clear skin [17]. Other studies found that JAK1 and Tyk2 are preferentially involved in the development of chronic plaque psoriasis [18]. Promising evidence in clinical trials (NCT02969018) of a selective Tyk2 inhibitor, deucravacitinib, and a JAK1/Tyk2 inhibitor demonstrated efficacy in treating moderate to severe psoriasis [19, 20].

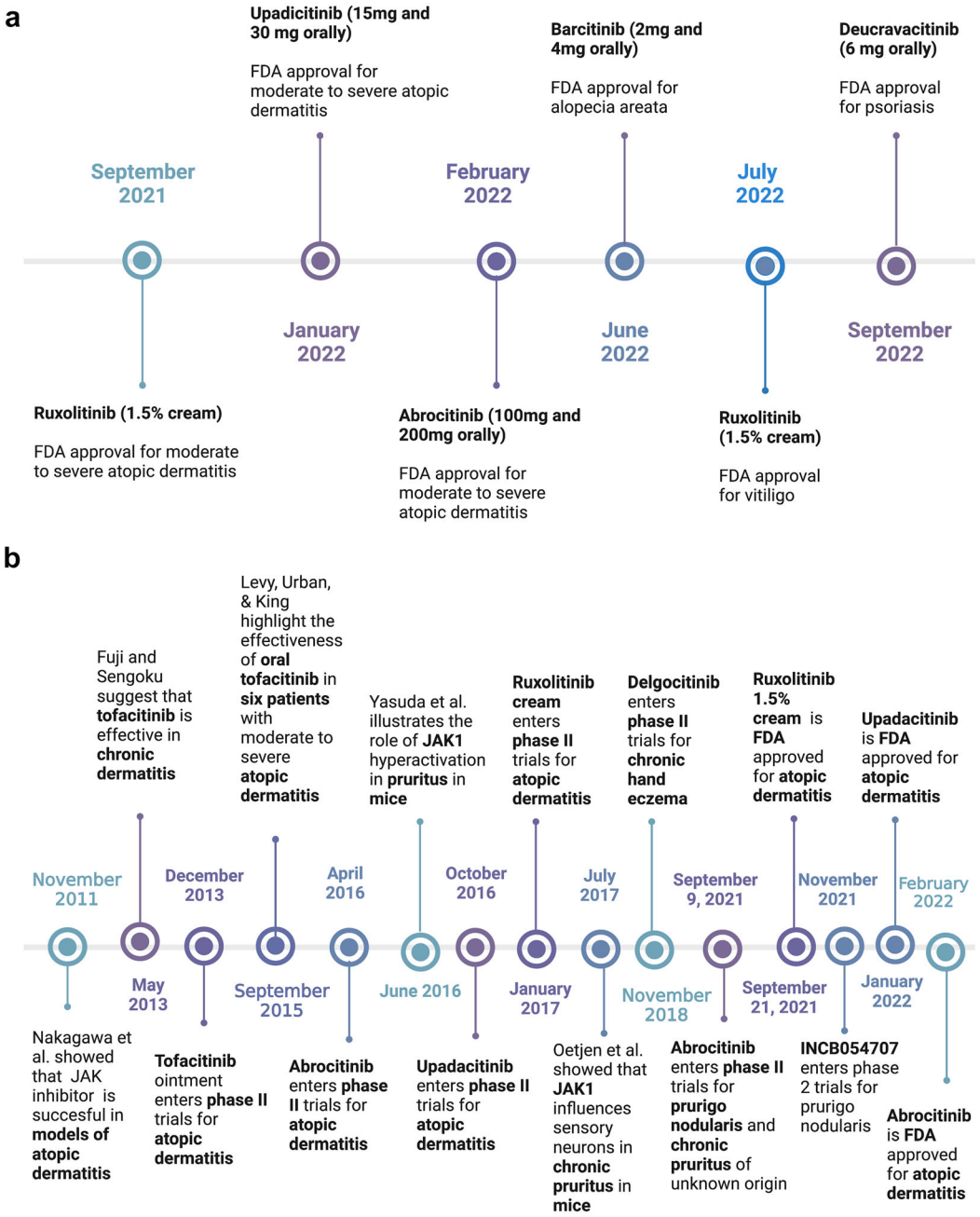


Fig. 3 **a** Timeline of FDA approval of JAK inhibitors in dermatology. **b** Timeline of milestones facilitating the use of JAK Inhibitors in chronic pruritic dermatoses

Deucravacitinib was recently approved by the FDA in 2022.

Chronic Pruritic Dermatoses (CPDs)

Recognition of the utility of JAK inhibitors as a promising therapeutic option for the treatment of chronic pruritic dermatoses (CPDs) began over a decade ago. In 2011, Nakagawa et al. revealed preclinical evidence of the ability of a pan-JAK inhibitor to attenuate both the Th1 and Th2 pathways in mice with AD skin lesions (Fig. 3b) [21]. JAK inhibitors soon garnered

significant attention with tofacitinib, an inhibitor of JAK1/2/3, which entered phase 2 trials (NCT02001181) for AD in 2013 and was effective in treating recalcitrant AD in six patients in a clinical setting in 2015 [22–25] . In 2021, the FDA approved ruxolitinib 1.5% cream, a JAK1/2 inhibitor, as the first drug in this class for the treatment of AD (Fig. 3B). JAK1 inhibitors, such as upadacitinib and abrocitinib, exhibit combined anti-inflammatory and anti-itch properties. A timeline of the pathway of JAK inhibitors in CPDs is displayed in Fig. 3B [26–28].

Ongoing trials are investigating several JAK inhibitors in treating a variety of CPDs, given the detrimental effects of chronic itch in the health-related quality of life of a number of conditions [29]. Gusacitinib, a pan JAK-SYK (spleen tyrosine kinase) inhibitor, was recently granted a Fast Track designation by the FDA for the treatment of chronic hand eczema. In addition, topical delgocitinib, another pan-JAK inhibitor, entered clinical trials (NCT03826901, NCT03683719) for chronic hand eczema in both pediatric and adult patients [30, 31]. Furthermore, similar to AD, the pathogenesis of prurigo nodularis (PN) involves Th2- and Th17/Th22-mediated inflammation, which can both be attenuated through JAK inhibition [32–34]. Other phase 2 studies (NCT05038982, NCT05061693) are examining the role of abrocitinib and INCB054707 in the treatment of prurigo nodularis (PN) and chronic pruritus of unknown origin [35]. Thus, the therapeutic armamentarium for chronic pruritus is rapidly expanding and offers promise in enhancing the management of these conditions.

SAFETY AND TOLERABILITY OF JAK INHIBITORS

Why Did the FDA Place a Black Box Warning on JAK Inhibitors?

Safety concerns, such as the risk for venous thromboembolism (VTE), have recently emerged in the post-marketing studies of tofacitinib in rheumatoid arthritis (RA) [36–38]. These findings prompted the FDA to place boxed warning to tofacitinib label in 2019. They also mandated further long-term safety data as part of the ORAL Surveillance study, which compared the safety profiles of tofacitinib with anti-tumor necrosis factor (TNFi) therapy in older patients with RA and cardiovascular risk factors. This study found that risks of cancers, VTE, and major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction, and stroke) were higher with tofacitinib compared with TNFi in patients with similar baseline comorbidities [36]. These results impacted the FDA's decision to place a black box warning on all approved JAK inhibitors in 2021, which did not include the novel Tyk2 inhibitors such as deucravacitinib.

Post hoc analyses of the ORAL Surveillance study demonstrate that baseline risk factors, such as a history of VTE, hypertension, or coronary artery disease (CAD), age > 65 years, smoking, and hormone replacement therapy/oral contraceptive use, significantly increase the risk of VTE or MACE in patients on JAK inhibitors [39, 40]. Hazard ratios (HRs) of MACE in tofacitinib-treated patients (25/333, 7.5%) with a history of CAD was 1.56 compared with TNFi-treated patients (8/164, 4.8%). Likewise, the HR of VTE was 1.34 in tofacitinib-treated patients (8/333, 2.4%) with a history of CAD compared with TNFi-treated patients (3/164, 1.8%). The HR of malignancy was 1.38 in tofacitinib-treated patients (21/333, 6.3%) with a history of CAD compared with TNFi-treated patients (8/164, 4.8%). On the other hand, additional post-hoc exploratory analyses found that any absolute MACE risk excess was low among patients without a history of atherosclerotic cardiovascular disease in the tofacitinib 5 mg (mg) twice daily (30/1251, 2.4%) compared with TNF-i (28/1237, 2.3%) treatment groups [41]. When evaluating the results of this study, it is important to consider whether some of the risk is related to the cohort's underlying RA, which alone is associated with MACE, VTE, and malignancy [42–45].

These findings have stimulated discussions regarding the risk–benefit ratio of using various JAK inhibitors, which have been recently approved by the FDA for dermatologic conditions. The target population in dermatology includes patients with AD, AA, and vitiligo, who

Table 2 Summary of adverse events in phase 3 clinical trials of FDA-approved JAK Inhibitors in dermatology

Author/clinical trial	Dermatologic condition	Study duration	Study intervention (*N*)	Adjudicated adverse cardiovascular events (*n*, %)	Adjudicated venous thromboembolism (*n*, %)	Serious infection (*n*, %)	Malignancy, NMSC (*n*, %)	Malignancy, non-NMSC (*n*, %)	Death (*n*, %)
2020/Simpson et al. JADE MONO-1 [28]	Atopic dermatitis	12 weeks	Abrocitinib 100 mg (n = 156)	0	0	Not reported	0	0	0
			Abrocitinib 200 mg (n = 154)	0	0		0	0	0
			Placebo (n = 77)	0	0		0	0	0
2020/Silverberg et al. JADE MONO-2 [48]	Atopic dermatitis	12 weeks	Abrocitinib 100 mg (n = 155)	1 (0.6)	0	3 (1.9)	0	0	1 (0.6)
			Abrocitinib 200 mg (n = 158)	0	0	0	0	0	0
			Placebo (n = 78)	0	0	1 (1.3)	0	0	0
2021/Blauvelt et al. JADE REGIMEN [56]	Atopic dermatitis	40 weeks	Abrocitinib 100 mg (n = 200)	Not reported	1 (0.5)	2 (0.8)	Not reported	Not reported	Not reported
			Abrocitinib 200 mg (n = 200)		0	5 (1.9)			
			Placebo (n = 200)		0	2 (0.7)			
2020/Guttman-Yassky et al. [49]	Atopic dermatitis	16 weeks	Upadacitinib 7.5 mg (n = 42)	0	0	2 (4.8)	0	0	0
			Upadacitinib 15 mg (n = 42)	0	0	1 (2.4)	0	0	0
			Upadacitinib 30 mg (n = 42)	0	0	0	0	0	0
			Placebo (n = 41)	0	0	0	0	0	0

Table 2 continued

Author/clinical trial	Dermatologic condition	Study duration	Study intervention (*N*)	Adjudicated adverse cardiovascular events (*n*, %)	Adjudicated venous thromboembolism (*n*, %)	Serious infection (*n*, %)	Malignancy, NMSC (*n*, %)	Malignancy, non-NMSC (*n*, %)	Death (*n*, %)
2021/Guttman-Yassky et al. (MEASURE UP-1) [50]	Atopic dermatitis	16 weeks	Upadacitinib 15 mg (*n* = 281)	1(0.4)	0	2 (0.7)	1 (0.4)	0	0
			Upadacitinib 30 mg (*n* = 285)	0	0	2 (0.7)	0	2 (0.7)	0
			Placebo (*n* = 281)	0	0	0	0	0	0
2021/Guttman-Yassky et al. (MEASURE UP-2) [50]	Atopic dermatitis	16 weeks	Upadacitinib 15 mg (*n* = 276)	0	0	1 (0.4)	2 (0.7)	0	0
			Upadacitinib 30 mg (*n* = 282)	0	0	2 (0.7)	1 (0.4)	1 (0.4)	0
			Placebo (*N* = 278)	0	0	2 (0.7)	0	0	0
2021/Reich et al. (AD Up) [64]	Atopic dermatitis	16 weeks	Upadacitinib 15 mg + corticosteroids (*n* = 300)	0	0	3 (1.0)	0	0	0
			Upadacitinib 30 mg + corticosteroids (*n* = 297)	0	0	0	1 (0.3)	1 (0.3)	0
			Placebo + corticosteroids (*n* = 304)	0	0	3 (1.0)	0	0	0
2022/Simpson et al. [27]	Atopic dermatitis	52 weeks	Upadacitinib 15 mg (*n* = 797)	1 (0.1)	1 (0.1)	21 (2.6)	4 (0.5)	2 (0.3)	0
			Upadacitinib 30 mg (*n* = 811)	0	1 (0.1)	35 (4.3)	4 (0.5)	5 (0.6)	1 (0.1)
2022/King et al. (BRAAVE-1) [52]	Alopecia areata	36 weeks	Baricitinib 2 mg (*n* = 183)	1(0.5) 0 0	0	0	0	0	0
			Baricitinib 4 mg (*n* = 270)	0	0	0	0	0	0
			Placebo (*n* = 189)	0	0	0	0	0	0

Table 2 continued

Author/clinical trial	Dermatologic condition	Study duration	Study intervention (*N*)	Adjudicated adverse cardiovascular events (*n*, %)	Adjudicated venous thromboembolism (*n*, %)	Serious infection (*n*, %)	Malignancy, NMSC (*n*, %)	Malignancy, non-NMSC (*n*, %)	Death (*n*, %)
2022/King et al. (BRAAVE-2) [52]	Alopecia areata	36 weeks	Baricitinib 2 mg (n = 155)	0	0	2 (1.3)	0	1 (0.6)	0
			Baricitinib 4 mg (n = 233)	0	0	1 (0.4)	0	0	0
			Placebo (n = 154)	0	0	0	0	1 (0.6)	0
2022/Armstrong et al. POETYK PSO-1 [54]	Psoriasis	52 weeks	Deucravacitinib 6 mg (n = 531)	1 (0.2)	1 (0.2)	6 (1.1)	2 (0.4)	2 (0.4)	0
			Apremilast 30 mg (n = 168)	2 (1.2)	0	3 (1.8)	0	0	0
			Placebo (n = 165)	2 (1.2)	0	1 (0.6)	0	0	1 (0.6)
2022/Strober et al. POETYK PSO-2 [55]	Psoriasis	52 weeks	Deucravacitinib 6 mg (n = 833)	2 (0.4)	1 (0.1)	11 (2.0)	5 (0.9)	1 (0.2)	0
			Apremilast 30 mg (n = 254)	1 (0.9)	0	1 (0.9)	1 (0.9)	1 (0.9)	0
			Placebo (n = 501)	1 (0.5)	0	1 (0.5)	0	0	0

tend to be younger and with fewer comorbidities compared with patients with RA. A large-scale cohort study reported that chronic inflammatory skin diseases, including AD, AA, psoriasis, and vitiligo, were not associated with increased incidence of VTE after controlling for VTE risk factors [46]. Other studies in AD have shown that it was not associated with an increased risk of VTE [47]. Collectively, these results illustrate the importance of placing the safety data of JAK inhibitors within the context of the underlying risk in the respective disease populations. In this review, we discuss the safety profiles of oral JAK inhibitors, namely abrocitinib, baricitinib, deucravacitinib, and upadacitinib, and topical ruxolitinib in pivotal phase 3 clinical trials.

METHODS

The Medline database was searched via PubMed to identify articles on clinical trials of various JAK inhibitors in dermatology. We focused on data regarding the contextual timeline of FDA-approved JAK inhibitors as well as their safety profiles published from November 2011 to October 2022. Search terms included "phase 3 trials" AND "atopic dermatitis" OR "alopecia areata" OR "psoriasis" OR "vitiligo" AND "abrocitinib" OR "upadacitinib" OR "ruxolitinib" OR "baricitinib" OR "deucravacitinib." Inclusion criteria included phase 3 randomized control clinical trials in dermatology patients as well as follow-up data to phase 3 trials. Exclusion criteria included non-dermatology patient populations and phase 1 and phase 2 clinical trials. Assessment of retrieved references as well as input and suggestions from clinical experts were used as the foundation of this narrative review. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

MACE

AD

Oral JAK Inhibitors In phase 3 clinical trials on abrocitinib (JADE MONO-1 and MONO-2), abrocitinib had 1/155 (0.6%) MACE during the trials compared with no events in the placebo (Table 2) [28, 48]. Sudden cardiac death was reported in a patient who had aortic valve sclerosis and untreated hypertension 3 weeks after discontinuation of the 100-mg dose of abrocitinib in the JADE MONO-2 study. Similarly, in trials investigating upadacitinib (MEASURE UP-1/2), 1/797 patients (0.1%) had a myocardial infarction related to coronavirus disease 2019 (COVID-19) in the 30-mg group (Table 2) [49, 50]. This patient was in their 60s and had relevant risk factors, including uncontrolled hypertension, type 2 diabetes mellitus, obesity, and hypercholesterolemia.

Topical JAK Inhibitors There was no adjudicated MACE in patients with AD treated with ruxolitinib cream. Topical ruxolitinib in AD was associated with a mean steady-state plasma concentration that was significantly below the level expected for systemic effects [51].

AA

In a phase 3 clinical trial, 1/183 patients (0.5%) had a myocardial infarction in the baricitinib 2-mg group with 0/270 in the 4-mg group compared with no events in the placebo [52]. The patient was 48 years old with the following risk factors: tobacco use, obesity, atrial fibrillation, hypertension, and hypercholesterolemia.

Vitiligo

Trials reported a consistent incidence of 0.3% (1/311, 1/326) in ruxolitinib-treated patients compared with 0/109 in placebo, with one patient developing myocarditis and another developing coronary artery stenosis, both of which were deemed unrelated to treatment [53].

Psoriasis

The rates of MACE were 1/531 (0.2%) and 2/833 (0.4%) in deucravacitinib compared with 2/168 (1.2%) and 1/501 (0.5%) in the placebo in two phase 3 trials [54, 55]. One patient receiving deucravacitinib experienced non-ST elevation myocardial infarction. Other MACEs included heart failure and cerebrovascular accident.

VTE

AD

The rates of VTE were very rare, namely 0/310 and 1/200 (0.5%) compared with no events in the placebo in phase 3 trials of abrocitinib with one patient having a nonfatal retinal vein thrombosis, leading to discontinuation of abrocitinib 100-mg dose in one study (Table 2) [56]. In follow-up data collected over a longer duration of 52 weeks, 2/1608 patients had an adjudicated VTE in upadacitinib-treated groups accounting for an overall incidence of 0.1% [27]. These included one patient in their 40s with a deep vein thrombosis (DVT) prior to upadacitinib therapy, who developed a new one while on upadacitinib 15 mg. Another case was a pulmonary embolism related to COVID-19, which is associated with VTE, in a patient in their 70s taking upadacitinib 30 mg [57]. Both events were reported to be unrelated to treatment. These results are consistent with a meta-analysis of two cohort studies and 15 randomized control trials with a total of 466, 993 participants, which concluded that patients with AD on JAK inhibitors did not have an increased risk of VTE [47]. Specifically, 3/5,722 patients with AD (0.05%) who were treated with JAK inhibitors experienced VTE compared with 1/3065 patients with AD (0.03%) receiving placebo or dupilumab (Mantel–Haenszel risk difference, 0; 95% CI 0–0).

AA

In a 36-week treatment period, there were no adjudicated VTE in AA patients receiving baricitinib [52].

Psoriasis

The rates of VTE in deucravacitinib-treated patients were 1/531 (0.2%) and 1/833 (0.1%) compared with no events in the placebo [54, 55]. One patient was a 48-year-old male with history of smoking and hypertension, who developed an acute ascending aortic dissection complicated by a pulmonary artery thrombus. Another patient developed a radial artery thrombosis in the setting of an infection for which he needed intravenous antibiotics.

Malignancy

AD

There were no reported events of nonmelanoma skin cancer (NMSC) in the abrocitinib phase 3 trials, whereas the incidence rates in upadacitinib trials ranged from 0.4% to 0.7% in upadacitinib 15 mg and no event to 0.5% in upadacitinib 30 mg compared with no events in the placebo [27, 28, 50]. In addition, there were no events of non-NMSC malignancy in abrocitinib phase 3 trials and upadacitinib trials in patients receiving the 15 mg dose for 16 weeks, whereas the rates of non-NMSC ranged from 0.3% to 0.7% in upadacitinib 30 mg groups compared with no events in the placebo. The exposure-adjusted event rate of malignant neoplasm in follow-up data was 0.6/100 patient years (PYs) with upadacitinib 15 mg and 0.9/100 PYs with upadacitinib 30 mg [27]. Nonmelanoma skin cancer (NMSC) was the most reported malignancy occurring in 4/797 (0.5%) and 4/811 (0.5%) patients on upadacitinib 15 mg and 30 mg, respectively, compared with no event in the placebo over a 52-week period. In a total of 1608 patients treated with upadacitinib, other non-NMSC malignancies were noted: breast cancer (n = 1), gastric cancer (n = 1), and anal cancer (n = 1) (Table 2). In two large cohort studies conducted in England and Denmark, AD was associated with an increased risk of lymphoma, especially non-Hodgkin lymphoma [58]. There was no evidence of increased baseline risk of most other cancers in AD, however.

AA

The incidence of malignancy was 0/183 and 1/155 (0.6%) in AA patients compared with 1/154 (0.6%) in placebo [52]. One baricitinib-treated patient developed B-cell lymphoma, and one receiving placebo had prostate cancer.

Psoriasis

Rates of NMSC were 2/531 (0.4%) and 5/833 (0.9%) among deucravacitinib-treated patients compared with no events in the placebo [54, 55]. Three patients had basal cell carcinoma and two had squamous cell carcinoma in the

deucravacitinib group. Rates of non-NMSC were 2/531 (0.4%) and 1/833 (0.2%) in deucravacitinib compared with no events in the placebo. The following malignancies were noted: Hodgkin's lymphoma ($n = 1$), breast cancer ($n = 1$), and hepatocellular carcinoma ($n = 1$). These rates are lower than the background rates previously reported in psoriasis in the MarketScan studies [59].

Serious Infection

AD

Oral JAK Inhibitors In the JADE trials with abrocitinib, the rates of serious infections ranged from 0.8% to 1.9% for abrocitinib 100 mg and no events to 1.9% in abrocitinib 200 mg compared with 0.7–1.3% in the placebo (Table 2) [28, 48, 56]. Adverse events pertinent to treatment were reported for 2/155 patients in the 100 mg group: herpangina, and pneumonia. Both instances required treatment cessation. In comparison, 2/200 patients had a serious infection, namely eczema herpeticum and staphylococcal infection, while receiving the placebo. Pooled analysis of trials on abrocitinib did not reveal a significant difference in serious adverse events between either dose of abrocitinib and the placebo ($p > 0.05$) [60]. Furthermore, serious infections were reported in 1/281 (0.4%), 1/42 (2.4%), and 21/797 (2.6%) receiving 15 mg upadacitinib and in 2/285 (0.7%) and 35/811 (4.3%) receiving 30 mg upadacitinib compared with none or 2/278 (0.7%) in placebo [27, 50]. The most common serious infection in upadacitinib-treated groups overall was pneumonia in Measure Up-1 and eczema herpeticum in Measure Up-2. The presence of eczema herpeticum with upadacitinib and placebo treatments in AD and not in other disease indications may be due to the underlying association of this event with AD [61].

Topical JAK Inhibitors Two trials in AD report 1/999 patients developing an abscess on the lower extremity that was deemed unrelated to treatment with ruxolitinib cream [62].

AA

The incidence of serious infections in patients with AA was 0–1.4% and 0–0.4% in the baricitinib 2 mg and 4 mg groups, respectively, compared with no events in the placebo [52]. One of 155 patients (0.6%) developed COVID-19 pneumonia, and 2/388 (0.5%) had pyelonephritis in the baricitinib-treated groups.

Psoriasis

Rates of serious infections were 6/531 (1.1%) and 11/833 (2%) in deucravacitinib compared with 1/165 (0.6%) and 1/501 (0.5%) in the placebo [54, 55]. Community-acquired pneumonia was the most common serious infection, occurring in 3/833 (0.4%) of patients on deucravacitinib compared with no events in the placebo.

COMMON ADVERSE EFFECTS OF JAK INHIBITORS

Infections

AD

Oral JAK Inhibitors JAK inhibitors may dampen the immune response, thereby theoretically impacting host defense against pathogens. The most frequently reported (> 5% of patients) infections include upper respiratory tract infections (URIs) and nasopharyngitis. The incidence rates of URIs in various clinical trials on abrocitinib and upadacitinib in patients with AD were 7–9% and 6–13%, compared with 4–5% and 4–7% in placebo, respectively [28, 48, 50]. However, pooled analysis of four phase 3 trials did not find a statistically significant difference between the abrocitinib-treated groups and placebo ($p > 0.05$) [60]. In addition, the proportion of patients reporting nasopharyngitis was up to 15% (23/156) and 12% (33/285), in the abrocitinib-treated and upadacitinib-treated groups compared with 6–10% and 5–6% in placebo, respectively [28, 50, 63]. Of note, pooled analysis of trials on abrocitinib did not find a statistically significant difference in nasopharyngitis risk between the abrocitinib-treated groups and the placebo [60].

Herpes simplex was reported more frequently in patients with AD receiving upadacitinib (3.3–7.7% compared with 1.7% in placebo) than those on abrocitinib (0–2% in abrocitinib compared with 1.8% in placebo) [28, 50, 63, 64]. Herpes zoster was less common than herpes simplex, with rates of 1.3% in abrocitinib 200 mg and no event to 0.6% in abrocitinib 100 mg compared with no events in the placebo. In addition, the rates of herpes zoster over a 16-week period were 1.8–2.2% in upadacitinib 15 mg and 1.1–2.1% in upadacitinib 30 mg compared with 0–0.7% in the placebo. The risk of herpes zoster was slightly higher in follow-up data over 52 weeks, with rates of 3.5–3.7% in upadacitinib 15 mg and 5.2–5.6% in upadacitinib 30 mg with no placebo data reported in the follow-up study. Additionally, tuberculosis (TB) reactivation was not reported in either abrocitinib- or upadacitinib-treated patients in 12- and 16-week study periods, respectively.

Topical JAK Inhibitors Infections, including URIs and nasopharyngitis were less common (< 3%) in patients receiving topical ruxolitinib [6]. Studies have demonstrated a relatively low bioavailability of ruxolitinib cream, which allows for enhanced targeted delivery of the active drug to AD skin lesions [65].

AA

Common infections in baricitinib-treated patients included URI and urinary tract infections. Two trials found similar incidence rates of patients developing a URI in the baricitinib-treated and placebo groups (4.9–7.7% versus 5.3–7.3% in the placebo group) [52]. Furthermore, the frequency of nasopharyngitis in patients with AA was 7.5% in the baricitinib-treated patients compared with 4.5–6.6% in the placebo groups [52]. Another side effect was urinary tract infection, which was reported in 11/155 patients (4.7%) and 12/233 patients (7.7%) in the baricitinib 2 mg and 4 mg groups, respectively, compared with 2/154 patients (1.3%) in the placebo group in the BRAVE-AA2 study.

The incidence of herpes simplex was higher in the placebo groups than the baricitinib-treated groups. It occurred in 5/270 patients (1.8%) in the baricitinib 4 mg group compared with 4/189 patients (2.1%) in the placebo in BRAAVE-AA1. It occurred in 8/154 patients (5.2%) in the placebo compared with 6/155 patients (3.9%) and 2/233 patients (0.9%) in the baricitinib 2 mg and 4 mg, respectively. Herpes zoster was less common, with an incidence rate of 0.5–1.9% compared with around 0.5% in placebo. TB activation was not reported in baricitinib-treated patients.

Vitiligo

Nasopharyngitis occurred in 9/221 (4.1%) and 10/228 (4.4%) in ruxolitinib-treated patients compared with 4/109 (3.7%) and 1/115 (0.9%) in placebo [53].

Psoriasis.

Rates of URIs and nasopharyngitis were 21/322 (6.3%) each in deucravacitinib compared with 6/165 (3.6%) and 7/165 (4.2%) in placebo [54, 55]. Herpes zoster was uncommon, occurring in 5/322 (1.2%) of patients compared with none in the placebo.

Gastrointestinal Disorders

AD

The most common gastrointestinal side effect was nausea. It was reported in 14/156 (9%) in abrocitinib 100 mg, 31/154 (20%) in abrocitinib 200 mg, and 2/77 (3%) in placebo [28]. Meta-analysis of four trials on abrocitinib revealed that the 100 mg and 200 mg doses were associated with a higher incidence of nausea than placebo (RR 2.83; 95% CI 1.26, 6.35) (RR 6.98; 95% CI 3.27, 14.92), respectively [60]. The median duration of nausea was reported to be 13 days in the abrocitinib 100 mg group and 39 days in the 200 mg group in the JADE MONO-1 trials [28]. A higher frequency of patients reported nausea with 2.4% in the 15 mg upadacitinib group and 7.1% in the 30 mg group versus 2.5% in placebo [63]. Another gastrointestinal side effect was diarrhea, which was reported in < 7% of patients on upadacitinib and abrocitinib with a higher rate of 9.1% in patients on 200 mg abrocitinib [63].

AA

GI disorders were not reported among the common adverse events in patients with AA receiving baricitinib [52].

Psoriasis

Nausea and diarrhea had an incidence of 7/322 (2.1%) and 13/322 (3.9%), respectively, compared with 4/165 (2.4%) and 6/165 (3.6%) in the placebo [54, 55].

Neurological Disorders

AD

Headaches were the most common neurologic side effect. It was reported in 12/156 (8%) in abrocitinib 100 mg, 15/154 (10%) in 200 mg, and 2/77 (3%) in placebo groups. Pooled analysis of abrocitinib did not report a difference between the 100 mg abrocitinib group and the placebo. However, the 200 mg group was associated with a higher incidence of headache than the placebo (RR 2.22; 95% CI 1.18, 4.16) [60]. In the JADE MONO-1 study, the headaches were relatively short-lived with a mean duration of 4 days in the abrocitinib 100 mg group and 3 days in the 200 mg group [28]. They were mild and short in duration (median < 1 day). In comparison, 5–9.5% of patients on upadacitinib reported headaches versus 2.5–5.5% in the placebo [63].

AA

Headaches occurred in 4.4–9% of patients on baricitinib compared with 4.8–6.5% in placebo.

Vitiligo

Headaches occurred in 6/221 (2.7%) and 11/228 (4.8%) compared with 2/109 (1.8%) and 4/115 (3.5%) in placebo [53].

Psoriasis

Headaches had an incidence of 16/332 (4.8%) compared with 5/165 (3%) in placebo [54, 55].

Dermatologic Side Effects

AD

Oral JAK Inhibitors

The most common dermatologic adverse events were acne and atopic dermatitis. In the abrocitinib trials, acne was recorded in < 2% of patients on the 100 mg dose and in 4.7–5.8% of patients on the 200 mg dose [28, 63]. It was reported in 3.6% of patients on the 30 mg upadacitinib with < 1.5% in the 15 mg group. It had a much higher frequency in the upadacitinib-treated group with a range of 4.8–17% observed in various trials [63]. Post hoc integrated analysis of three phase 3 randomized trials of upadacitinib, alone or in combination with topical corticosteroids found that acne associated with upadacitinib for AD treatment is usually mild/moderate in severity and can be managed with topical therapies or no interventions [66]. It was more frequent among younger, female, and non-white patients. It also required no intervention in 40.5% and 46.6% of patients receiving upadacitinib 15 and 30 mg, respectively. The remaining patients were treated with topical antibiotics, benzoyl peroxide, and/or retinoids.

AD was reported as a side effect in 14% of patients on abrocitinib 100 mg and in 5% of patients on the 200 mg dose versus 17% in the placebo [28]. Pooled analysis did not report a difference between 100 mg abrocitinib and placebo, while the 200 mg dose was associated with a lower incidence of dermatitis atopic than the placebo (RR 0.50; 95% CI 0.30, 0.82) [60]. In comparison, 1% of patients in the upadacitinib 15 mg groups and 9% of patients in the 30 mg groups versus 3% in the placebo reported dermatitis atopic [50].

Topical JAK Inhibitors In patients with AD treated with topical application of ruxolitinib (1.5% cream), AD and application site burning or pruritus were reported in < 1% of patients [6].

AA

Acne was more common in the baricitinib-treated groups than in the placebo [52]. It

occurred in 16/270 patients (5.7%) with 4-mg baricitinib, 10/183 patients (5.5%) with 2-mg baricitinib, and 1/189 patient (0.5%) with placebo in BRAVE-AA1 and in 11/233 patients [6] (4.7%), 9/155 patients (5.8%), and 3/154 patients (1.9%), respectively, in BRAVE-AA2.

Vitiligo
Application site acne was reported in up to 13/228 (5.9%) in the ruxolitinib-treated group compared with 2/115 (1.7%) in placebo [67]. Application site pruritus was reported in 12/228 (5.4%) and 2/115 (1.7%), respectively.

Psoriasis
Acne occurred in 15/531 (2.8%) in deucravacitinib compared with no events in placebo.

Laboratory Abnormalities

Complete Blood Count
AD In the JADE MONO studies, there was a dose-related decrease in platelet counts in patients treated with abrocitinib. A nadir was observed on the fourth week along with a recovery to baseline with continued therapy [28]. There were no significant changes in neutrophil, hemoglobin, or lymphocyte counts in patients receiving abrocitinib. In comparison, no cases of grades 3 or 4 thrombocytopenia were noted in the upadacitinib studies [50]. More patients reported transient neutropenia in the upadacitinib 30 mg treatment group compared with the 15 mg group (15/285 versus 4/281, respectively).

AA In the BRAVE-AA studies, 1/281 (0.4%) patient with a history of GI bleeding developed anemia on the 4 mg baricitinib dose, resulting in treatment cessation. Also, 2/390 (0.5%) patients developed grade 4 neutropenia and 3/465 (0.6%) developed thrombocytosis [52]. These patients continued treatment, and their laboratory values normalized.

Vitiligo and Psoriasis
There were no clinically significant laboratory changes reported in phase 3 trials [54, 55, 68].

Creatine Phosphokinase (CPK)

AD
The most common lab abnormality was elevated serum creatine phosphokinase (CPK). Increases in CPK were observed at a frequency of $\leq$ 6% in patients with AD on upadacitinib or abrocitinib in various phase 3 trials [50, 63].

AA
Increases in creatine kinase to more than five times the upper limit of normal was observed in a small percentage of patients.

Psoriasis
Increases in CPK were noted with reported incidence of 3.8/100 PY for deucravacitinib and 2.1/100 PY for placebo [54]. It was often associated with physical exertion.

Lipids

AD
There was a dose-related elevation of approximately 10% in high- and low-density lipoprotein cholesterol (HDL, LDL) levels for both abrocitinib doses compared with placebo [28, 56]. There were no clinically significant changes in the high-density lipoprotein/low-density lipoprotein ratio, however.

AA
In baricitinib-treated patients, elevations in LDL cholesterol level were noted in approximately 25% of the patients, and elevations in HDL cholesterol level were noted in approximately 40% of patients [52].

Vitiligo and Psoriasis
There were no clinically significant laboratory changes reported in phase 3 trials [54, 55, 67].

MANAGEMENT OF RISKS ASSOCIATED WITH JAK INHIBITORS

Risk factors for developing complications should be assessed, including age > 65, obesity,

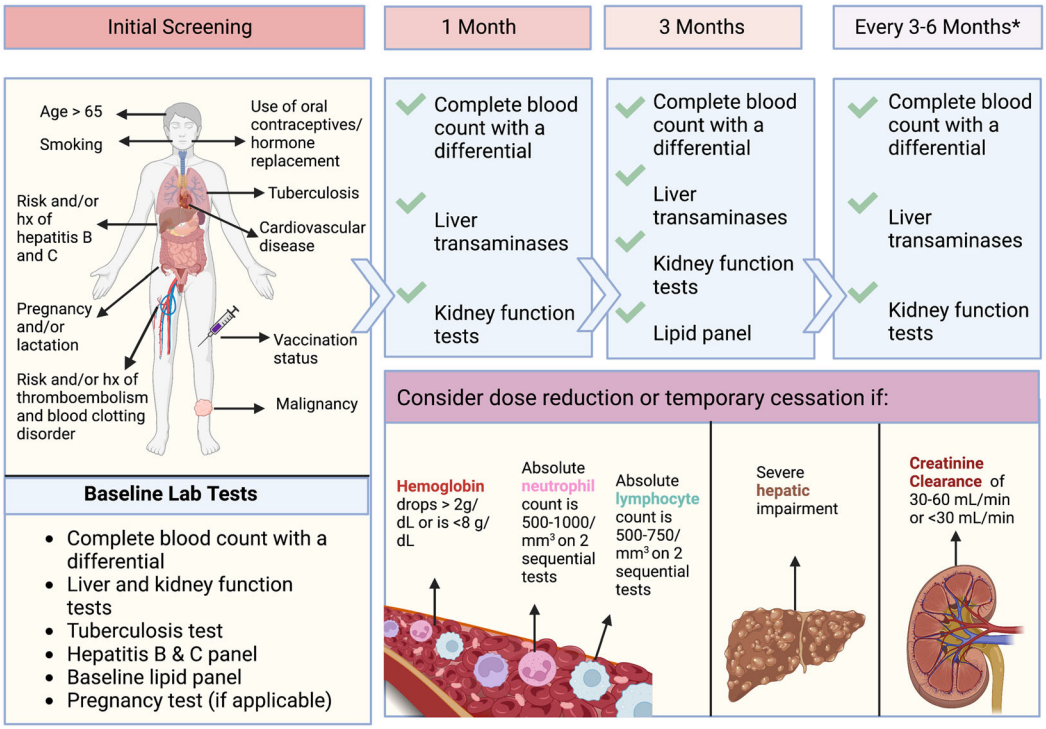


Fig. 4 Screening and laboratory monitoring for patients on JAK inhibitors. *Depending on prior laboratory results and patient risk factors

Table 3 Conditions where JAK inhibitor use is not appropriate

JAK inhibitor use has higher risks in the following conditions:
Active cancer (or history of several cancers)
Active or recurrent shingles despite vaccination
Severe recurrent infections and/or frequent hospitalizations for serious infections
Previous DVT and/or high risk for DVT without receiving anticoagulation
Pregnancy, breast-feeding, and/or patients considering pregnancy
Patients receiving other immunosuppressive therapies, such as transplant patients
Severe organ failure such as decompensated cirrhosis and end-stage renal disease requiring dialysis due to limited data in these populations

tobacco use, cardiovascular disease, coagulation disorder, or history of thromboembolism or malignancy (Fig. 4). There are limited data on treating pregnant women with JAK inhibitors, which is challenging as there are no large clinical studies on their effects on conception, pregnancy, lactation, and the fetus [69]. Table 3 displays clinical conditions where JAK inhibitor usage is not appropriate. Clinical judgment in assessing the severity of the disease and its responsiveness to other first-line therapies is necessary prior to starting patients with baseline risk factors, such as a smoking history and oral contraceptive use, on JAK inhibitors.

Prior to treatment with JAK inhibitors, it is recommended to perform peripheral blood testing, including complete blood count with a differential, kidney and hepatic function panel, and baseline lipid panel as well as hepatitis B and C, tuberculosis testing, and screening for human immunodeficiency virus (HIV) (Fig. 4) [70]. In addition, it is recommended that adult patients receive their pneumococcal and Shingrix vaccine [71]. Subsequently, monitoring

complete blood count with a differential, kidney, and hepatic function panel 1 month after treatment and then every 3–6 months thereafter depending on patient's prior laboratory results and risk factors is recommended. Lipid panels should also be obtained 3 months after the initial screening. Tuberculosis screening should also be performed annually. We suggest lowering or temporarily stopping treatment if hemoglobin drops > 2 g/dL or is < 8 g/dL, absolute neutrophil count is 500–1000/mm^3, absolute lymphocyte count is 500–750/mm^3, creatinine clearance is 30–60 or < 30 mL/min, or the patient has severe hepatic impairment [72–74].

CONCLUSION

JAK inhibitors have exhibited robust efficacy in some dermatologic conditions with a deleterious impact on quality of life. With data from clinical trials, providers will be able to better counsel patients on therapeutic decisions. Clinicians should engage in shared decision-making conversations on the benefits and risks with their patients on a case-by-case basis.

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