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Practical Management of the JAK1 Inhibitor Abrocitinib for Atopic Dermatitis in Clinical Practice: Special Safety Considerations

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ABSTRACT

Abrocitinib, an oral, once-daily, Janus kinase (JAK) 1-selective inhibitor, is approved for the treatment of adults and adolescents with moderate-to-severe atopic dermatitis (AD). Abrocitinib has shown rapid and sustained efficacy in phase 3 trials and a consistent, manageable safety profile

Prior Publication: This practical approach article summarizes recommendations for abrocitinib use based on published clinical trial data, safety evaluations of the JAK inhibitor class by regulatory authorities, and the authors' experience. The published primary studies from the JADE clinical program describing the abrocitinib safety data summarized in this article are listed below:

Gooderham MJ et al. *JAMA Dermatol.* 2019;155(12):1371–1379. (ClinicalTrials.gov number, NCT02780167).

Simpson EL et al. *Lancet.* 2020;396(10246):255–266. (ClinicalTrials.gov number, NCT03349060).

Silverberg JI et al. *JAMA Dermatol.* 2020;156(8):863–873. (ClinicalTrials.gov number, NCT03575871).

Bieber T et al. *N Engl J Med.* 2021;384(12):1101–1112. (ClinicalTrials.gov number, NCT03720470).

Eichenfield LF et al. *JAMA Dermatol.* 2021;157(10):1165–1173. (ClinicalTrials.gov number, NCT03796676).

Blauvelt A et al. *J Am Acad Dermatol.* 2022;86(1):104–112. (ClinicalTrials.gov number, NCT03627767).

Reich K et al. *Lancet.* 2022;400(10348):273–282. (ClinicalTrials.gov number, NCT04345367).

Reich K et al. *J Eur Acad Dermatol Venereol.* 2023;37(10):2056–2066. (ClinicalTrials.gov number, NCT03422822).

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in long-term studies. Rapid itch relief and skin clearance are more likely to be achieved with a 200-mg daily dose of abrocitinib than with dupilumab. All oral JAK inhibitors are associated with adverse events of special interest and laboratory changes, and initial risk assessment and follow-up monitoring are important. Appropriate selection of patients and adequate monitoring are key for the safe use of JAK inhibitors. Here, we review the practical use of abrocitinib and discuss characteristics of patients who are candidates for abrocitinib therapy. In general, abrocitinib may be used in all appropriate patients with moderate-to-severe AD in need of systemic therapy, provided there are no contraindications, e.g., in patients with active serious systemic infections and those with severe hepatic impairment, as well as pregnant or breastfeeding women. For patients aged ≥ 65 years, current long-time or past long-time smokers, and those with risk factors for venous thromboembolism, major adverse cardiovascular events, or malignancies, a meticulous benefit–risk assessment is recommended, and it is advised to start with the 100-mg dose, when abrocitinib is the selected treatment option.

Keywords: Abrocitinib; Atopic dermatitis; JAK1-selective inhibitor; Monitoring; Safety

Key Summary Points

Abrocitinib, an oral, once-daily Janus kinase (JAK) 1-selective inhibitor, is approved for the treatment of adults and adolescents with moderate-to-severe atopic dermatitis (AD).

Abrocitinib has shown a favorable benefit–risk profile in long-term studies with both the 100 and 200 mg/day doses.

In patients who are over 65 years of age, are current long-time or past long-time smokers, or have risk factors for cardiovascular events, venous thrombosis, infections, or malignancy, a thorough benefit–risk assessment is recommended and the lowest effective dose of abrocitinib is preferred.

Prior to starting treatment, clinicians should advise patients initiating abrocitinib about vaccination recommendations, the most frequent tolerability issues, family planning, risk of adverse events, and the need for blood monitoring.

INTRODUCTION

Atopic Dermatitis Treatment Landscape

Atopic dermatitis (AD) can have a profound effect on patients' quality of life (QoL) [1]. AD is a heterogeneous disease, and not all patients can sufficiently manage their AD with available topical or systemic therapies [2, 3]. Dupilumab was the first new systemic therapy to receive approval for the treatment of moderate-to-severe AD [4]. However, more than 60% of patients in dupilumab phase 3 randomized controlled trials did not achieve pre-established efficacy endpoints [5] and up to approximately 30% of dupilumab-treated patients in real-world studies did not achieve adequate disease control, as assessed using the patient-reported Atopic Disease Control Tool, after approximately 1 year of treatment [6–8], indicating the need for additional, more effective treatments.

JAK Inhibitor Safety Overview

To date, three Janus kinase (JAK) inhibitors—abrocitinib, baricitinib, and upadacitinib—have been approved for the treatment of moderate-to-severe AD in several countries worldwide, including the European Union; abrocitinib and upadacitinib, but not baricitinib, are also approved in the USA and Canada. Treatment with JAK inhibitors is associated with achievement of high-threshold efficacy endpoints (e.g., $\geq 90\%$ improvement from baseline in the Eczema Area and Severity Index) [9–11], with an overall favorable tolerability and safety profile [12]. Head-to-head trials have shown advantages of abrocitinib and upadacitinib over dupilumab in regards to speed of onset and depth of responses

[13–15]. However, the JAK class has been associated with rare serious adverse events (AEs), such as infections, major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and malignancies, especially in patients aged ≥ 65 years, current long-time or past long-time smokers, and those at a higher baseline risk of these conditions (e.g., with history of atherosclerotic cardiovascular disease [ASCVD]) [12, 16, 17]. Lower incidence of these AEs was seen in patients with AD receiving abrocitinib indirectly compared with tofacitinib, another JAK inhibitor, used in patients with rheumatoid arthritis (RA) who had at least one additional cardiovascular (CV) risk factor; this is consistent with the younger age and lower prevalence of CV risk factors in patients with AD [18]. Abrocitinib may have an improved safety profile over tofacitinib since it provides more selective JAK1 inhibition and it would likely be used by a younger and healthier population without concomitant use of immunosuppressant therapies, as reported in the tofacitinib trial [16, 18, 19]. Indeed, integrated safety analysis of over 3000 patients with moderate-to-severe AD treated with abrocitinib found safety event rates to be lower than those observed in the tofacitinib studies in patients with RA [18].

The efficacy and safety of abrocitinib, an oral, once-daily, JAK1-selective inhibitor, has been studied extensively in the JADE clinical development program, which involved more than 4000 adults and adolescents with moderate-to-severe AD [14, 20–25]. In the JADE clinical trials, abrocitinib dosages of 200 or 100 mg/day were efficacious as monotherapy [20–22] or in combination with medicated topical therapies [23–25] in improving skin lesions, pruritus, sleep disturbance, and QoL. Abrocitinib provided itch relief, as early as 24 h after the first dose, followed by rapid improvements in skin symptoms [14, 26]. Abrocitinib was infrequently discontinued as a result of AEs, which were mostly mild, transient, and manageable [19, 27, 28]. Long-term abrocitinib efficacy has been demonstrated at 48 and 96 weeks of treatment, with no unexpected safety findings observed [28–30].

This article provides a pragmatic approach to abrocitinib use in patients with AD using expert opinion to optimize patient selection, dosing,

and monitoring. It is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Recommendations are based on clinical trial data, safety evaluations of the JAK inhibitor class by regulatory authorities, and the authors' experience [31–33].

Clinical Considerations Before Starting Abrocitinib

Abrocitinib may be used in most adults and adolescents with moderate-to-severe AD (Fig. 1) after individually assessing the benefit–risk balance for each patient [31–33]. In the USA, abrocitinib is indicated for use in adults and adolescents with moderate-to-severe AD with refractory disease that is not adequately controlled with other systemic therapies, including biologics or when use of those therapies is inadvisable [32]. The recommended dose is 100 mg in both adults and adolescents, and the 200 mg dose is recommended for patients not responding to 100 mg. In the European Union, abrocitinib is indicated for adults and adolescents with moderate-to-severe AD who are candidates for systemic therapy [31]. The recommended starting dose for both adults and adolescents is 100 or 200 mg, depending on individual patient characteristics, and the lowest effective dose should be considered for maintenance. In adolescents with body weight 25 to <59 kg, abrocitinib should be started at 100 mg and increased to 200 mg if the patient does not respond adequately to the 100 mg dose; adolescents with body weight >59 kg can be started at either 100 or 200 mg [31]. Abrocitinib is contraindicated in patients who are pregnant or breastfeeding [31, 32]. Patients who have active or untreated infections such as tuberculosis or hepatitis B or C should not take abrocitinib until these conditions are addressed appropriately [31, 32]. Patients who previously had hepatitis B or C, human immunodeficiency virus (HIV), or those who may be at high risk of undiagnosed disease should be assessed prior to initiating treatment for active infection.

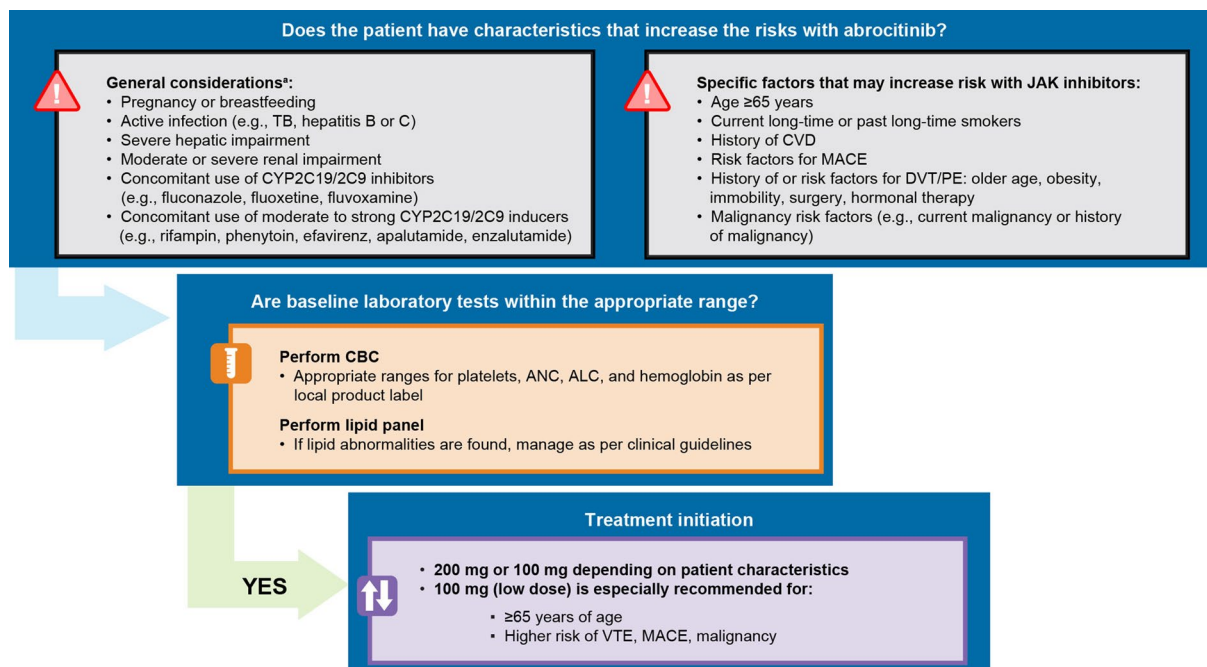


Fig. 1 Patient selection and considerations prior to initiation of abrocitinib. *ALC* absolute lymphocyte count, *ANC* absolute neutrophil count, *CBC* complete blood count, *CVD* cardiovascular disease; *CYP* cytochrome P450, *JAK* Janus kinase, *MACE* major adverse cardiovascular events, *PE* pulmonary embolism; *TB* tuberculosis, *VTE* venous

thromboembolism. ^aAbrocitinib is contraindicated, initiation is not recommended, or dose should be reduced for these groups of patients; verify the local product label to see the specific recommendations for your country or region

Abrocitinib can be used with or without topical corticosteroids but is not recommended to be used in combination with other JAK inhibitors, biologic immunomodulators, or other immunosuppressants such as cyclosporine and methotrexate [31, 32]. The combination of abrocitinib with these systemic therapies has not been studied and their concomitant use with abrocitinib in clinical practice is not recommended because of potential risk of additive immunosuppression [31]. Concomitant use of abrocitinib with phototherapy has also not been studied and is not recommended because of potential increased risk of malignancies, such as melanoma or nonmelanoma skin cancer. Abrocitinib is primarily eliminated by metabolism involving cytochrome P450 (CYP) enzymes, mainly CYP2C19 and CYP2C9, with minor involvement of CYP3A4 and CYP2B6 enzymes [34–36]. Co-administration of abrocitinib and moderate to strong CYP2C19/2C9 inducers, including

rifampin (antituberculosis drug), phenytoin (antiepileptic drug), efavirenz (antiviral drug used for HIV infection), and apalutamide and enzalutamide (anticancer drugs used for prostate cancer), reduces the exposure to abrocitinib and is not recommended [31, 32, 34]. Furthermore, co-administration with strong CYP2C19 inhibitors, including fluvoxamine and fluoxetine (antidepressants), ticlopidine (antiplatelet drug), and fluconazole (antifungal drug), increases the exposure to abrocitinib and therefore requires dosage adjustments per label recommendations [31, 32, 34]. Organic anion transporter 3 (OAT3) inhibitors (e.g., probenecid, used for the treatment of gout and gouty arthritis, and teriflunomide, used for the treatment of multiple sclerosis) were found to increase abrocitinib exposure; however, these effects were not considered clinically relevant. Thus, no abrocitinib dose adjustment is necessary in patients taking OAT3 inhibitors [34].

Given the potential risk of MACE, VTE, and malignancies associated with JAK inhibitor use [16, 17, 33, 37], clinicians should consider the baseline risk before initiating abrocitinib. Higher rates of these AEs were seen in patients with RA who had increased risk for cardiovascular disease and received the JAK inhibitor, tofacitinib, indirectly compared with patients with AD who received abrocitinib treatment in randomized clinical trials and in an ongoing long-term extension study, highlighting the importance of evaluating the baseline risks for each unique patient [18]. Special considerations should be exercised when treating individuals aged ≥ 65 years because of high risk of serious AEs in this age group, current long-time or past long-time smokers, and those at increased risk of MACE (e.g., previous history of ASCVD, including myocardial infarction or stroke) or VTE (e.g., personal or family history of pulmonary embolism [PE] or deep vein thrombosis [DVT]) or with malignancy risk factors (e.g., current malignancy or history of malignancy) [16, 31–33]. Abrocitinib should be also used with caution in patients with other VTE risk factors, including obesity, prothrombotic disorder, recent trauma or major surgery, or prolonged immobilization [31, 38, 39]. Studies have also suggested that estrogen-containing oral contraceptive pills and hormone replacement therapy pose a risk for VTE, independent of JAK inhibitor use [40, 41]. However, no VTE cases were reported in abrocitinib-treated female patients who received hormonal contraceptives; a single case of VTE (non-fatal bilateral PE) was reported in a patient who received hormone replacement therapy [42]. The benefits and risks of JAK inhibitor use in patients with known malignancy should be evaluated on a case-by-case basis [16, 17, 31–33, 37].

If abrocitinib is considered the appropriate treatment, a complete blood count (including platelets, absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and hemoglobin), lipid parameter measurements, measurements of transaminases, renal function testing, and screening for hepatitis B or C and HIV in accordance with clinical guidelines and local regulations prior to immunosuppressive treatment should be performed before initiating treatment [31, 32]. Patients should also be

evaluated and tested for tuberculosis before initiating abrocitinib; yearly screening should be considered for patients in highly endemic areas for tuberculosis. The use of screening tests, including interferon- γ release assays (e.g., QuantiFERON), tuberculin skin tests, enzyme-linked immunosorbent assay (ELISA) tests, and/or chest X-rays, before treating adult and adolescent patients with JAK inhibitors, varies depending on local regulations and clinical guidelines. Chest X-ray may be used in conjunction with the QuantiFERON test, or only if a patient tests positive using the QuantiFERON test according to local regulations. In the abrocitinib clinical trials, including adult and adolescent patients, a dose-dependent decrease in platelet count was noted, with a nadir at week 4 [19, 25]. Median platelet counts subsequently increased and reached a plateau at week 12, with final 12-week values remaining below baseline but within the normal range [19]. Thrombocytopenia ($<75 \times 10^3$ platelets/ mm^3) was rare but more common in patients aged ≥ 65 years and in those receiving abrocitinib 200 mg/day [19, 43]. No change over time was seen in ANC, ALC, or hemoglobin; however, rare cases of lymphopenia have been observed [19, 31, 32].

Blood lipid levels should be assessed before beginning abrocitinib and at 4 weeks following treatment initiation and managed, if needed, per dyslipidemia management guidelines [31, 32, 44, 45]. In clinical trials, abrocitinib was associated with a dose-related increase in low-density lipoprotein cholesterol (LDL-C) from baseline to week 16, with no notable change in the LDL-C/high-density lipoprotein cholesterol (HDL-C) ratio over 16 weeks [19].

Abrocitinib dose selection should consider patient characteristics. Patients aged ≥ 65 years are at a higher risk of AEs and should start with the 100-mg/day dosage [31–33]. Patients with mild (Child–Pugh class A, 5–6 points) or moderate (Child–Pugh class B, 7–9 points) hepatic impairment [46] can be treated with abrocitinib without dose adjustment; however, abrocitinib must not be used in patients with severe hepatic impairment (Child–Pugh class C, 10–15 points) [31, 32]. In abrocitinib clinical trials, both moderate (estimated glomerular filtration rate [eGFR] ≥ 30 to <60 mL/min) and severe

renal impairment (eGFR < 30 mL/min but not requiring dialysis) led to higher exposure to abrocitinib active metabolites, requiring dosage adjustment as stated in the label [31, 32, 47]. A lower abrocitinib dose (50 mg) is available for dose adjustment in special populations (i.e., patients with renal impairment or concomitant use of medications that interact with abrocitinib).

Advising the Patient Initiating Abrocitinib

Shared decision-making between the healthcare practitioner and the patient should take into account each patient's risk factors and medical history before treatment initiation with abrocitinib. Risk factors for herpes zoster (HZ) during abrocitinib treatment included the higher dosage (200 mg/day), age ≥ 65 years, ALC < $1.0 \times 10^3/\text{mm}^3$, and prior history of HZ [28]. If feasible, all patients should complete age-appropriate vaccines, including non-live HZ vaccination (e.g., Zoster Vaccine Recombinant, Adjuvanted) around 2–4 weeks before abrocitinib initiation,

especially those who are at a higher risk of HZ (≥ 50 years old, immunosuppressed, or immunodeficient) [31, 32, 48, 49] (Fig. 2). In patients who have already initiated abrocitinib, non-live vaccines can be given at any point during therapy without stopping treatment. Patients should avoid vaccination with live vaccines immediately prior to, during, and immediately after abrocitinib treatment [31, 32]. We recommend stopping live vaccines up to at least 1 week prior to initiating abrocitinib, and a waiting time of 2–4 weeks after stopping treatment, depending on the vaccine product label.

Potential tolerability concerns include nausea, headache, and acne [31]. Nausea typically occurred within the first week of treatment, was generally mild or moderate, and resolved spontaneously within a median time of 15 days [19]. Taking abrocitinib with food or reducing abrocitinib dose may help alleviate nausea [31, 50]. Headache (not severe or serious) usually occurred within the first week of treatment and resolved in a median time of 4 days [19]. Acne was not severe or serious, was less frequent with abrocitinib 100 mg, and should be managed

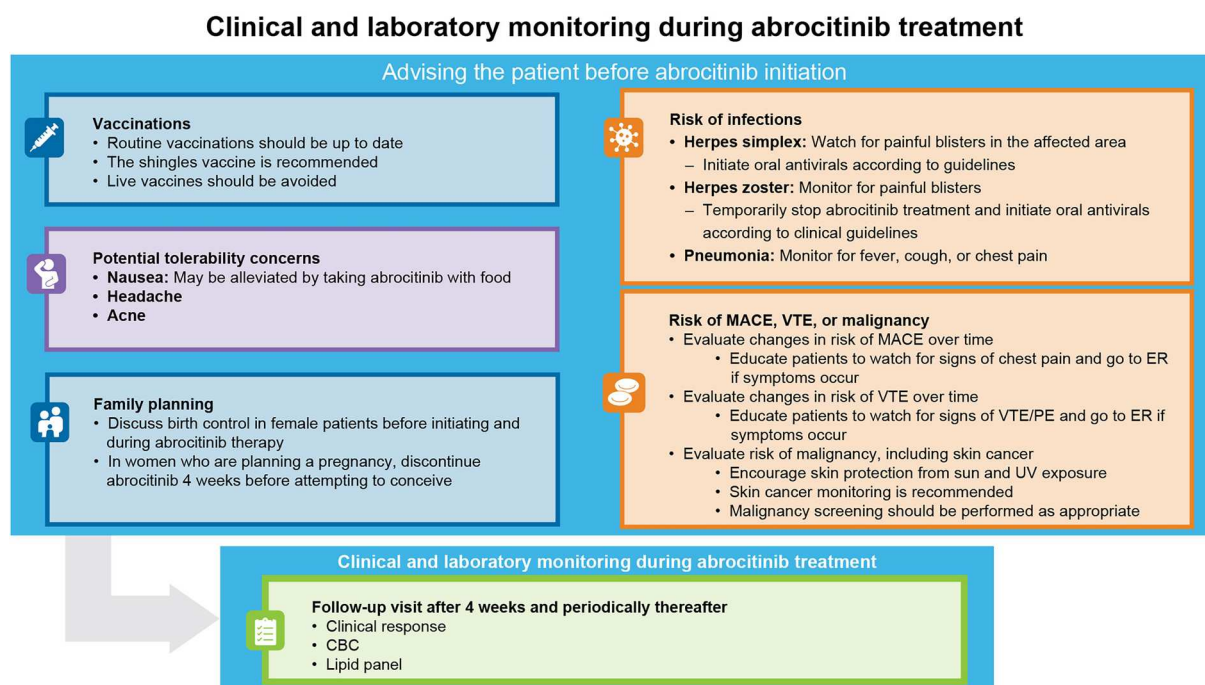


Fig. 2 Patient monitoring during abrocitinib treatment. *CBC* complete blood count, *ER* emergency room, *MACE* major adverse cardiovascular events, *PE* pulmonary embolism, *UV* ultraviolet, *VTE* venous thromboembolism

according to guidelines (e.g., with topical clindamycin-benzoyl peroxide, retinoid, dapson, azelaic acid, or oral antibiotics) [19, 51].

Abrocitinib has not been studied in pregnant women; birth control is recommended in women of childbearing potential who are taking abrocitinib [31]. Women who are planning a pregnancy should discontinue abrocitinib for 4 weeks before attempting to conceive. Abrocitinib has no effects on male fertility and is not genotoxic [31, 32].

An increased infection risk during abrocitinib treatment has been reported in clinical trials; the most common serious infections were herpes simplex (<5%), HZ (<2%), and pneumonia (<1%) [19, 28]. Herpes simplex medical history was a risk factor for herpes simplex infection [19]. Orally administered valaciclovir, aciclovir, or famciclovir may be used in patients who develop herpes simplex infection [52], and prophylactic use may be considered in individuals with a history of frequent herpes simplex outbreaks. In clinical trials, cases of HZ were typically mild or moderate [19]. Abrocitinib treatment may be temporarily stopped in case of HZ infection [31, 32], and patients may be treated with aciclovir, famciclovir, or valaciclovir per treatment guidelines [52, 53].

Healthcare professionals should discuss with their patients the risks of MACE, VTE, and malignancies associated with JAK inhibitors [33]. Age-appropriate malignancy screening (e.g., mammogram, prostate exam) should be performed in all patients with AD. Protection from the sun and monitoring for skin cancer are recommended in patients receiving abrocitinib [31, 32, 50].

Follow-up

Patients should be evaluated for clinical response to abrocitinib after the first 4 weeks of treatment, and laboratory monitoring for hematologic and lipid abnormalities should be conducted at this time and then every 8–12 weeks (Fig. 2) [19, 31, 32, 44, 54]. Interruption or discontinuation of abrocitinib may be needed if low levels of platelets ($<50 \times 10^3/\text{mm}^3$), ANC ($<1 \times 10^3/\text{mm}^3$), ALC ($<0.5 \times 10^3/\text{mm}^3$), or hemoglobin ($<8 \text{ g/}$

dL) are detected [31, 32]. Lipid levels should be assessed at the 4-week follow-up visit; in the case of hyperlipidemia, use of lipid-lowering therapy (e.g., statins) may be required [44]. Dose adjustments because of lipid abnormalities are not needed, nor is regular monitoring of renal and liver functions. Although a dose-related increase in creatine phosphokinase (CPK) was observed in clinical trials, no meaningful differences in the proportions of patients with CPK levels exceeding five- or tenfold the upper limit of normal were reported between abrocitinib doses and placebo [19]. Rhabdomyolysis has been reported rarely with JAK inhibitors [19, 55, 56]. Monitoring CPK levels in abrocitinib-treated patients who increase their physical activity or experience muscle pain is reasonable, as rhabdomyolysis can lead to kidney damage [57, 58].

CONCLUSIONS

Abrocitinib may be used in most patients with moderate-to-severe AD as indicated per label. In addition, cautious evaluation is needed in patients aged ≥ 65 years, current long-time or past long-time smokers, and those with risk factors for VTE, MACE, or malignancies [28, 33].

Abrocitinib availability at three doses (50, 100, and 200 mg) allows for treatment adjustment based on patients' characteristics. Patients with tolerability concerns with abrocitinib 200 mg/day may have their dosage reduced to 100 mg/day with a reasonable likelihood of maintaining their response [24]. Clinical data showed that 60% of patients who switched to abrocitinib 100 mg and 22% of those who switched to placebo after achieving good response with abrocitinib 200 mg treatment for 3 months maintained control over their AD for almost a year thereafter. Additionally, for most of patients who experience flaring, a 3-month rescue treatment with abrocitinib 200 mg and topical medication successfully recaptured their previous response [24].

Clinicians can improve the benefit–risk ratio of JAK inhibitors by appropriate patient selection and evaluation as well as patient education.

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Declarations

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Ethical Approval. 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.

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