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PRACTICAL APPROACH

Practical Recommendations on Laboratory Monitoring in Patients with Atopic Dermatitis on Oral JAK Inhibitors

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ABSTRACT

Oral Janus kinase inhibitors (JAKi), a class of advanced targeted systemic therapy, have demonstrated efficacy and safety in the treatment of moderate-to-severe atopic dermatitis (AD). Like other small molecules, oral JAKi have the potential for off-target effects including laboratory-related adverse events (AEs). Product labels for oral JAKi recommend an initial laboratory assessment and follow-up 4–12 weeks later to monitor for potential changes, based on evidence from clinical trials across therapeutic indications for oral JAKi, which may not reflect a population of moderate-to-severe AD patients typically seen in routine clinical practice. To address this gap, a panel of eight dermatologists with clinical and research experience with

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oral JAKi for the management of AD conducted a targeted review of the literature focused on key laboratory-related AEs associated with oral JAKi in the moderate-to-severe AD population. Based on the synthesis of evidence and informed opinion, a set of best practice statements related to fundamental standards of care and consensus recommendations on laboratory monitoring were suggested, and level of agreement was ascertained using a Likert scale from 0 to 100. There was a high level of agreement on three of the four suggested recommendations related to assessment and monitoring of key laboratory parameters and to dose reduction or switching in response to laboratory changes; there was a lower level of agreement related to the frequency of ongoing laboratory monitoring. Appropriate patient selection and laboratory assessment is an important strategy to mitigate the potential risks associated with oral JAKi when treating AD.

Keywords: Atopic dermatitis; Monitoring; JAK inhibitors; Safety; Tolerability

Key Summary Points

Oral Janus kinase inhibitors (JAKi) have emerged as an important addition to the management of moderate-to-severe atopic dermatitis (AD).

Appropriate patient selection and laboratory assessment can mitigate the potential risks associated with oral JAKi treatment when treating patients with AD.

Baseline assessment of laboratory parameters should be conducted prior to initiating oral JAKi treatment in patients with AD.

Repeat laboratory parameters between 8 and 12 weeks will identify the majority of patients with AD who are susceptible to drug-related adverse events from oral JAKi treatment.

Ongoing laboratory assessment is generally unnecessary in patients with AD treated with oral JAKi who do not exhibit clinically meaningful changes between 8 and 12 weeks.

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INTRODUCTION

Atopic dermatitis (AD), an inflammatory skin disease affecting a large proportion of children and a smaller proportion of adults, is a common reason for dermatology referral [1]. Since AD is often variable in intensity and usually of lower disease burden, emollients and topical therapies are the mainstay of treatment. Systemic therapies are arguably more likely to succeed in treating higher disease burden AD when success is measured by skin clearance, itch control, and quality of life (QoL) improvement [2, 3]. Biologics that are therapeutically beneficial have identified cytokines which play key roles in the immune-mediated inflammatory pathways underlying AD including interleukin (IL)-4, IL-13, and IL-31. Signaling of these cytokines is primarily mediated through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway [4–6], making JAK inhibition a rational therapeutic target for reducing inflammation in AD.

Janus kinases are ubiquitous cytoplasmic proteins comprised of four different receptor-associated tyrosine kinases: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) [6]. JAK inhibitors (JAKi) are small molecules that block one or more JAK isoforms and prevent the transduction of signals from the cell surface to the nucleus where gene transcription is regulated [6]. Non-selective oral JAKi such as tofacitinib and ruxolitinib were first approved for treating

rheumatoid arthritis (RA) and myelodysplastic disorders, respectively [7]. More recently, JAKi have been studied in inflammatory skin diseases including AD. To date, three oral agents (the non-selective JAKi, baricitinib, and the selective JAK1 inhibitors, abrocitinib and upadacitinib) and two topical agents (the non-selective JAKi, ruxolitinib and delgocitinib) [8–10] have been approved by regulatory authorities for the treatment of AD (Table 1) [11–19]; several other JAKi are in various stages of development. JAKi have reported promising outcomes in numerous other inflammatory skin diseases [20], with expanded indications expected in the near future [12].

Like many small molecules, oral JAKi increase the risk of off-target effects including laboratory-related adverse events (AEs). As a class, they have been associated with signals for serious AEs, largely based on data from the first-generation, non-selective JAKi. Indeed, the US Food and Drug Administration (FDA) [21], the European Medicines Agency (EMA) [22], and Health Canada [23] have mandated boxed warnings for the entire class of oral JAKi. Boxed warnings were recently updated based on findings from a surveillance study of oral tofacitinib versus tumor necrosis factor (TNF) inhibitors in RA that showed an increased incidence of major adverse cardiac events (MACE) and malignancy, with a resultant increase in mortality [24]. This is in stark contrast to other real-world studies, which do not substantiate an increased risk of MACE in RA patients treated with oral JAKi [25, 26]. Moreover, patients with RA have different characteristics, risk profiles, and prior drug exposures relative to patients with AD, who tend to be younger with a lower prevalence of cardiometabolic comorbidities, such as hypertension and chronic kidney disease [27]. Reassuringly, systematic reviews on the safety of oral JAKi used in AD populations suggest low rates of these serious AEs overall [28, 29] and relative to traditional systemic therapies used in moderate-to-severe AD, such as methotrexate and cyclosporine [30].

There is currently limited published literature to help dermatologists navigate appropriate laboratory monitoring of AD patients treated with oral JAKi. Product labels incorporate conservative recommendations to inform clinical decision-making, including appropriate patient selection and subsequent monitoring (Table 2). However, the recommendations are agnostic to indication and are based on evidence from clinical trials in a broad range of patient populations including those with systemic inflammatory disorders unrelated to AD. To address this gap, this review summarizes the available evidence on the laboratory-related AEs associated with oral JAKi and offers a practical approach to monitoring in AD patients treated with these agents.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed in the study.

METHODS

The lead authors (Mark G. Kirchhof, Vimal H. Prajapati, and Kim A. Papp) convened a panel of dermatologists with clinical and research experience with oral JAKi for the management of AD and agreed on key laboratory-related AEs to address based on an overview of the literature on oral JAKi used in the treatment of AD. Subsequently, they conducted a directed PubMed literature search for each identified AE with a focus on integrated safety analyses from the Phase 2 and Phase 3 clinical trials for each oral JAKi. Evidence from real-world studies was excluded since it is derived from poorly defined populations thereby making it difficult to extract drug-associated events from population-associated events. The available evidence for safety of oral JAKi in AD was supplemented, where applicable, by evidence reported in other indications, recognizing that differences in risk rates may be attributable to differences in populations, underlying disease pathology, and concomitant medications as well as comorbidities.

The lead authors proposed practical suggestions on the approach to monitoring laboratory-related AEs based on a synthesis of the evidence, risk stratification, and informed opinion. Statements were categorized as those that are best practices that are fundamental to current standards of care and consensus recommendations that are based on expert opinion.

Table 1 Product characteristics of oral Janus kinase inhibitors (JAKi) used in the treatment of atopic dermatitis (AD)

	Baricitinib [Olumiant®], Eli Lilly [11–13]	**Abrocitinib [Cibinqo®], Pfizer [14–16]**	**Upadacitinib [Rinvoq®], AbbVie [17–19]**
Indications	AD: Adults (most European, Asian, and Middle Eastern countries; not in Canada or the US) and children aged ≥ 2 years in Europe Also approved for adults with rheumatoid arthritis (RA) (Canada, the US, and Europe), alopecia areata (Europe), and COVID-19 (US) and children aged ≥ 2 years with juvenile inflammatory arthritis (JIA)	AD: Adults (Canada, Europe and the US) and adolescents aged ≥ 12 years (Canada)	AD: Adults and adolescents aged ≥ 12 years (widely approved in Canada, Europe, US, and Asia) Also approved in adults with RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease and ulcerative colitis (UC) (Canada, Europe, US, and Asia)
Approved doses in AD	4 mg once daily is the recommended dosage 2 mg once daily is recommended for patients aged ≥ 75 years, patients with history of chronic infections, or for patients with sustained control of disease activity with 4 mg and are eligible for dose tapering	100 mg or 200 mg once daily 50 mg once daily is recommended for patients with moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] < 60 ml/min/m^2)	15 mg, 30 mg or 45 mg once daily 15 mg once daily is the recommended initial dosage in adolescents weighing ≥ 40 kg and adults, and can be increased to 30 mg once daily if adequate response is not achieved or 30 mg as a starting dose for some patients with severe disease 15 mg once daily is the recommended dosage for adults aged ≥ 65 years
Janus kinase (JAK) receptor binding selectivity (half-maximal inhibitory concentration [IC_{50}])	JAK1 & JAK2 reversible inhibitor IC_{50} JAK1 = 5.9 nM IC_{50} JAK2 = 5.7 nM IC_{50} JAK3 = 400 nM IC_{50} TYK2 = 53 nM	Highly selective JAK1 reversible inhibitor IC_{50} JAK1 = 29 nM IC_{50} JAK2 = 803 nM IC_{50} JAK3 > 10,000 nM IC_{50} TYK2 = 1250 nM	Selective JAK1 reversible inhibitor IC_{50} JAK1 = 43 nM IC_{50} JAK2 = 120 nM IC_{50} JAK3 = 2300 nM IC_{50} TYK2 = 4700 nM
Metabolism	~ 1 h	1 h	2–4 h
Median time to peak drug concentration (T_{max})	12.9 h	4.3 (100 mg)—5.9 (200 mg) h	9–14 h
Mean half-life	CYP3A4 (< 10%)	CYP2C19 (~ 53%), CYP2C9 (~ 30%), CYP3A4 (~ 11%), and CYP2B6 (~ 6%)	CYP3A4 (34%)
Cytochrome P450 (CYP) metabolism			

Table 1 continued

	Baricitinib [Olumiant®], Eli Lilly [11–13]	Abrocitinib [Cibinqo®], Pfizer [14–16]	Upadacitinib [Rinvoq®], AbbVie [17–19]
Treatment arms of Phase 3 randomized controlled trials (RCTs)	16-week clinical trials BREEZE-AD1 ($N=497$): baricitinib (BARI) 2 mg, BARI 4 mg, or placebo (PL) [51] BREEZE-AD2 ($N=490$): BARI 2 mg, BARI 4 mg, or PL [51] BREEZE-AD7 ($N=329$): BARI 2 mg + topical corticosteroid (TCS), BARI 4 mg + TCS, or PL + TCS [52] 52-week clinical trial BREEZE-AD4 ($N=463$ with failure, intolerance, or contraindication to oral cyclosporine): BARI 2 mg + TCS, BARI 4 mg + TCS, PL + TCS [53]	12-week clinical trials MONO-1 ($N=387$): abrocitinib (ABRO) 100 mg, ABRO 200 mg, or PL [54] MONO-2 ($N=391$): ABRO 100 mg, ABRO 200 mg, or PL [55] JADE-TEEN ($N=297$): ABRO 100 mg, ABRO 200 mg, or PL [56] 20-week clinical trial JADE-COMPARE ($N=838$): ABRO 100 mg, ABRO 200 mg, dupilumab (DUPI) 300 mg, or PL [57] 26-week clinical trial JADE-DARE ($N=727$): ABRO 200 mg or DUPI 300 mg Q2W + topical therapy [58] 52-week clinical trial JADE-REGIMEN ($N=798$): ABRO 200 mg open-label for 12 weeks, responders randomized to ABRO 100 mg, ABRO 200 mg, or PL [59] 52-week long-term extension trial JADE-EXTEND: ABRO 100 mg and ABRO 200 mg [60]	16-week clinical trials MEASURE-UP 1 ($N=847$): upadacitinib (UPA) 15 mg, UPA 30 mg, or PL [61] MEASURE-UP 2 ($N=836$): UPA 15 mg, UPA 30 mg, or PL [61] AD Up ($N=901$): UPA 15 mg + TCS, UPA 30 mg + TCS, or PL + TCS [62] 24-week clinical trial HEADS Up ($N=692$): UPA 30 mg or DUPI 300 mg every 2 weeks (q2w) [63] 52-week long-term extension MEASURE-UP 1/MEASURE-UP 2 ($N=1609$): UPA 15 mg and UPA 30 mg [64]

Unless otherwise indicated, all data are derived from the respective product labels. The order of oral JAKi agent is based on their relative selectivity

ABRO abrocitinib, *AS* ankylosing spondylitis, *BARI* baricitinib, *DUPI* dupilumab, *eGFR* estimated glomerular filtration rate, IC_{50} half-maximal inhibitory concentration, *JAK* janus kinase, *JIA* juvenile idiopathic arthritis, *PL* placebo, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *TCS* topical corticosteroid, T_{max} time to maximum observed plasma concentration, *UC* ulcerative colitis, *UPA* upadacitinib, *TYK2* tyrosine kinase 2

The following definitions and principles were used during the development of the statements:

- Drug exposure (exposure) is the average serum level of a drug [31].
- Adverse drug reactions (ADR) are exposure dependent with the likelihood of observing an abnormal drug-related AE increasing with an increase in exposure [32]. ADR are identified by observing dose-dependent event rates in a treated population that differ from the event rates seen in an untreated population. ADR include laboratory values that change as a result of treatment. In determining the importance of these changes, it is necessary to assess the potential for associated, consequential outcomes. Minimal changes relative to the range of normal are very unlikely to be of any consequence. Other parameters may be associated with future risk.

Following an approach similar to Papp et al. [33], all authors then independently voted on their level of agreement for each of the consensus recommendations (rated on a Likert scale from 0 to 100) with consensus expressed as the average level of support and a zone of confidence (i.e., lower and upper limit of agreement). The panel of authors agreed on a final set of best practice and consensus recommendations and finalized the content for the article through discussion and review.

RESULTS

Overview of Laboratory-Related AEs and Safety Concerns Associated with Oral JAKi in Patients with AD

Integrated safety analyses for each oral JAKi approved in moderate-to-severe AD have been published and are described here in chronologic order from the date of their original publication [34–36]. Bieber et al. pooled baricitinib data from one Phase 2 study, five Phase 3 studies (BREEZE-AD1; BREEZE-AD2; BREEZE-AD4; BREEZE-AD5; BREEZE-AD7), and two long-term extension (LTE) studies (BREEZE-AD3; BREEZE-AD6) [37]. This integrated analysis was subsequently updated with an additional 105 patients and 2381 patient-years (PY) of follow-up; it thus offers the longest duration of follow-up (median 1.6 years, up to 3.9 years of continuous treatment) of the three oral JAKi approved in AD [34]. Simpson et al. pooled abrocitinib data from one Phase 2b study, four Phase 3 studies (MONO-1; MONO-2; COMPARE; REGIMEN), and one LTE study (EXTEND) of abrocitinib from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) clinical trial program [35]. The maximum duration of drug exposure was 108 weeks, but only a minority of patients (6.9%) were exposed for 72 weeks or longer. Guttman-Yassky et al. pooled upadacitinib data from one Phase 2b study and three Phase 3 studies (MEASURE UP1; MEASURE UP2; AD Up) [36]. The mean duration of exposure was 405–415 days, with a maximum exposure of 818 days at the time of analysis. Unless otherwise noted, the incidence rates of laboratory-related AEs described below are derived from the integrated safety analyses.

A. Lipids

There is a consistent body of evidence from genetic, epidemiologic, and clinical studies implicating elevated levels of serum lipoproteins as a causal factor for the development of atherosclerotic cardiovascular disease and MACE [38]. The product labels for baricitinib, abrocitinib, and upadacitinib all include boxed warnings regarding a potentially increased risk of MACE [11–19]. These warnings are based on data that showed an increased risk of MACE (defined as cardiovascular death, nonfatal myocardial infarction [MI], and nonfatal stroke) with oral tofacitinib compared with TNF inhibitors in patients with RA aged ≥ 50 years who had at least one cardiovascular risk factor [24].

A.1 In the pooled safety analyses of AD clinical trials, the incidence rates of MACE were 0.1–0.2 per 100 PY for baricitinib [34], 0.2 per 100 PY for abrocitinib [35], and ≤ 0.1 per 100 PY for upadacitinib [36]. In the baricitinib studies, patients who experienced MACE had at least one cardiovascular risk factor, except for one patient who had a hemorrhagic stroke as a result

Table 2 Recommended monitoring of oral Janus kinase inhibitor (JAKi) in routine atopic dermatitis (AD) patient management according to product labels [11–19]

Laboratory parameters	Baricitinib [13]	Abrocitinib [16]	Upadacitinib [19]
Lipids: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)	■ Baseline ■ 12 weeks after treatment initiation ■ Periodically thereafter	■ Baseline ■ 4 weeks after treatment initiation ■ Thereafter according to routine patient management	■ Baseline ■ 12 weeks after treatment initiation ■ Thereafter according to clinical guidelines for hyperlipidemia
Complete blood count (CBC): absolute lymphocyte count (ALC), absolute neutrophil count (ANC), hemoglobin, and platelets	■ Baseline ■ 4–8 weeks after treatment initiation ■ Periodically thereafter	■ Baseline ■ 4 weeks after treatment initiation ■ Thereafter according to routine patient management	■ Baseline ■ No later than 12 weeks after treatment initiation ■ Thereafter according to individual patient management
Liver enzymes: transaminases	■ Recommended	■ Not stated	■ Baseline ■ Thereafter according to individual patient management
Creatine phosphokinase (CPK)	■ Check in patients with symptoms of muscle pain/weakness	■ Not stated	■ Check in patients with symptoms of muscle pain/weakness
Renal function: estimated glomerular filtration rate (eGFR)	■ Baseline ■ Reduced dose (2 mg) in patients with eGFR 30 to 60 ml/min; not recommended in patients with eGFR < 30 ml/min	■ Baseline ■ Reduce dose by 50% in patients with moderate-to-severe renal impairment (eGFR < 30 to < 60 ml/min)	■ Baseline ■ Reduced dose (15 mg) in patients with severe renal impairment

ALC absolute lymphocyte count, *ANC* absolute neutrophil count, *CBC* complete blood count, *CPK* creatine phosphokinase, *eGFR* estimated glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides

of a cerebral aneurysm that was not considered related to the study drug [39]. There were no associations between changes in lipid levels and MACE or other cardiovascular events reported with any of the three oral JAKi in clinical populations of AD patients [35–37].

A.2 In the pooled analyses of safety data from AD clinical trials for baricitinib, abrocitinib, and upadacitinib, dose-dependent increases in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed, without any notable changes in the LDL-C/HDL-C ratio [34–36].

A.3 The increases in LDL-C and HDL-C generally occurred early and remained elevated during long-term treatment; however, most patients had lipid levels below threshold values for dyslipidemia (3.5 mmol/L and 1.5 mmol/L, respectively) at baseline and most categorical increases remained below these levels [35, 37].

A.4 Elevations in triglycerides were reported only for baricitinib. In the placebo-controlled

period (to Week 16), the incidence rates (IR) for triglycerides ≥ 5.6 mmol/l were similar between baricitinib treatment arms and placebo (0.6–0.8%) and they remained similar across both baricitinib groups during the extended follow-up (1.1–1.2%) [37].

A.5 The long-term clinical risk associated with elevated LDL-C, total cholesterol (TC)/HDL-C ratio, and non-HDL-C (which includes LDL-C, very LDL-C, and intermediate-density lipoprotein) is MACE [40, 41]. Evidence suggests that age-adjusted risk of MACE increases linearly with every 1 mmol/l increase in these values in both men and women, with the strongest associations for TC/HDL-C and non-HDL-C [42, 43].

Oral JAKi have been observed to increase some lipid parameters in RA patients, without any notable associations between lipid changes and MACE [44, 45]; this is not surprising since lipids must generally be elevated for decades before the risk of MACE increases appreciably [43]. In the AD clinical trials of oral JAKi, dose-dependent increases in both LDL-C and HDL-C were observed and relatively stable, but levels remained below threshold levels for dyslipidemia treatment [34–36]. Similar to RA clinical trials, there was no association between lipid elevations and MACE.

B. Hematologic

JAK inhibition has been associated with hematologic abnormalities including anemia, lymphopenia, neutropenia, and thrombocytopenia.

B.1 Platelet counts increased with baricitinib by Week 4 and remained elevated throughout treatment; however, there were no AEs related to increased platelets [34, 37]. Changes in hemoglobin, lymphocyte, and neutrophil counts were uncommon and mild or moderate in severity. No patients discontinued treatment with baricitinib due to changes in hematologic laboratory test results [37].

B.2 A dose-dependent decrease in median platelet count was observed by Week 4 after abrocitinib initiation and then subsequently increased and plateaued by Week 12, and levels remained below baseline values thereafter [35]. Only two patients (0.1%) receiving abrocitinib met discontinuation criteria for thrombocytopenia, both in the 200 mg group, and neither had a bleeding-related event. Abrocitinib was not associated with any significant changes in hemoglobin, lymphocyte, or neutrophil counts [35]. Four patients in the abrocitinib 200 mg group discontinued treatment due to lymphopenia; these events occurred in older patients (aged ≥ 65 years) with three of four events occurring during the first 4 weeks of treatment [35].

B.3 Upadacitinib was associated with dose-dependent increases in rates of anemia, neutropenia, and lymphopenia [36]. Grade 3 events were reported for anemia (≤ 0.3%), neutropenia (≤ 1.5%), and lymphopenia (≤ 1.0%), while Grade 4 neutropenia occurred in two patients (0.2%) in the 30 mg group. Most neutropenia events occurred during the first 16 weeks of upadacitinib exposure, whereas mean lymphocyte levels initially increased before returning to baseline with continued treatment. Few patients discontinued treatment because of cytopenias [36].

The available data suggest that hematologic changes observed with baricitinib, abrocitinib, and upadacitinib in patients with AD were generally mild and/or not clinically meaningful and not associated with cellular dysfunction that would potentially increase the risk of infections. Most hematologic changes occurred early after treatment initiation, generally resolved over time, infrequently led to treatment discontinuation, and were not associated with AEs including infections [35–37].

C. Hepatobiliary

C.1 In pooled analyses of safety data from AD clinical trials, no or very few clinically meaningful changes in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels were observed with baricitinib [34, 37]. Overall, treatment with baricitinib was associated with a small dose-dependent increase in ALT levels, but rates were similar to placebo [34, 37]; most cases of elevated transaminases were transient and asymptomatic, with no relation to liver injury [37].

C.2 While there were no clinically meaningful changes in ALT over time with abrocitinib and no associations between changes in liver

enzyme levels and hepatic-related AEs, there was a low incidence of ALT > 3 times the upper limit of normal in all study arms (0.5% for each of abrocitinib 100 mg and 200 mg relative to 1.5% for placebo) [35, 46].

C.3 Dose-dependent elevations in ALT and AST were observed with upadacitinib [36]. Most of these AEs were transient and mild or moderate in severity; Grade 2 events (defined as ≥ 3 times the upper limit of normal) were uncommon overall (≤ 1.4% for increased ALT and ≤ 1.2% for increased AST vs. 1.1% and 0.9%, respectively, for placebo) [19]. No hepatic abnormalities were considered serious and treatment discontinuations due to these events were rare (≤ 0.4 per 100 PY).

Although the clinical risk associated with elevated liver enzymes is hepatic injury, there was no association observed between changes in liver enzyme tests and hepatic-related AEs in the AD clinical trials for baricitinib, abrocitinib, or upadacitinib [34–37].

D. Creatine Phosphokinase

D.1 JAK inhibition has been associated with increases in creatine phosphokinase (CPK) levels [47]. A preclinical study suggests that this effect may be related to reversal of inflammation-associated inhibition of myoblast differentiation [48], but other studies suggest that CPK is inversely associated with systemic inflammatory markers in the general population [49]. The relationship between CPK and inflammation, and its clinical implications, has yet to be confirmed.

In the integrated safety analyses from AD clinical trials for baricitinib, abrocitinib, and upadacitinib, increased CPK was the most common laboratory-related AE and occurred in a dose-dependent manner with each agent [34–36].

D.2 Most cases of increases in CPK levels occurred early during treatment and were transient, asymptomatic, and nonserious and infrequently led to treatment discontinuation.

There were no rhabdomyolysis events reported with baricitinib [34] or abrocitinib [35]. One rhabdomyolysis event was reported with upadacitinib in a 23-year-old male patient; the event resolved after intravenous hydration, and the investigators considered there to be a reasonable possibility that it was etiologically related to upadacitinib [36]. Other than this single case, there was no apparent clinical consequence of elevations in CPK levels.

An Approach to Monitoring and Management of Oral JAKi-Associated Laboratory AEs and Other Safety Concerns in Patients with AD

Based on the above synthesis of the evidence and informed opinion of the authors, six best practice statements related to fundamental standards of care were proposed (Table 3). Four additional consensus recommendations were proposed and level of agreement was ascertained (Table 4). Overall, there was a high level of agreement (i.e., ≥ 90) for three of four proposed recommendations for laboratory monitoring of AD patients receiving oral JAKi in the clinical setting.

DISCUSSION

There is an accumulating body of evidence supporting the safety of oral JAKi in the treatment of AD [29, 34–36, 39]. Nonetheless, the respective product labels of the three currently approved oral JAKi for the treatment of moderate-to-severe AD recommend laboratory assessments prior to initiating treatment and after 4–12 weeks of treatment initiation and then according to routine patient management thereafter [11–19]. These recommendations are based on evidence from clinical trials across all indications for oral JAKi, and they may not be representative of the moderate-to-severe AD patients routinely seen in clinical practice. Therefore, a practical set of suggestions on the approach to monitoring laboratory-related AEs was proposed based on a thorough review of the available evidence from clinical trials including their long-term extensions, risk stratification, and informed opinion. Six best practice statements related to standards of care were suggested, and four additional recommendations were voted on by a panel of dermatologists with clinical and

research expertise with oral JAKi for treating AD to ascertain the level of support for each of these recommendations.

The statement with the lowest level of agreement and the widest spread was related to ongoing laboratory monitoring (median level of agreement, 80 [range 59–100]). This could reflect individual dermatologists' level of comfort with monitoring and managing laboratory-related AEs and the evolving evidence base on the long-term safety of oral JAKi in AD. To date, the longest published follow-up of AD patients treated with an oral JAKi was reported by Bieber et al. (2023) [34]. In their integrated safety analysis of eight randomized controlled trials (RCTs), the median duration of treatment with abrocitinib was 1.6 years with some patients having over 3.5 years of continuous exposure. Changes in laboratory parameters, including LDL-C, HDL-C, platelets, lymphocytes, neutrophils, and ALT, generally occurred during the first 4 to 8 weeks of treatment and then stabilized thereafter out to 120 weeks. Although these observations are derived from mean changes in the study population and not individual-level data, it is reassuring that there were no changes of clinical relevance over > 2 years of continuous treatment. The probability of a causal association between an oral JAKi and a de novo laboratory-related AE after 12 or more months of treatment is extremely small; however, dermatologists should use their clinical judgement in the context of an individual patient as well as regional standards of practice to guide their decisions related to ongoing laboratory monitoring.

Oral JAKi are small molecules, and, as such, they are associated with a potential for drug-drug interactions. As a part of appropriate patient selection and good clinical practice, dermatologists should consider the concomitant medications an individual patient is taking when prescribing an oral JAKi. The three available oral JAKis for the treatment of moderate-to-severe AD differ in their drug metabolism and thus potential for cytochrome P450 (CYP)-mediated drug interactions (Table 1) [13, 14, 17]; dermatologists should therefore consult the respective product labels for each

Table 3 Best practice statements related to fundamental standards of care

Recommendation statement
1. The primary care physician as well as the patient should be informed of the potential risks associated with oral Janus kinase inhibitor (JAKi) treatment in atopic dermatitis (AD)
2. Baseline assessment of laboratory parameters, specifically a complete blood count (CBC), including absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelets, and hemoglobin (Hgb); lipids, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides; alanine aminotransferase (ALT); and renal function (to guide dose selection) should be conducted prior to initiating oral JAKi treatment in patients with AD
3. Repeat laboratory parameters (CBC, lipids, and ALT) between Weeks 8 and 12 will identify the majority of AD patients who are susceptible to drug-related adverse events from oral JAKi treatment
4. Patients with AD receiving oral JAKi treatment with documented hematologic, lipid, and/or hepatic abnormalities should be managed according to current regional standards and with dose adjustment as recommended in the respective product labels
5. End-organ toxicity is unlikely to occur with chronic administration of oral JAKi in patients with AD without pre-existing end-organ disease
6. Changes in laboratory parameters in patients with AD receiving oral JAKi treatment are independent of age and gender

AD atopic dermatitis, *ALC* absolute lymphocyte count, *ALT* alanine aminotransferase, *ANC* absolute neutrophil count, *CBC* complete blood count, *HDL-C* high-density lipoprotein cholesterol, *JAKi* Janus kinase inhibitor, *LDL-C* low-density lipoprotein cholesterol

Table 4 Consensus recommendations and level of agreement

Recommendation statement	Median level of agreement	Range (mininum, maximum)
1. Routine assessment and monitoring of creatine phosphokinase (CPK) levels in patients with atopic dermatitis (AD) receiving oral Janus kinase inhibitor (JAKi) treatment is not recommended	100	90, 100
2. Unless observed changes in laboratory values between baseline and Weeks 8 and 12 are clinically meaningful, ongoing laboratory monitoring of patients with AD receiving oral JAKi treatment is generally unnecessary	80	59, 100
3. Dose reduction or switching oral JAKi treatment for patients with AD in response to meaningfully altered lipid levels may result in improvement in lipid levels	90	75, 100
4. In patients with AD receiving oral JAKi treatment, profound changes in laboratory parameters that reverse upon treatment discontinuation are likely to recur on treatment re-initiation; therefore, alternative treatment options, including an oral JAKi that does not result in the same risk profile or treatments other than oral JAKi, might be considered	97	80, 100

AD atopic dermatitis, *CPK* creatine phosphokinase, *JAKi* Janus kinase inhibitor

agent and concomitant medications when prescribing. Notably, multiple CYP enzymes are involved in the metabolism of abrocitinib; its dose should be reduced by half in patients concomitantly receiving strong inhibitors of CYP2C19 (e.g., fluconazole; fluvoxamine; fluoxetine) or moderate inhibitors of CYP2C9 (e.g., amiodarone; fluconazole), and it should be avoided in patients who are taking strong inducers of CYP enzymes (e.g., rifampin) [14]. In contrast, baricitinib and upadacitinib are minimally metabolized by CYP34A (10% and 34%, respectively) [11, 17]. Beyond drug interactions, there is also the theoretical potential for additive adverse effects on laboratory parameters. Therefore, prescribers should consult the respective product labels of concomitantly prescribed medications and consider their propensity for causing abnormalities in hematologic parameters, lipid profile, as well as liver enzyme and CPK levels when co-prescribing oral JAKi.

To our knowledge, this is the first set of practical consensus recommendations on the laboratory monitoring of patients receiving oral JAKi for the treatment of moderate-to-severe AD. Strengths include the practical and non-prescriptive nature of the recommendations that are informed by the available evidence from RCTs, physiologic plausibility, and risk stratification and informed opinion of a panel of dermatologists with clinical and research expertise in the use of oral JAKi in patients with AD. Unlike formal guidelines [50], our approach allows for flexibility such that final decisions are made between the clinician and patient. Our approach has limitations including the inclusion of clinical trial data only, which captures a limited duration of treatment, and the inability to account for individual clinical situations and the exclusion of real-world evidence, which also plays a role in informing clinical management decisions.

CONCLUSIONS

Oral JAKi have emerged as an important addition to the management of moderate-to-severe AD. As with any medication, appropriate patient selection and laboratory assessment is an important strategy to mitigate the potential risks associated with oral JAKi when treating AD. This set of practical recommendations offers an approach to laboratory monitoring in AD

patients receiving oral JAKi based on a synthesis of the available evidence, risk stratification, and informed opinion. As oral JAKi are integrated into the clinical management of moderate-to-severe AD, expanding experience and comfort in monitoring and managing laboratory-related AEs will increase.

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Declarations

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