ORIGINAL ARTICLE

Bringing the Treatment of Atopic Eczema Into a New Era with Janus Kinase Inhibitors: A Position Statement By the Persatuan Dermatologi Malaysia

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Abstract

Atopic eczema (AE) is a complex, chronic and recurrent inflammatory pruritic skin condition that impacts the quality of life and exerts an economic toll on patients and their families. One of the factors contributing to AE is the immune dysregulation of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) inflammatory pathway. This has prompted the conduct of various large clinical trial programs to evaluate the efficacy and safety of Janus kinase inhibitors (JAK-i) for AE. The overall and significant benefit of these drugs from clinical studies resulted in regulatory approvals for JAK-i to treat moderate-to-severe atopic eczema. The objective of this position paper was to evaluate the safety, efficacy and role of upadacitinib, baricitinib and abrocitinib in managing AE and update the current recommended treatment algorithm within the 2018 Malaysian Clinical Practice Guidelines for the Management of Atopic Eczema. The Persatuan Dermatologi Malaysia recommends that these JAK-i can be considered as an option for systemic therapy in severe AE.

Key Words: *Atopic dermatitis, JAK-i, Recommendations*

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Introduction

Atopic eczema (AE), also known as atopic dermatitis, is a complex, chronic and recurrent inflammatory pruritic skin condition that develops in early childhood and can persist into adulthood.

The global prevalence of AE ranges between 15-30% in children[1,2] and 2-10% in adults.[1] In

Malaysia, the prevalence of AE has not been well studied. Malaysia participated in the International Study of Asthma and Allergies in Childhood (ISAAC). The prevalence of childhood AE in 1996 in the 6-7 year and 13–14 year age groups increased from 9.5% and 8.9% in 1996 to 12.6% and 9.9% in 2006, respectively.[3] A more recent cross-sectional survey by Goh YY, *et* al. involving 384 children aged 1-6 years old attending kindergarten in Kuala Lumpur revealed eczema in 13.4%.[4] In a retrospective, cross-sectional study conducted in the Department of Dermatology, Hospital Kuala Lumpur, from the 1st January 2008 to 31st December 2014, eczema was the most common disease (39.07%) treated in the skin clinic, of which 6.9% were AE.[5]

AE, particularly in those with moderate-to-severe disease, significantly impacts the patient's and their family's quality of life (QoL).[2,6-8] The symptoms of AE are significantly associated with the severity of disease. AE symptoms lead to sleep disturbance, anxiety, depression and embarrassment in children and adults.[6,8] The effects of AE on children extend beyond the short-term and have been associated with an increased risk of developing psychosocial, cognitive and functional impairment and behavioural problems.[2] A more recent study demonstrated an increased risk in children with allergic disorders developing attention deficit hyperactivity disorders or autism spectrum disorder.[9]

AE incurs a hefty financial burden on the families of children with AE and adult patients. The direct cost of AE is estimated to range from USD199-USD743[10] and €2242 to €6924.[7] Indirect cost including loss of work and productivity ranges from €7277 to €14,236 in adult AE patients.[7]

The Malaysian Clinical Practice Guideline (CPG) for the management of AE was published in 2018. The objectives are to guide the correct and early diagnosis, and outline effective and safe treatments for AE.[11] It contains evidence-based recommendations for the diagnosis, severity assessment, investigations, and available therapy for AE. The Janus kinase inhibitors (JAK-i), which are small molecule agents for targeted therapy, have been available for use in various diseases such as rheumatoid arthritis and psoriatic arthritis. These drugs have recently been approved by the Ministry of Health, Malaysia for treating moderate-to-severe AE. Baricitinib was approved for moderate-to-severe AE in adults in September 2021,[12] and upadacitinib in adults and adolescents aged 12 years and above in May 2022.[13]

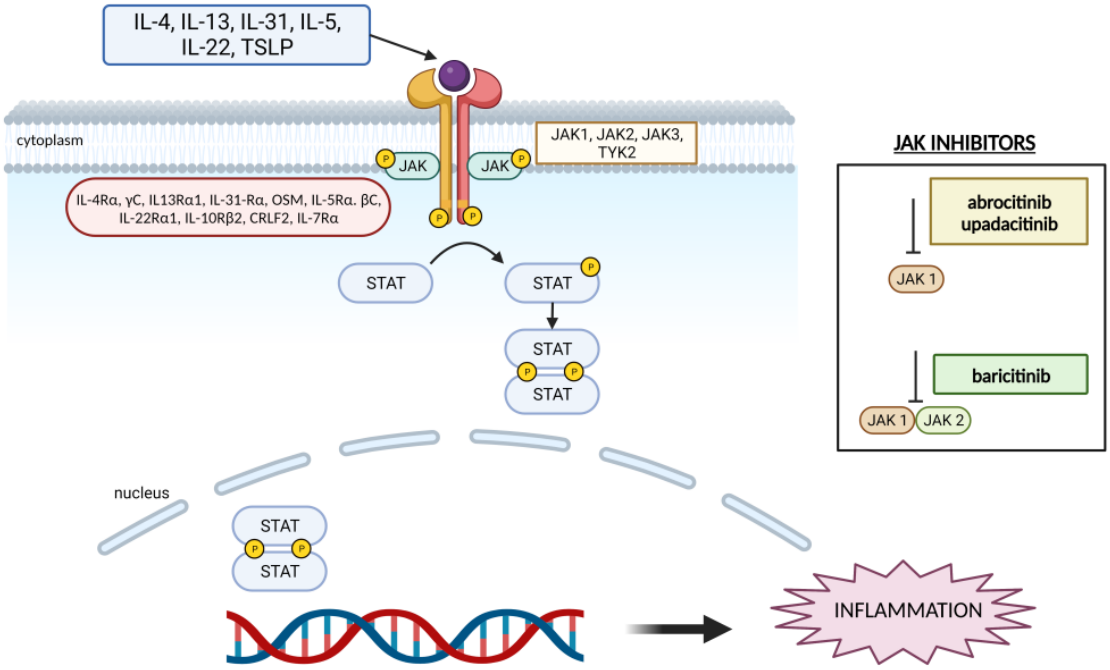
The recent (September 2022) EuroGuiDerm Guideline on Atopic Eczema recommends JAK-i for AE patients who are candidates for systemic treatment.[14] In Asia, the 2021 Japanese guidelines for atopic dermatitis (ADGL) and 2022 Taiwan guidelines for the diagnosis and management of paediatric atopic dermatitis recommend JAK-i as a treatment option for severe AE.[15,16] Hence, the primary objective of this paper is to revisit and update the current AE treatment recommendations with regard to the position of JAK-i for treating AE within the Malaysian context. We examine the role of the Janus kinase (JAK) enzyme in AE pathophysiology and the mechanism of action, safety and efficacy of JAK-i for this purpose.

The role of JAK enzymes in AE

The various pathophysiological factors contributing to AE development are complex and include skin barrier dysfunction, immune dysfunction and altered cutaneous microbiome.[17]

The JAK enzymes constituting JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) are a class of cytoplasmic tyrosine kinases. The skin barrier dysfunction activates T-helper cells (T_H) resulting in different cytokine expressions. After binding to their receptor, these cytokines activate the JAK-STAT signalling pathway to mediate their cytokine response. This contributes to the inflammatory cascade leading to AE. (Figure 1).[18,19]

Figure 1. JAKs attach to the intracellular sections of the cytokine receptor chains to produce functional signalling complexes and regulate the inflammatory process through activating the intracytoplasmic transcription factors (STATS). These STATs move into the nucleus and regulate downstream inflammatory mediators



CRLF2, cytokine receptor-like factor 2; IL, interleukin; JAK, Janus kinase; OSM; oncostatin M; STAT, signal transducer and activator of transcription; TSLP, thymic stromal lymphopoietin; TYK2, tyrosine kinase 2. Adapted from Chovatiya R, et al. J Allergy Clin Immunol 2021.[19]

The mechanism of action of JAK-i in AE

JAK-i are small molecule compounds that target AE-associated cytokine-mediated inflammatory pathways. By inhibiting the JAK enzymes selectively and reversibly, they allow for a targeted approach to treating AE. The three JAK-i currently available for AE are indicated for treating moderate-to-severe disease. Abrocitinib and upadacitinib inhibit JAK1, whilst Baricitinib inhibits both JAK1 and JAK2 enzymes (Figure 1). The inhibition of JAK-dependent cytokines (e.g., interleukin [IL]-6 and IL-31) reduces the inflammation and itch in AE, while the inhibition of the JAK2 appears to reduce the pathological changes.[18,20]

Efficacy and safety of JAK-i in treating AE

Efficacy outcomes compared to placebo

Among the three JAK-i available for treating AE, the BREEZE-AD clinical programme for baricitinib has the most extensive number of clinical trials (BREEZE-AD 1-7). However, all the studies were placebo-controlled. The landmark trials for baricitinib are BREEZE-AD 1 and 2,[21] while BREEZE-7[22] investigated its efficacy in combination with topical corticosteroid (TCS).

The study population involved in the BREEZE-AD were patients aged ≥18 years, who had a diagnosis of AE for ≥12 months before screening and a documented history of an inadequate response to topical therapies and failure to systemic immunosuppressants.[23] Eczema Area and Severity Index (EASI) score of ≥16, a validated Investigator's Global Assessment (vIGA) score of ≥3 and ≥10% body surface area (BSA) involvement were other inclusion criteria. Some important exclusion criteria were a history of eczema herpeticum a year before screening or ≥2 prior episodes of eczema herpeticum and current or recent serious infections, including herpes zoster and tuberculosis (TB).[23]

Upadacitinib (MEASURE UP) and abrocitinib (JADE) efficacy trials were similar. They involved patients who were ≥12 years old with a body weight of ≥40 kg and were placebo-controlled. These trials' inclusion and exclusion criteria were similar to the BREEZE-AD.[24,25] Like in BREEZE-AD 7, the abrocitinib trial involving adolescents (JADE TEEN)[26] investigated its efficacy on a background of TCS use.

The trials all had a fair representation of the Asian population with 20-30% of the total subjects in each treatment and placebo arm. Significantly more patients in the treatment arms for all agents achieved vIGA (0,1) and EASI 75 compared to placebo (Tables 1-3). The efficacies were dose-dependent, with higher doses and concomitant use of TCS eliciting better outcomes.

Table 1. Baricitinib vs placebo efficacy outcomes

Study (Total subjects)	Parameters	Proportion of patients achieving outcomes at 16 weeks (%)		
		Baricitinib 4 mg	Baricitinib 2 mg	Placebo
BREEZE-AD1[21] (N=624)	vIGA (0,1)	16.8***	11.4*	4.8
	EASI 75	24.8***	18.7**	8.8
	Itch NRS	21.5***	12.0	7.2
BREEZE-AD2[21] (N=615)	vIGA (0,1)	13.8***	10.6*	4.5
	EASI 75	21.1***	17.9***	6.1
	Itch NRS	18.7***	15.1**	4.7
BREEZE-AD7[22] (N=329)	vIGA (0,1)	31	24	15
	EASI 75	48***	43	23
	Itch NRS	44***	38	20

*Significance compared with placebo: *P≤0.05; **P≤0.01; ***P≤0.001. The primary outcome was the proportion of patients achieving vIGA (0,1) with 4 mg and 2 mg baricitinib at 16 weeks, and those achieving EASI 75 and Itch NRS were secondary outcomes. Itch NRS referred to patient-rated improvement in itch with a change of ≥4 points.*
BREEZE-AD 7 allowed concomitant TCS during the study, and BREEZE-AD 1,2 allowed TCS as rescue treatment only.
EASI 75, 75% improvement from baseline Eczema Area and Severity Index; NRS, Numeric Rating Scale; TCS, topical corticosteroids; vIGA (0,1), validated Investigator's Global Assessment achieving clear or almost clear skin.

A network meta-analysis comparing the efficacies of targeted systemic therapies used in treating AE without the addition of topical corticosteroids and/or topical calcineurin was recently published.[27] It included phase 3 and 4 placebo- or active intervention-controlled studies involving JAK, interleukin-4 and interleukin-13 inhibitors in adults and adolescents with moderate to severe AE. Based on 11 clinical trials (N=6254), upadacitinib 30 mg daily demonstrated better and earlier efficacy, followed by abrocitinib 200 mg daily, upadacitinib 15 mg daily, abrocitinib 100 mg daily and baricitinib 4 mg daily. However, caution must be applied as network meta-analyses are susceptible to the methodological quality of the included studies, reporting biases and choices of study eligibility criteria and do not replace comparisons of multiple head-to-head RCTs.[27]

Table 2. Upadacitinib vs placebo efficacy outcomes

Study (Total subjects)	Parameters	Proportion of patients achieving outcomes at 16 weeks (%)		
		Upadacitinib 30 mg	Upadacitinib 15 mg	Placebo
MEASURE UP-1[28] (N=847)	vIGA (0,1)	62***	48***	8
	EASI 75	80***	70***	16
MEASURE UP-2[28] (N=836)	vIGA (0,1)	52***	39***	5
	EASI 75	73***	60***	13

*Significance compared with placebo: ***P≤0.001. The proportion of patients achieving vIGA (0,1) and EASI 75 were the co-primary outcomes for both studies. Concomitant TCS and other medicated topical therapy were prohibited, but rescue therapy was permitted from week 4.*
EASI 75, 75% improvement from baseline Eczema Area and Severity Index; TCS, topical corticosteroids; vIGA (0,1), validated Investigator's Global Assessment achieving clear or almost clear skin.

Table 3. Abrocitinib vs placebo efficacy outcomes

Study (Total subjects)	Parameters	Proportion of patients achieving outcomes at 16 weeks (%)		
		Abrocitinib 200 mg	Abrocitinib 100 mg	Placebo
JADE MONO-1[29] (N=387)	IGA (0,1)	44***	24*	8
	EASI 75	63***	40***	12
JADE MONO-2[30] (N=391)	IGA (0,1)	38.1***	28.4***	9.1
	EASI 75	61***	44.5***	10.4
JADE TEEN[26] (N=285)	IGA (0,1)	46.2**	41.6**	24.5
	EASI 75	72**	68.5**	41.5

*Significance compared with placebo: *P=0.0037; **P≤0.05; ***P≤0.001. The proportion of patients achieving vIGA (0,1) and EASI 75 were the co-primary outcomes for all studies.*
In the JADE-MONO 1,2, concomitant use of TCS and other medication topical medications were not allowed, and rescue medications were prohibited. In the JADE-TEEN study, standardised regimens of non-medicated and medicated topical therapy were required, and oral histamines were also permitted.
EASI 75, 75% improvement from baseline Eczema Area and Severity Index; TCS, topical corticosteroids; vIGA (0,1), validated Investigator's Global Assessment achieving clear or almost clear skin.

Head-to-head studies with dupilumab

Dupilumab is a human monoclonal immunoglobulin (Ig) G4 antibody that binds to IL-4Rα and inhibits IL-4 and IL-13 signalling. It

has been approved for the treatment of moderate to severe AE in adults and children aged 6 and above.[31]

Head-to-head comparison between JAK-i and dupilumab has been conducted with upadacitinib and abrocitinib.[32,33] Upadacitinib 30 mg daily and abrocitinib 200 mg daily had significantly better primary outcomes (EASI 75 for both and IGA for abrocitinib only) compared with dupilumab 300 mg every other week at week 12 and 16, respectively. The efficacy of abrocitinib 100 mg daily was comparable to dupilumab. Upadacitinib 30 mg and abrocitinib 200 mg demonstrated superiority for improving itch scores as early as the first (mean 31.4% vs 8.8%; $p<0.001$) and second week (difference from dupilumab 22.1%; $p<0.001$), respectively. A longer-term trial, JADE DARE, to determine the efficacy of abrocitinib 200 mg compared to dupilumab is ongoing (treatment duration – 26 weeks).[34]

Long-term efficacy

So far, baricitinib has the longest follow-up data for efficacy at 68 weeks from BREEZE-AD 3. The subjects were derived from the BREEZE-AD 1, 2 trials. The efficacy outcomes [vIGA (0,1), EASI 75 and Itch NRS] remained relatively stable in both responders and partial responders, indicating that baricitinib could be an option for long-term therapy for adult patients with moderate-to-severe AE.[35] Upadacitinib has demonstrated sustained efficacy up to 52 weeks from treatment initiation among the patients from the MEASURE UP 1, 2 studies.[36] The JADE REGIMEN trial evaluated the sustainability of abrocitinib-induced responses over 40 weeks. The primary outcome to determine the probability of a flare during the maintenance period was 18.9%, 42.6% and 80.9% with abrocitinib 200 mg, abrocitinib 100 mg and placebo, respectively.[37]

Safety outcomes

The three JAK-i available for treating AE have good safety and tolerability profiles. The most frequent treatment-emergent adverse events (TEAE) were mild to moderate in severity and included upper respiratory tract infections, nasopharyngitis, gastrointestinal symptoms (e.g., nausea, vomiting and diarrhoea) and headache.[21,28-30] The younger population in the upadacitinib and abrocitinib trials could explain the development of acne in up to 17% of patients.[28] The most frequent biochemical TEAE in all treatment arms was elevated plasma creatine phosphokinase (CPK).

The occurrences of TEAE of eczema herpeticum and herpes zoster were very low for all three JAK-i (none to two cases per study).[21,28-30] However, the proportion of patients developing TEAE of herpes simplex with baricitinib was slightly higher than in the placebo arms (range: 3.3%-7.2%) and was not dose-dependent.[21] There was no reactivation of TB reported in any of the trials. The rate of discontinuation of the drug due to adverse events was low in all studies.

Serious adverse events were uncommon and similar across the treatment and placebo arms in all studies. The serious adverse events were dose-independent and ranged from none to approximately 4%, except for baricitinib 1 mg in the BREEZE-AD2 (7.3%).

Baricitinib's long-term safety profile was derived based on a pooled safety analysis across its clinical programme and included the long-term extension studies (N=2531 with 2247 patient-years). The most common serious adverse events were eczema herpeticum (n=11; incidence rate 0.5), cellulitis and pneumonia.[38] Nasopharyngitis, headache, elevated CPK levels and diarrhoea were the most frequently reported TEAE.

Long-term (52 weeks) safety studies of upadacitinib revealed that treatment discontinuation due to TEAE was low overall. Both upadacitinib doses (15 mg and 30 mg) were well tolerated and did not demonstrate any new safety signals.[36]

Baseline investigations and monitoring

The recent EuroGuiDerm Guideline on Atopic Dermatitis (June 2022) recommends that

the same baseline screening and treatment monitoring investigations should be conducted for all JAK-i (Table 4).

Table 4. Baseline screening and monitoring for all JAK-i[14]

Baseline screening	Monitoring at 4 weeks after initiation and then 3-monthly while on treatment
• Full blood count • Renal and liver function tests • Fasting lipid profile • Serum creatine phosphokinase • Viral hepatitis and TB screening, including a chest radiograph	• Full blood count • Renal and liver function tests • Fasting lipid profile • Serum creatine phosphokinase

Precautions and contraindications

The JAK-i are contraindicated in patients with hypersensitivity to the active substance or any of its excipients and those with active TB or serious infections, severe hepatic impairment and pregnancy.[39-41] In case of latent TB or those with a high risk of TB infection, anti-TB therapy should be considered before starting these agents.

There is a dose-dependent increase in lipid parameters with JAK-i that can be monitored and controlled with statin therapy. If liver enzymes levels increase (alanine transaminase ≥5-times and aspartate transaminase ≥10-times the upper limit of normal) and drug-induced liver injury is suspected, the agents should be temporarily discontinued until liver injury is excluded.[41]

All three JAK-i have been associated with increased serum levels of creatine phosphokinase (CPK) in patients with inflammatory disorders but not in patients with myeloproliferative disease or healthy subjects treated for a limited duration.[42] Most patients do not report myalgia or other symptoms associated with CPK elevation. However, the exact mechanism of JAK-i-associated myalgias has not yet been fully elucidated.[43]

JAK-i should be used with caution in patients with risk factors for venous thromboembolism (e.g., older age, obesity and prior history of venous thromboembolic events) and discontinued if the patients exhibit any features of the condition. A recent meta-analysis of two large cohort studies and 15 RCTs (N=466 993) found no significant association of increased risk of venous thromboembolic events in AE patients treated with JAK-i.[44] Patients with diverticular disease should be prescribed baricitinib with caution.

Temporary discontinuation of these agents should be made if the absolute neutrophil count is <1 x 10^9 cells/L, absolute lymphocyte counts is <0.5 x 10^9 cells/L or haemoglobin is <8 g/dL. Treatment can be resumed once the levels reach above these values.

Women of childbearing age should use effective contraception during and for at least one week after stopping treatment.

The drug-drug interaction profiles relating to metabolization via the CYP450 enzymes also differ between JAK-i (Table 5).[45-47]

Table 5. Summary table for baricitinib, upadacitinib and abrocitinib

JAK-i	Target JAK	Dosing	Common adverse events
Baricitinib[21,41]	JAK 1 and JAK 2 (selective)	4 mg/day 2 mg/day if ≥75 years old or eGFR 30-60 ml/m^3	Nasopharyngitis, headache, increased blood CPK levels, URTI
Upadacitinib[†28,40]	JAK 1 more than JAK 2, JAK 3 or TYK2	15 mg/day Can be increased to 30 mg/day if necessary If ≥65 years old, 15 mg/day is recommended	Acne, URTI, nasopharyngitis, headache, increased CPK levels
Abrocitinib[‡30,39]	JAK 1 (selective)	100 mg/day Can be increased to 200 mg/day if necessary 50 mg/day is recommended if eGFR 30-60 ml/m^3	Nausea, nasopharyngitis, headache, URTI, acne, vomiting, upper abdominal pain, increased CPK levels, folliculitis, thrombocytopenia

CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; JAK, Janus kinase; JAK-i, Janus kinase inhibitors; TYK2, tyrosine kinase 2; URTI, upper respiratory tract infection.

Table 5. Summary of drug-drug interactions of the different JAK-i relating to CYP450 enzymes

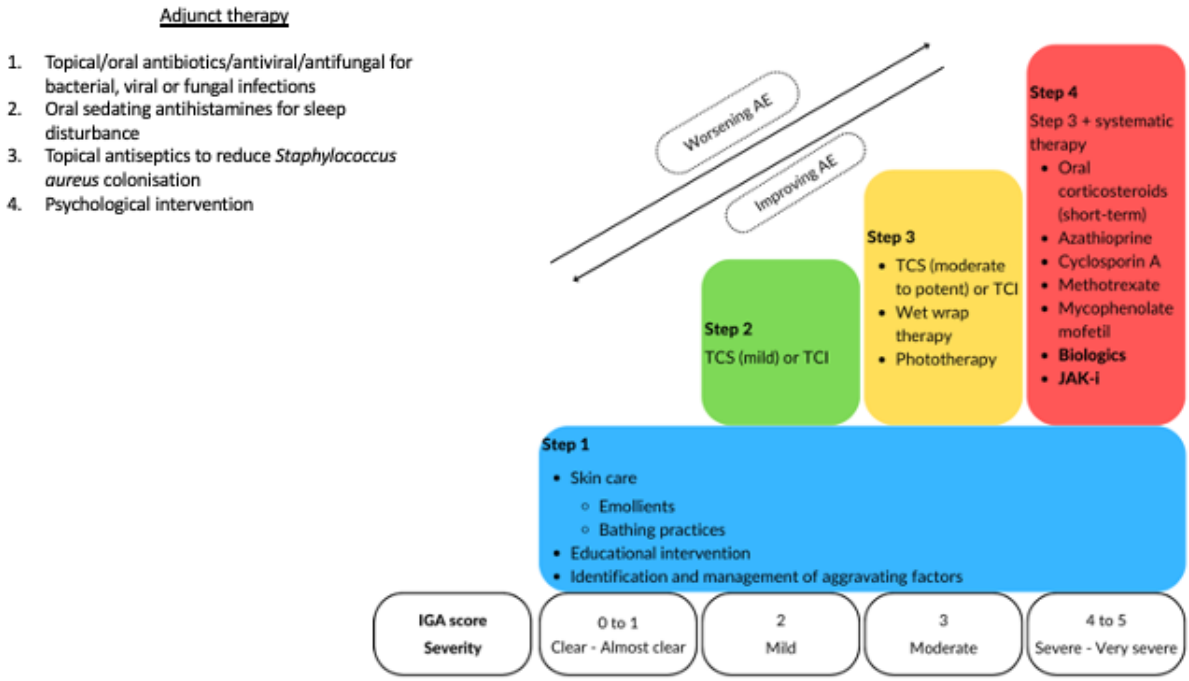
Interaction with CYP450 enzyme	Baricitnib[46]	Upadacitinib[45]	Abrocitinib[47]
Metabolization via CYP450 enzymes	<10% by CYP3A4	Mainly by CYP3A4	~53% by CYP2C19 ~30% by CYP2C9 ~11% by CYP3A4 ~6% by CYP2B6
Relevance for CYP450 drug interactions	None	Yes: CYP3A4 inducers or inhibitors can affect upadacitinib exposure	Yes: CYP2C19 and CYP2C9 inhibitors or inducers can affect abrocitinib exposure
Dosing considerations for CYP450 drug interactions		Upadacitinib 15 mg OD should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors (e.g. clarithromycin, erythromycin, diltiazem, verapamil, itraconazole, ketoconazole and ritonavir) Upadacitinib 30 mg OD dose is not recommended for patients with AE receiving chronic treatment with strong CYP3A4 inhibitors Food or drink containing grapefruit should be avoided during treatment with upadacitinib Patients should be monitored for changes in disease activity if upadacitinib is co-administered with strong CYP3A4 inducers	In patients receiving dual strong inhibitors of CYP2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone (e.g. fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended dose should be reduced by half to 100 mg or 50 mg once daily Treatment is not recommended concomitantly with moderate or strong inducers of CYP2C19/ CYP2C9 enzymes (e.g. rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin)

OD, once daily.

Important notice: As of September 1st 2021, and based on a review of a large, randomised safety clinical trial, the United States Food and Drug Administration (US FDA) requires a black box warning for all JAK-i for serious infections, malignancy and thrombosis. The US FDA concluded an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots and death with tofacitinib. This warning is to be extended to all JAK-i due to similar mechanisms of action.[47]

Updated AE treatment algorithm

Figure 2. The updated treatment algorithm for AE includes biologics and JAK-i. Biologics and JAK-i have been added as treatment options for severe to very severe AE. IGA, Investigators' Global Assessment; JAK-i, Janus kinase inhibitors; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors. Adapted from the Ministry of Health Malaysia, Persatuan Dermatology Malaysia. Clinical Practice Guidelines for the management of atopic eczema. 2018.[11]



Conclusion

After evaluating the data on the efficacy and safety of baricitinib, upadacitinib and abrocitinib, we recommend that JAK-i can be considered as an option for systemic therapy in severe AE. These newer agents are currently undergoing long-term extension studies, and thus, the recommendation may vary from time to time when more evidence arises.

Conflict of Interest Declaration

Dato' Dr Noor Zalmy Azizan has received honorarium for chairing meetings from Zuellig Pharma Therapeutics, Novartis and Eucerin. She is also the President of the Persatuan Dermatologi Malaysia (2020-2022), which is an unpaid position. Received drug samples from Zuellig Pharma Therapeutics and Abbvie.

Associate Professor Dr Adawiyah Jamil has received sponsorship for the Annual Dermatology Congress Malaysia 2022 from Zuellig Pharma Therapeutics and participated in an advisory board meeting by Boehringer Ingelheim.

Dr Chang Choong Chor has received drug samples from Zuellig Pharma Therapeutics.

Dr Dawn Ambrose, Dr Foong Boon Bee, Henry, Dr Rajalingam Ramalingam, Dr Sharifah Rosniza Binti Syed Nong Chek, Dr Sabeera Begum bt Kader Ibrahim and Dr Wong Hoi Ling have no conflict of interests to declare.

Dr How Kang Nien has received consulting fees from Boehringer Ingelheim and honoraria from Janssen, Beiersdorf and Zuellig Pharma Therapeutics. He has also received support for meeting attendance from Novartis, and is an Executive Committee Member in the Persatuan Dermatologi Malaysia.

Dr Tan Wooi Chiang has participated in advisory board meetings for Zuellig Pharma Therapeutics and Pfizer. He is also the vice president of the Persatuan Dermatologi Malaysia (2022-2024).

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