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REVIEW ARTICLE

Updated consensus guidelines for management of moderate-to-severe atopic dermatitis in Singapore: Integrating biologics, Janus kinase inhibitors and conventional therapies

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ABSTRACT

Introduction: Since 2016, several therapies have been approved for treating atopic dermatitis (AD) in Singapore, including biologics, oral Janus kinase (JAK) inhibitors and topical crisaborole. This study supplements the 2016 Singapore treatment guidelines for AD, focusing on newer therapies for moderate-to-severe disease, while revisiting older treatment regimens to accommodate changes in knowledge and practice.

Method: A modified Delphi panel was held, led by 2 co-chairs. The voting expert panel consisted of 12 dermatologists experienced in managing AD in Singapore. Delphi survey rounds were conducted between 24 July and 27 October 2023. Panellists indicated their agreement with drafted statements using a 5-point Likert scale. Consensus was defined as ≥80% agreement. An expert meeting was held to facilitate the consensus process between rounds 1 and 2 of voting.

Results: All expert panellists participated in both survey rounds, with a 100% response rate. Thirty-nine statements, classified into general principles, conventional treatments, biologics and JAK inhibitors, were proposed. Of these, 27 statements reached consensus at the end of round 1. After the expert meeting, 17 statements were included in round 2, of which 16 statements reached consensus. One statement did not reach consensus. Key updates are the inclusion of dupilumab and JAK inhibitors as potential first-line treatments for moderate-to-severe AD, in certain populations.

Conclusion: This modified Delphi study generated consensus among Singapore dermatology experts, to update treatment guidelines in moderate-to-severe atopic dermatitis. The consensus statements developed are intended to supplement the 2016 Singapore treatment guidelines for AD. Further revisions may be required when new evidence and/or treatments become available.

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Keywords: biologics, calcineurin inhibitors, corticosteroids, eczema, Janus kinase inhibitors, phosphodiesterase-4 inhibitors

CLINICAL IMPACT

What is New

- This updated treatment guideline for moderate-to-severe atopic dermatitis (AD) is based on consensus statements generated via a modified Delphi panel of dermatologists in Singapore.

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- The statements address newer approved treatments such as biologics and oral Janus kinase (JAK) inhibitors, while revisiting older therapies to accommodate changes in knowledge and practice.

Clinical Implications

- The consensus statements are intended to supplement the 2016 Singapore treatment guideline for AD.
- Dupilumab and JAK inhibitors have been included as potential first-line treatments for moderate-to-severe AD in certain populations.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by dry skin, localised red scaly patches, intense itching and skin pain.[1-4] Although its onset most commonly occurs before the age of 5, AD can develop during later childhood, adolescence or adulthood.[1-3] Recurrence can also follow extended periods of remission.[1-3] A 2018 community-based cross-sectional survey confirmed a high AD prevalence of 13.1% in Singapore (20.6% in children aged ≤18 years; 11.1% in adults).[5] Heat, dust and physical exercise were the most common aggravating factors.[5]

In the 2021 Global Burden of Disease study, AD was ranked first among skin diseases in terms of burden measured by disability-adjusted life years.[6] Among children and adults in Singapore, a significantly higher proportion of AD patients (89%) reported suboptimal quality of life (QoL), measured using the EQ-5D visual analogue scale, compared to those without AD (77.4%).[5]

Several treatment options can alleviate the symptoms of AD and improve QoL.[7] In the 2016 guidelines developed by the Dermatological Society of Singapore (DSS), treatment strategies are tailored to the severity of AD.[8] In general, patients are advised to moisturise their skin with emollients and are prescribed topical anti-inflammatory therapies such as corticosteroids or topical calcineurin inhibitors (TCIs).[8] For severe disease, more potent topical corticosteroids, phototherapy and systemic therapy can be considered.[8] Individualised therapy,[4] in combination with patient education, is key to achieving good outcomes.[8]

Since 2016, several new therapies have been approved for the treatment of AD in Singapore, including biologics (e.g. dupilumab) in 2019,[9-11] as well as oral Janus kinase (JAK) inhibitors (e.g. abrocitinib,[12,13] baricitinib,[14,15] upadacitinib[16,17]) and crisaborole ointment in 2022.[18,19]

The objective of this study was to supplement the 2016 Singapore treatment guidelines for AD, focusing on the newer therapies for moderate-to-severe AD, while revisiting older treatment regimens to reflect any changes in current practice. A modified Delphi panel method—a technique widely used in health services research to generate consensus[20]—was employed as it offers a systematic, robust and reproducible methodology for developing consensus statements via iterative rounds of anonymised voting.[21,22]

METHOD

This guideline update was initiated by the DSS, led by 2 co-chairs (YWY and HYL), who provided subject matter expertise in developing consensus statements for voting by an expert panel. Costello Medical, a third-party healthcare consultancy, generated evidence to inform statements by completing a targeted literature review and coordinated anonymised voting on consensus statements by the expert panel, ensuring that all experts were blinded from each other's inputs.

Recruited panellists were practising dermatologists in Singapore with expertise and interest in managing AD in adults and/or children, as demonstrated by authorship of AD publications (including the previous 2016 AD guidelines), participation in advisory boards or as invited speakers on relevant topics, experience as primary or site investigators for AD trials/research studies, and extensive senior consultant experience at specialist clinics, including eczema clinics at hospitals in Singapore. Additionally, recruitment aimed to ensure representation from both the public restructured healthcare institutions and the private sector. To avoid bias, the co-chairs did not participate in voting on consensus statements during the Delphi rounds. All participating experts are authors of this guideline.

Targeted literature review

Key recommendations from the 2016 Singapore AD treatment guidelines were summarised.[8] The reference list for the Global Guidelines in Dermatology Mapping Project (GUIDEMAP) systematic literature review (SLR) publication was hand-searched to identify international AD guidelines published between 1 April 2016 and 1 April 2021.[23] Additional supplementary Google searches were performed to identify guidelines published after 1 April 2021 up to 10 April 2023. Google was used because some treatment guidelines published in grey literature (e.g. medical society websites) may not be indexed in medical literature databases like MEDLINE.

Identified guidelines were assessed for relevance based on the population of interest being patients

with moderate-to-severe AD, discussion of new therapies such as JAK inhibitors, biologics and topical crisaborole, and inclusion of treatment recommendations outside of the 2016 Singapore guidelines. Consensus statements were drafted based on the outputs of the targeted literature review and finalised with feedback from the co-chairs.

Modified Delphi process

The Delphi technique refers to a structured method for consensus generation, characterised by its iterative process, allowing the incorporation of controlled feedback, with participant anonymity, to avoid social pressure to conform to a dominant view.[24, 25]

Delphi survey rounds were conducted between 24 July 2023 and 27 October 2023, using an online survey platform that maintained anonymity. During each survey round, panellists indicated their agreement with each statement on a 5-point Likert scale (strongly disagree; disagree; neutral; agree; strongly agree).[26] In addition, free text boxes allowed for qualitative feedback and comments, which were used to inform revisions or the formulation of additional statements. An a priori consensus threshold of ≥80% agreement (selection of "strongly agree"/"agree") or disagreement (selection of "strongly disagree"/"disagree") among the expert panel was defined.

An expert meeting was convened following the circulation of results from round 1. The meeting allowed for the exchange of clinical opinions, insights and knowledge to support the reformulation of statements that did not reach consensus. During the expert meeting, panellists were advised to prioritise the best available treatment approaches, without being influenced by cost considerations, given that subsidy status in Singapore may change over time.

Revisions of non-consensus statements and the formulation of additional statements were conducted under the guidance of the co-chairs, based on the discussions during the expert meeting. Panellists then voted on the updated statements in round 2 of the Delphi survey. All voting took place via online surveys under standard Delphi conditions of participant anonymity.[24] Statements that did not reach consensus in round 2 were excluded from the final guideline supplement.

RESULTS

Targeted literature review

A total of 54 AD guidelines were identified from the literature search. Prioritisation strategies were implemented to identify the most relevant guidelines for the Singapore context. Guidelines not in the English language (n=8) and with Appraisal of Guidelines for Research & Evaluation (AGREE) II average scores <5, as reported in the GUIDEMAP SLR, were deprioritised (n=21).[27] Additionally, only the most recent guideline from each country was included (n=4 excluded). For guidelines identified via supplementary Google searches, documents from lower-income countries (based on the World Bank categorisation of economies)[28] were deprioritised (n=3).

In total, 18 guidelines were included and reviewed (Supplementary Fig. S1). Data extraction focused on divergences from the 2016 Singapore guidelines, identifying 4 broad categories of treatment: new systemic, new topical, older systemic and older topical therapies. Where reported, the patient indication for each treatment, the recommendation (recommended, not recommended, unclear), and the level of evidence supporting the statements were extracted, in order to identify gaps that formed the basis for the development of consensus statements for voting in round 1 of the Delphi survey.

Delphi survey

The voting expert panel consisted of 12 experts, 58% (n=7) of whom practised primarily in public healthcare settings, with the remaining 42% (n=5) practising in private healthcare. The majority (58%, n=7) had an even mix of adult and paediatric patients, with 4 panellists who treated adults more often and 1 panellist who mostly treated children. The expert panel included members with subspecialty interests in paediatric dermatology (n=4), immunodermatology (n=4), inpatient dermatology (n=3) and photodermatology (n=1). All panellists participated in both survey rounds with no missing responses.

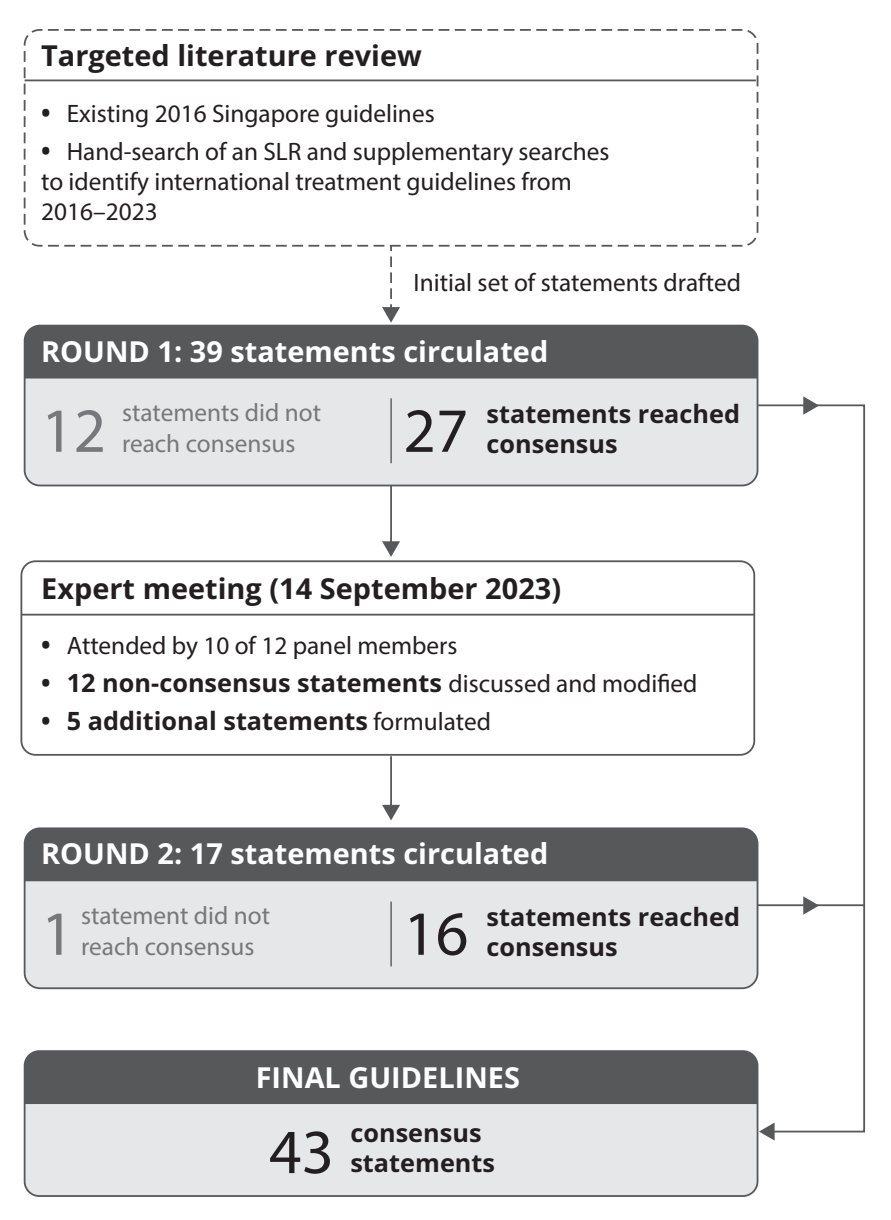
The virtual expert meeting was attended by 10 of 12 experts. While 2 individuals were unable to attend due to scheduling conflicts, all panellists were invited to comment over email and minutes were circulated post-meeting to collect any further feedback.

Fig. 1 summarises the results of the modified Delphi panel. There were 39 statements initially proposed, classified into general principles, conventional treatments, biologics and JAK inhibitors. Of these, 27 statements reached consensus at the end of round 1. After the expert meeting, 17 statements were included in the round 2 survey, of which 16 statements reached consensus. A full illustration of the evolution of the consensus statements in the Delphi rounds, alongside voting results, is available in Supplementary Table S1.

General principles

Table 1 summarises the consensus statements under general principles for the management of AD.

Fig. 1. Summary of results of the modified Delphi panel.



SLR: systematic literature review

Disease assessment

It is recommended to assess disease severity based on objective clinical signs, symptom severity and QoL impact. Outcome measures, such as the SCORing Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI),[29,30] may be useful for monitoring disease and guiding therapy.

Treatment goals

The establishment of disease control, minimisation of symptoms and reduction of QoL impact are key goals of AD treatment. Initial targets to measure treatment response are SCORAD-50, EASI-50, a ≥4-point reduction of Dermatology Life Quality Index (DLQI),[31] a ≥3-point reduction of Itch Numeric Rating Scale (NRS) or a ≥4-point reduction of Patient Oriented Eczema Measure (POEM) within 3 months of treatment initiation.[32,33] While not part of the consensus statement, the Investigator's Global Assessment (IGA) scale score is another possible tool to assess treatment success,[34] as noted by some panellists.

Treatment approach

A collaborative approach between patients, caregivers and healthcare providers is essential.

Table 1. Consensus statements on general principles of moderate-to-severe atopic dermatitis treatment.

No.	Statement	Voting results (% of panellists)
1	An assessment of AD disease severity should be performed. This assessment should encompass objective clinical signs, as well as the severity of symptoms and the impact of AD on the patient's quality of life.	83% Strongly agree 17% Agree
2	In addition to a dermatological examination, outcome measures such as SCORAD, EASI, DLQI, NRS and POEM complement the assessment, and are useful for monitoring disease activity and impact, as well as to guide overall therapy.	42% Strongly agree 58% Agree
3	The goal of AD treatment is to establish disease control, minimise symptoms and reduce impact on patients' quality of life.	92% Strongly agree 8% Disagree
4	Useful initial targets to measure treatment response among moderate-to-severe AD patients include achieving a 50% reduction of SCORAD points (SCORAD-50), achieving a 50% reduction of EASI points (EASI-50), a reduction of DLQI by at least 4 points, a reduction of NRS by at least 3 points or a reduction of POEM by at least 4 points within 3 months of treatment initiation.	83% Agree 17% Neutral
5	A collaborative approach involving shared decision-making among patients, caregivers and healthcare providers is essential. Discussions should involve treatment goals, expectations, treatment plans, treatment options, potential adverse effects, and the preferences of the patients and caregivers.	92% Strongly agree 8% Agree
6	The decision to initiate systemic therapies (conventional and novel [including biologics and small molecules]) for moderate-to-severe AD should be made by dermatologists, due to the potential for misdiagnoses (e.g. cutaneous T-cell lymphoma) and adverse reactions.	75% Strongly agree 17% Agree 8% Neutral

AD: atopic dermatitis; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; NRS: Itch Numeric Rating Scale; POEM: Patient Oriented Eczema Measure; SCORAD: SCORing Atopic Dermatitis

Discussions should encompass treatment goals, expectations, options and plans, taking into account potential adverse effects and patient/caregiver preferences in decision-making. This may also include consideration of the patient's medical comorbidities.

When indicated, systemic therapies should be initiated by dermatologists as specialty knowledge is required for assessment, to prevent misdiagnosis, as well as to monitor for adverse effects.

Conventional treatments

Table 2 summarises the consensus statements concerning conventional treatments in moderate-to-severe AD.

Treatment paradigm for moderate-to-severe AD

For moderate-to-severe AD, emollients remain the mainstay of general disease management. Additionally, topical corticosteroids (TCS) are first-line therapy for both acute exacerbations as well as maintenance of AD control for non-sensitive areas. For sensitive areas (e.g. eyelids, neck and genital areas), TCIs or topical phosphodiesterase-4 inhibitors (e.g. crisaborole) should be considered, as TCS use is likely to be associated with adverse events. Phototherapy could be considered as an alternative for the control of chronic moderate-to-severe AD, before using any systemic anti-inflammatory agents.

In cases of persistent moderate-to-severe AD, a holistic assessment is needed for the initiation of systemic therapy. The assessment should take into account the severity of disease, QoL, adherence, alternative diagnoses and response to previous treatments, such as intensive topicals and phototherapy.

Among conventional systemic anti-inflammatory agents, ciclosporin has the best evidence in the treatment of moderate-to-severe AD.[35] Systemic corticosteroids should be considered only as rescue therapy for acute flares, and not for long-term use in chronic AD. Similarly, long-term high-potency TCS use for moderate-to-severe AD is not recommended. Wet-wrap therapy should be used with caution in combination with high-potency TCS, to minimise potential adverse events.

Steroid tapering and phobia

TCS are an effective treatment for moderate-to-severe AD, but tapering should be initiated upon achieving adequate control. Tapering strategies may include using less potent TCS, reducing the application frequency of potent TCS or using TCS in combination with TCIs or phosphodiesterase-4 inhibitors.

There is a need to address steroid phobia in order to improve adherence to TCS in the management of AD. This should include screening for steroid phobia at treatment initiation and follow-ups,

Table 2. Consensus statements on conventional treatments for moderate-to-severe atopic dermatitis.

No.	Statement	Voting results (% of panellists)
7	For moderate-to-severe AD, emollients remain the mainstay of general disease management.	67% Strongly agree 17% Agree 16% Disagree
8	Topical corticosteroids are used as first-line therapy to treat acute exacerbations and maintain AD control in non-sensitive areas (e.g. hands and feet).	75% Strongly agree 17% Agree 8% Neutral
9	The use of topical calcineurin inhibitors should be considered, particularly for sensitive areas (e.g. neck, eyelids and genital areas) where topical corticosteroid use is likely to be associated with adverse events.	58% Strongly agree 42% Agree
10	The use of topical phosphodiesterase-4 inhibitors (e.g. crisaborole) should be considered, particularly for sensitive areas (e.g. neck, eyelids and genital areas) where topical corticosteroid use is likely to be associated with adverse effects.	50% Strongly agree 50% Agree
11	For the control of chronic moderate-to-severe AD, phototherapy could be considered as an alternative before using any systemic anti-inflammatory agents.	17% Strongly agree 75% Agree 8% Neutral
12	In cases of persistent moderate-to-severe AD, a holistic assessment is needed to decide when to initiate systemic therapy. This assessment should consider disease severity, quality of life, patient factors (e.g. adherence, avoidance of irritants and optimisation of treatment), alternative diagnoses and whether intensive topical treatment and phototherapy have been trialled.	83% Strongly agree 17% Agree
13	Among conventional systemic anti-inflammatory agents, ciclosporin has the best evidence in the treatment of moderate-to-severe AD.	8% Strongly agree 92% Agree
14	Systemic corticosteroids should be considered only as rescue therapy for acute flares, and not for long-term use in chronic AD.	83% Strongly agree 17% Agree
15	Long-term high-potency topical corticosteroid use for moderate-to-severe AD is not recommended.	17% Strongly agree 67% Agree 16% Disagree
16	Wet-wrap therapy in combination with high-potency topical corticosteroids should be used with caution to minimise potential adverse events.	42% Strongly agree 58% Agree
17	Topical corticosteroids are an effective treatment for moderate-to-severe AD. Tapering of corticosteroids should be initiated on adequate control of disease.	50% Strongly agree 42% Agree 8% Neutral
18	Tapering strategies can include using less potent corticosteroids, reducing application frequency of potent corticosteroids or using topical corticosteroids in combination with topical calcineurin inhibitors or phosphodiesterase-4 inhibitors.	33% Strongly agree 59% Agree 8% Neutral
19	There is a need to address steroid phobia to improve adherence to topical corticosteroids in the management of AD. At treatment initiation and follow-ups, healthcare providers should screen for steroid phobia (e.g. using the Topical Corticosteroid Phobia [TOPICOP] scale) and individualise patient education if patients express concerns about steroid use.	33% Strongly agree 59% Agree 8% Disagree

AD: atopic dermatitis

although not all panellists agreed on the Topical Corticosteroid Phobia (TOPICOP)[36] scale as the most appropriate instrument for assessment. If patients express concerns about steroid use, they should be provided with individualised education to address their concerns.

Biologics

Twelve statements on biologics reached consensus, as summarised in Table 3.

Dupilumab is currently approved for use in Singapore for the treatment of adult and paediatric patients aged ≥6 months, with moderate-to-severe AD requiring chronic treatment, and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[11] Dermatologists in Singapore agreed that dupilumab could be considered for first-line systemic treatment in patients with moderate-to-severe AD.

Dupilumab is recommended as a first-line systemic treatment for patients with concomitant type 2 allergic disease (e.g. moderate-to-severe asthma, severe chronic rhinosinusitis with nasal polyps).

Table 3. Consensus statements on biologics.

No.	Statement	Voting results (% of panellists)
20	Dupilumab could be considered for first-line systemic treatment in patients with moderate-to-severe AD.	42% Strongly agree 50% Agree 8% Disagree
21	Dupilumab is recommended as the first-line systemic treatment for patients with both moderate-to-severe AD and concomitant type 2 allergic disease.	25% Strongly agree 59% Agree 8% Neutral 8% Disagree
22	Dupilumab may be preferred in moderate-to-severe AD patients with severe comorbidities, such as end-stage organ disease/dysfunction, or cardiovascular and venous thromboembolism risk factors.	42% Strongly agree 41% Agree 17% Neutral
23	Based on the available evidence, dupilumab is considered safe and effective in elderly patients compared with conventional systemic agents.	33% Strongly agree 67% Agree
24	Dupilumab should be used with caution in patients who are pregnant or lactating due to the lack of safety/toxicity data in this subpopulation.	33% Strongly agree 67% Agree
25	Dupilumab-induced conjunctivitis can occur during treatment in AD patients. However, topical treatment with anti-inflammatory eyedrops can be considered for the management of conjunctivitis in selected cases, without the need to discontinue dupilumab treatment.	58% Strongly agree 42% Agree
26	In severe or persistent cases of dupilumab-induced conjunctivitis, referral to an ophthalmologist is recommended.	83% Strongly agree 17% Agree
27	For AD patients with a history of recurrent or moderate-to-severe eye inflammation, or ocular surface disorders such as conjunctivitis or keratitis, consider consulting an ophthalmologist before starting treatment with dupilumab.	50% Strongly agree 42% Agree 8% Neutral
28	There is no routine pre-treatment laboratory screening recommended prior to starting dupilumab.	17% Strongly agree 75% Agree 8% Disagree
29	Live attenuated vaccines should be avoided while on dupilumab treatment. Therefore, screening for age-appropriate vaccinations should be conducted at least 4 weeks prior to starting biologic treatment for AD patients.	25% Strongly agree 67% Agree 8% Neutral
30	There is no requirement for specific laboratory tests to monitor AD patients using dupilumab.	25% Strongly agree 67% Agree 8% Neutral
31	Rituximab, omalizumab and ustekinumab treatment are not recommended for use in AD patients due to lack of evidence for their efficacy.	50% Strongly agree 50% Agree

AD: atopic dermatitis; TOPICOP: topical corticosteroid phobia

Dupilumab may also be preferred in moderate-to-severe AD patients with severe comorbidities, such as end-stage organ disease/dysfunction, or cardiovascular and venous thromboembolism risk factors. Based on the available evidence, dupilumab is considered safe and effective in elderly patients (e.g. ≥65 years) compared with conventional systemic agents.[37,38] However, dupilumab should be used with caution in patients who are pregnant or lactating, due to the lack of safety and toxicity data in this subpopulation.

In terms of adverse events, dupilumab-induced conjunctivitis can occur during treatment in AD patients. However, topical treatment with anti-inflammatory eyedrops can be considered for the management of conjunctivitis in selected cases, without needing to discontinue dupilumab treatment. In severe or persistent cases of dupilumab-induced conjunctivitis, referral to an ophthalmologist is recommended. For AD patients with a history of recurrent or moderate-to-severe eye inflammation or ocular surface disorders, such as conjunctivitis or keratitis, clinicians should consider consulting an ophthalmologist before starting treatment with dupilumab.

There is no routine pre-treatment laboratory screening recommended prior to starting dupilumab, and no specific laboratory tests are required to monitor AD patients using dupilumab. However, as live attenuated vaccines should be avoided

while on dupilumab treatment, screening for age-appropriate vaccinations should be conducted at least 4 weeks prior to starting biologic treatment.

Rituximab, omalizumab and ustekinumab treatment are not recommended for use in AD patients, due to limited evidence for their efficacy.

JAK inhibitors

Consensus statements on JAK inhibitors are summarised in Table 4.

Baricitinib, abrocitinib and upadacitinib can be considered for first-line systemic treatment in certain adults with moderate-to-severe AD. In particular, systemic JAK inhibitor treatments can be considered when fast-acting treatments are required. Treatment with a JAK inhibitor can also be an option in moderate-to-severe AD patients with a history of severe ocular surface disease (e.g. corneal and conjunctival diseases). Abrocitinib and upadacitinib may be considered for adolescents (12–18 years old) with moderate-to-severe AD.

Table 4. Consensus statements on Janus kinase inhibitors.

No.	Statement	Voting results (% of panellists)
32	JAKi (baricitinib, abrocitinib, upadacitinib) can be considered for first-line systemic treatment in certain adults with moderate-to-severe AD.	58% Strongly agree 34% Agree 8% Disagree
33	JAKi treatments can be considered when fast-acting treatments are required.	58% Strongly agree 42% Agree
34	JAKi treatment could be used as an option in moderate-to-severe AD patients with a history of severe ocular surface disease.	42% Strongly agree 58% Agree
35	JAKi (abrocitinib and upadacitinib) may be considered for adolescents with moderate-to-severe AD (12–18 years old).	58% Strongly agree 25% Agree 17% Neutral
36	In moderate-to-severe AD patients with latent tuberculosis, JAKi treatments should only be used after the latent tuberculosis has been adequately treated or in consultation with relevant tuberculosis specialists.	50% Strongly agree 50% Agree
37	The use of JAKi in combination with other potent immunosuppressants, such as ciclosporin, is not recommended in AD treatment as it might cause an overly suppressed immune system and increased risk of infection and lymphoma.	34% Strongly agree 50% Agree 8% Neutral 8% Disagree
38	JAKi treatment should not be used during pregnancy, in patients planning for pregnancy or breastfeeding patients.	58% Strongly agree 34% Agree 8% Neutral
39	JAKi treatment should be used with caution in the following patient groups: patients aged ≥65 years, patients at increased risk of major cardiovascular problems (stroke or myocardial infarction), smokers or patients who had smoked for a long time in the past, patients at increased risk of cancer and patients with risk factors for venous thromboembolism.	50% Strongly agree 50% Agree
40	Prior to JAKi treatment initiation, routine screening for hepatitis B, hepatitis C and tuberculosis should be conducted. Screening for HIV should be conducted in at-risk individuals.	50% Strongly agree 50% Agree
41	In addition to routine infective screening, pre-treatment laboratory screening of baseline full blood count (including a differential white cell count), liver enzymes (especially transaminases), renal function and lipid levels is recommended before JAKi treatment initiation.	25% Strongly agree 75% Agree
42	Live attenuated vaccines should be avoided while on JAKi treatment. However, inactivated herpes zoster vaccination could be considered for all patients.	33% Strongly agree 59% Agree 8% Disagree
43	After JAKi treatment initiation, regular laboratory screening should be carried out as part of routine patient management.	25% Strongly agree 75% Agree

AD: atopic dermatitis; HIV: human immunodeficiency virus; JAKi: Janus kinase inhibitors

In moderate-to-severe AD patients with latent tuberculosis, JAK inhibitors should only be used after the latent tuberculosis has been adequately treated, or in consultation with relevant tuberculosis specialists. The use of JAK inhibitors in combination with other potent immunosuppressants, such as ciclosporin, is not recommended as it might cause an overly suppressed immune system and increased risk of infection and malignancies, such as lymphoma. Additionally, JAK inhibitors should not be used during pregnancy, in patients planning for pregnancy or lactating patients.

In the following patient groups, JAK inhibitor treatment should be used with caution: patients aged ≥65 years; patients at increased risk of major cardiovascular problems (stroke or myocardial infarction); smokers or patients who have smoked for a long time in the past; patients at increased risk of cancer; and patients with risk factors for venous thromboembolism.[39]

Laboratory screening

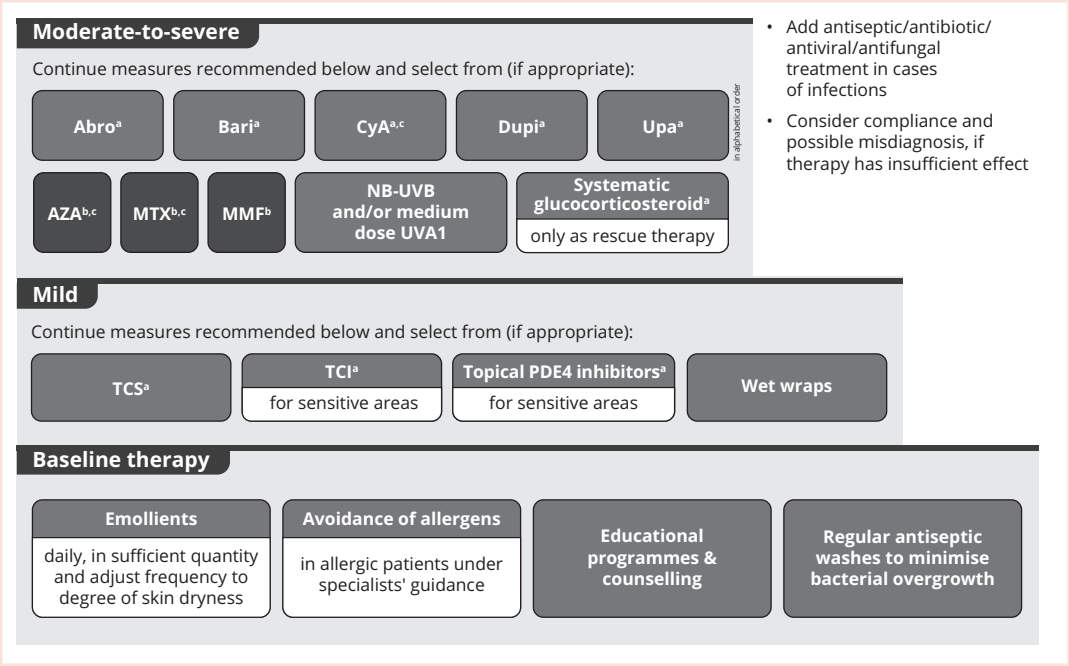
Prior to treatment initiation with JAK inhibitors, routine screening for hepatitis B, hepatitis C and tuberculosis should be conducted. HIV screening should also be conducted for at-risk individuals. Pre-treatment laboratory screening of baseline full blood count (including a differential white cell count), liver enzymes (especially transaminases), renal function and lipid levels, is also recommended. Live attenuated vaccines should be avoided while on JAK inhibitors, but inactivated herpes zoster vaccination could be considered for all patients in view of possible herpes zoster reactivation. After JAK inhibitor treatment initiation, regular laboratory screening should be carried out as part of routine patient management.

DISCUSSION

Consensus statements generally aligned with recommendations in other international AD consensus statements and guidelines, including those from Europe (EuroGuiDerm), Portugal, Japan and Saudi Arabia.[40-44] Fig. 2 illustrates a proposed treatment algorithm, developed based on the consensus statements generated. A key outcome of the consensus process was that, in the appropriate context, biologics and JAK inhibitors could be considered as first-line treatments for moderate-to-severe AD in Singapore, in addition to conventional treatments.

Nevertheless, efficacy, safety and cost should always be considered during the initiation of systemic treatments. At the time of this Delphi

Fig. 2. Proposed treatment algorithm based on the consensus statements.



Adapted from EuroGuiDerm guideline.[41]
Abro: abrocitinib; AZA: azathioprine; Bari: baricitinib; CyA: ciclosporin A; Dupi: dupilumab; MMF: mycophenolate mofetil; MTX: methotrexate; NB-UVB: narrow-band ultraviolet B; PDE4: phosphodiesterase-4; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; Upa: upadacitinib; UVA1: ultraviolet A1.
[a] Licensed indication.
[b] Off-label treatment.
[c] Refer to restrictions as listed within this guideline and EuroGuiDerm.[41]

survey, many newer AD treatments were not eligible for subsidy in Singapore via the Medication Assistance Fund (MAF) or the Ministry of Health Standard Drug List. Hence, treatment with such agents may result in significant out-of-pocket costs.

A common theme expressed in open-ended comments and during the expert meeting was the importance of considering the affordability of a treatment for a specific patient, when making treatment decisions in clinical practice.[45]

However, as of 1 March 2024, after the conclusion of the Delphi voting, abrocitinib has since been listed for subsidy under the MAF for the treatment of moderate or severe atopic dermatitis (Physician Global Assessment score of 3 or 4 and EASI ≥16) in patients who have had an inadequate response, intolerance or contraindication to at least 1 systemic therapy such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil.[46] This decision was based on an assessment of patient population size and unmet need, clinical effectiveness, cost-effectiveness, incremental cost and budget impact.[46] Initiatives like the MAF are crucial for mitigating financial barriers to effective treatments and promoting societal health equity.

Additionally, it was highlighted that the decision to initiate systemic treatments should be made by dermatologists. Specialist knowledge is necessary to appreciate the differential diagnoses (such as mycosis fungoides, psoriasis, tinea),[47] reduce misdiagnosis as well as monitor adverse events. A skin biopsy may be considered prior to therapy initiation in cases where the AD diagnosis is unclear, especially for elderly patients.[48-50]

As outlined in Supplementary Fig. S1, a number of statements did not reach consensus in round 1. After discussion and modification, almost all statements were able to reach consensus in round 2, except for 1 statement regarding the discontinuation of phototherapy. Panellists did not agree on the acceptability of co-administration of phototherapy with systemic anti-inflammatory agents. In the comments, it was highlighted that the contraindication may be true of some agents, such as ciclosporin and/or azathioprine, but that phototherapy may be used together with methotrexate and dupilumab. Experts also noted evidence that the risk of photocarcinogenesis may be lower in the Asian population,[51] and highlighted that temporary overlaps between treatments may occur in clinical practice while bridging treatments.

The consensus statements reflect the current treatment availability in Singapore at the time of the study. Other treatment options, such as topical JAK inhibitors (delgocitinib ointment and ruxolitinib cream) and other biologics (tralokinumab, lebrikizumab and nemolizumab), may become available in the future and could play a role in AD management.[52,53] In clinical practice, some treatments may also be used off-label, such as mycophenolate mofetil, an oral systemic immunosuppressant that is considered by some clinicians in Singapore as third- or fourth-line treatment, when licensed options are exhausted.

The strengths of this supplementary guideline update include the use of Delphi methodology, which is a structured and robust technique for collecting opinions from experts and generating group consensus.[24] The process allows for controlled feedback between rounds, such that panellists are informed of the current status of collective opinion and may be reminded of considerations that they may have previously missed.[24] The Delphi process was modified in this study to include an expert meeting to support statement reformulation following round 1 voting. While this meant that members of the expert panel were aware of each other while exchanging clinical opinion, voting records were kept confidential and no voting took place during this meeting. This ensured that dominant perspectives did not shape the consensus generation.

Limitations

While a full systematic review to assess the level of evidence supporting each statement was not conducted, many existing guidelines are already available globally for AD. Thus, the statements were developed based on a review of relevant international treatment guidelines, with expert input from the co-chairs.

The sample size for the Delphi panel was limited to 12 participants; however, recruitment aimed to identify key opinion leaders in the field of dermatology in Singapore, who would have the expertise and experience to advise on best practice,[54] while ensuring representation across public and private practice. Future updates (supplementary or full) to the 2016 guidelines should consider including patients and policymakers, to gather input on the feasibility of implementing recommendations in clinical practice.

Lastly, although the current consensus discussed the risks associated with the use of biologics and JAK inhibitors, including the importance of pre-treatment screening and ongoing monitoring, it did not provide detailed guidance on specific monitoring timelines or adverse event management. This omission stems from the restricted scope of a 2-round Delphi panel and the intention to remain non-prescriptive, allowing flexibility for clinicians to tailor approaches based on local circumstances. While relevant screening and monitoring guidance has already been published,

for example by Samuel et al. (2023),[55] these considerations should be included in future updates to the 2016 guidelines.

CONCLUSION

This modified Delphi study was undertaken to develop updated guidance, based on consensus among dermatologists in Singapore, regarding newer treatments in moderate-to-severe AD. The consensus statements developed are intended to supplement the original guidelines,[8] particularly in treatment approaches for moderate-to-severe AD, and to ensure that the guidelines account for changing treatment paradigms. Further revisions to this guideline may be required when new evidence and/or new treatments in AD become available.

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Ethics statement

This study did not involve collection of patients' confidential data that could violate patients' right to privacy.

REFERENCES

1. Ständer S. Atopic Dermatitis. N Engl J Med 2021;384:1136-43.
2. van Zuuren EJ, Fedorowicz Z, Christensen R, et al. Emollients and moisturisers for eczema. Cochrane Database Syst Rev 2017;2:Cd012119.
3. International League of Dermatological Societies. 2022. Global report on atopic dermatitis. https://www.eczemacouncil.org/assets/docs/global-report-on-atopic-dermatitis-2022.pdf Accessed 21 March 2023.
4. Foo HL, Tey HL. A clinico-pathological approach to management of atopic dermatitis. Ann Acad Med Singap 2021;50:171-3.
5. Cheok S, Yee F, Song Ma JY, et al. Prevalence and descriptive epidemiology of atopic dermatitis and its impact on quality of life in Singapore. Br J Dermatol 2018;178:276-7.
6. Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. Br J Dermatol 2021; 184:304-9.
7. Wolter S, Price HN. Atopic dermatitis. Pediatr Clin North Am 2014;61:241-60.
8. Tay YK, Chan YC, Chandran NS, et al. Guidelines for the management of atopic dermatitis in Singapore. Ann Acad Med Singap 2016;45:439-50.

9. Torres T, Ferreira EO, Gonçalo M, et al. Update on Atopic Dermatitis. Acta Med Port 2019;32:606-13.
10. Health Sciences Authority. Infosearch for health products and services: Dupilumab (Dupixent Solution for Injection) [Product Insert]. https://www.hsa.gov.sg/e-services/infosearch. Updated February 2023. Accessed 11 May 2023.
11. Health Sciences Authority. Infosearch for health products and services: Dupilumab (DUPIXENT) 100 mg solution for injection in a pre-filled syringe [Full Prescribing Information]. https://www.hsa.gov.sg/e-services/infosearch. Updated July 2023. Accessed 17 January 2024.
12. Crowley EL, Nezamololama N, Papp K, et al. Abrocitinib for the treatment of atopic dermatitis. Expert Rev Clin Immunol 2020;16:955-62.
13. Health Sciences Authority. Infosearch for health products and services: Abrocitinib (CIBINQO Film-Coated Tablet) [Product Insert]. https://www.hsa.gov.sg/e-services/infosearch. Updated March 2023. Accessed 11 May 2023.
14. Hoy SM. Baricitinib: A Review in Moderate to Severe Atopic Dermatitis. Am J Clin Dermatol 2022;23:409-20.
15. Health Sciences Authority. Infosearch for health products and services: Baricitinib (OLUMIANT film-coated tablet) [Product Insert]. https://www.hsa.gov.sg/e-services/infosearch. Updated 14 October 2022. Accessed 11 May 2023.
16. Simpson EL, Papp KA, Blauvelt A, et al. Efficacy and Safety of Upadacitinib in Patients With Moderate to Severe Atopic Dermatitis: Analysis of Follow-up Data From the Measure Up 1 and Measure Up 2 Randomized Clinical Trials. JAMA Dermatol 2022;158:404-13.
17. Health Sciences Authority. Infosearch for health products and services: Upadacitinib (RINVOQ Extended-release tablet) [Product Insert]. Updated 2020. Accessed 11 May 2023.
18. McDowell L, Olin B. Crisaborole: A Novel Nonsteroidal Topical Treatment for Atopic Dermatitis. J Pharm Technol 2019;35:172-8.
19. Health Sciences Authority. Infosearch for health products and services: Crisaborole (Staquis Ointment 2% w/w) [Product Insert]. https://www.hsa.gov.sg/e-services/infosearch. Updated September 2022. Accessed 11 May 2023.
20. Akins RB, Tolson H, Cole BR. Stability of response characteristics of a Delphi panel: application of bootstrap data expansion. BMC Med Res Methodol 2005;5:37.
21. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: How to decide its appropriateness. World J Methodol 2021;11:116-29.
22. Stewart D, Gibson-Smith K, MacLure K, et al. A modified Delphi study to determine the level of consensus across the European Union on the structures, processes and desired outcomes of the management of polypharmacy in older people. PLoS One 2017;12:e0188348.
23. Arents BWM, van Zuuren EJ, Vermeulen S, et al. Global Guidelines in Dermatology Mapping Project (GUIDEMAP), a systematic review of atopic dermatitis clinical practice guidelines: are they clear, unbiased, trustworthy and evidence based (CUTE)? Br J Dermatol 2022;186:792-802.
24. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32:1008-15.
25. Gattrell WT, Hungin AP, Price A, et al. ACCORD guideline for reporting consensus-based methods in biomedical research and clinical practice: a study protocol. Res Integr Peer Rev 2022;7:3.
26. Sullivan GM, Artino AR Jr. Analyzing and Interpreting Data From Likert-Type Scales. J Grad Med Educ 2013;5:541–42.
27. AGREE Next Steps Consortium. 2013. The AGREE II Instrument [Electronic version]. https://www.agreetrust.org/resource-centre/agree-ii/. Accessed 21 March 2023.
28. World Bank Country and Lending Groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed 27 April 2023.
29. Hanifin JM, Baghoomian W, Grinich E, et al. The Eczema Area and Severity Index—A Practical Guide. Dermatiti 2022;33:187-92.
30. Severity Scoring of Atopic Dermatitis: The SCORAD Index Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23-31.
31. Finlay AY, Khan G. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-16.
32. Newton L, DeLozier AM, Griffiths PC, et al. Exploring content and psychometric validity of newly developed assessment tools for itch and skin pain in atopic dermatitis. Journal of patient-reported outcomes 2019;3:1-12.
33. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol 2004;140:1513-9.
34. Simpson E, Bissonnette R, Eichenfield LF, et al. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): the development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. J Am Acad Dermatol 2020;83:839-46.
35. Roekevisch E, Spuls PI, Kuester D, et al. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J Allergy Clin Immunol 2014;133:429-38.
36. Moret L, Anthoine E, Aubert-Wastiaux H, et al. TOPICOP©: a new scale evaluating topical corticosteroid phobia among atopic dermatitis outpatients and their parents. PLoS One 2013;8:e76493.
37. Adam DN, Gooderham MJ, Beecker JR, et al. Expert consensus on the systemic treatment of atopic dermatitis in special populations. J Eur Acad Dermatol Venereol 2023;37:1135-48.
38. Napolitano M, Fabbrocini G, Scalvenzi M, et al. Efficacy and safety of dupilumab in atopic dermatitis in elderly patients: a retrospective study. Clin Exp Dermatol 2020;45:888-90.
39. European Medicines Agency. EMA recommends measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders. https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic-inflammatory-disorders. Accessed 15 February 2024.
40. Saeki H, Ohya Y, Furuta J, et al. English Version of Clinical Practice Guidelines for the Management of Atopic Dermatitis 2021. J Dermatol 2022;49:e315-e75.
41. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema: part I - systemic therapy. J Eur Acad Dermatol Venereol 2022;36:1409-31.
42. Ministry of Health (Saudi Arabia). National Saudi Guidelines for the Management of Atopic Dermatitis. 2021. https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Documents/Atopic-Dermatitis-Guidelines.pdf. Accessed 13 December 2023.

43. T Torres T, Gonçalo M, Paiva Lopes MJ, et al. Portuguese recommendations for the treatment of atopic dermatitis with biologic therapy and JAK inhibitors in adult patients. Drugs Context 2021;10.
44. De Bruin-Weller M, Biedermann T, Bissonnette R, et al. Treat-to-Target in Atopic Dermatitis: An International Consensus on a Set of Core Decision Points for Systemic Therapies. Acta Dermato-Venereologica 2021;101.
45. Olsson M, Bajpai R, Wee LWY, et al. The cost of childhood atopic dermatitis in a multi-ethnic Asian population: a cost-of-illness study. Br J Dermatol 2020;182:1245-52.
46. Agency for Care Effectiveness (ACE). Technology Guidance: Abrocitinib, baricitinib, upadacitinib and dupilumab for treatment atopic dermatitis. https://www.ace-hta.gov.sg/docs/default-source/drug-guidances/abrocitinib-baricitinib-upadacitinib-and-dupilumab-for-treating-atopic-dermatitis-(published-2-jan-2024).pdf. Accessed 1 March 2024.
47. Siegfried EC, Hebert AA. Diagnosis of atopic dermatitis: mimics, overlaps, and complications. J Clin Med 2015; 4:884-917.
48. Wollenberg A, Christen-Zäch S, Taieb A, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol 2020;34:2717-44.
49. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema: part I - systemic therapy. J Eur Acad Dermatol Venereol 2022; 36:1409-31.
50. Boesjes CM, van der Gang LF, Bakker DS, et al. Dupilumab-associated lymphoid reactions in patients with atopic dermatitis. JAMA Dermatol 2023;159:1240-47.
51. Murase JE, Lee EE, Koo J. Effect of ethnicity on the risk of developing nonmelanoma skin cancer following long-term PUVA therapy. Int J Dermatol 2005;44:1016-21.
52. Nakagawa H, Nemoto O, Igarashi A, et al. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. J Am Acad Dermatol 2020;82:823-31.
53. Papp K, Szepietowski JC, Kircik L, et al. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: results from two phase 3 studies. J Am Acad Dermatol 2023;88:1008-16.
54. Jünger S, Payne SA, Brine J, et al. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. Palliat Med 2017;31:684-706.
55. Samuel C, Cornman H, Kambala A, et al. A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring. Dermatol Ther (Heidelb) 2023;13: 729-49.