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COMMENTARY

Advanced Systemic Treatments in Patients with Moderate-to-Severe Atopic Dermatitis: Key Learnings from Physicians Practicing in Nine Asian Countries and Territories

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ABSTRACT

Introduction: Rapid progress made in the management of atopic dermatitis (AD) in recent years and the differences in patient journey between Asian and non-Asian populations call for a review of current atopic dermatitis landscape in Asia.

Methods: A roundtable meeting with nine regional dermatological experts was held in June 2023 to discuss the optimal management approaches for moderate-to-severe AD, focusing on the use of advanced therapies.

Results: Disease burden on patients' quality of life, treatment adherence, and financial constraints were identified as major concerns when managing patients with moderate-to-severe AD in parts of Asia. It was agreed that the Hanifin and Rajka's criteria or the UK Working Party's Diagnostic Criteria for Atopic Dermatitis can be used

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to guide the clinical diagnosis of AD. Meanwhile, patient-reported outcome scales including the Dermatology Life Quality Index and Atopic Dermatitis Control Tool can be used alongside depression monitoring scales to monitor treatment outcomes in patients with AD, allowing a better understanding for individualized treatment. When managing moderate-to-severe AD, phototherapy should be attempted after failure with topical treatments, followed by conventional disease-modifying antirheumatic drugs and, subsequently, biologics or Janus kinase inhibitors. Systemic corticosteroids can be used as short-term therapy for acute flares. Although these advanced treatments are known to be effective, physicians have to take into consideration safety concerns and limitations when prescribing these treatments.

Conclusions: Treatments in AD have evolved and its management varies country by country. Unique challenges across Asian countries necessitate a different management approach in Asian patients with AD.

Keywords: Antirheumatic agents; Asia; Biologics; Dermatitis; Atopic; Janus kinase inhibitors

Key Summary Points
Patients with atopic dermatitis (AD) in Asia may have a different clinical presentation compared with individuals with non-Asian populations.
To address the unique challenges of managing patients with moderate-to-severe AD in Asia, current landscape and management of AD in the nine territories across Asia were reviewed and discussed.
When managing moderate-to-severe AD, phototherapy should be attempted after failure with topical treatments, followed by conventional disease-modifying antirheumatic drugs and subsequently, biologics or Janus kinase inhibitors. Systemic corticosteroids can be used as short-term therapy for acute flares.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease in Asia [1–4]. Data from the International Study of Asthma and Allergies in Childhood Phase Three (1999–2004) showed that the prevalence of AD in Asia Pacific was 10.1% in children aged 6–7 years and 5.3% in adolescents aged 13–14 years, with severe AD reported in approximately 1.2% and 0.7%, respectively [2, 3]. Another international survey published in 2023 involving adult respondents (aged 18–65 years) from China, Hong Kong, Malaysia, Taiwan, Thailand, and Singapore found that the prevalence of AD, measured using the Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD), ranged from 11.9% in Singapore to 33.7% in Thailand; of these respondents, 55.3–64.3% and 13.4–27.6% had moderate and severe AD, respectively [5]. A report by the Philippine Dermatological Society in 2017 showed that the prevalence of AD was 12.7% in the under-18-year-old population and 2% in the adult population, indicating a greater disease burden in younger patients [6]. Meanwhile, a separate study found that the prevalence of AD in young Singaporean/Malaysian Chinese adults (mean age 22.19 years) was 13.5% in 2005–2019, of which 40.5% had moderate or severe AD [7].

Patients in Asia generally have a different AD phenotype and clinical presentation compared with individuals with non-Asian populations. Clinically, Asian patients with AD show a clearer demarcation of lesions with more prominent scaling and lichenification than European American patients [8]. Increased epidermal hyperplasia, with a thickness measure similar to that observed in patients with psoriasis, and higher T_H17 activation are also more frequently seen in Asians [8]. Filaggrin (FLG) null mutations, a major factor in the development of AD, are present in up to 50% of European patients but only around 27% of Asians [9]. Moreover, FLG mutations most commonly seen in Europeans—R501X and 2282del4—are rare among Asian patients as they exhibit mutations that are unique to their respective ethnic groups, such as c.3321delA in Chinese, Korean, and Japanese individuals [9–12].

The management practice of AD varies across Asian countries and territories (Table S1), including Hong Kong, India, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam. When managing patients with moderate-to-severe AD, countries tend to follow their own national guidelines [6, 13–19]. In geographically diverse India, hospitals across the country even developed individualized guidelines in response to the different setting-specific management approaches used. However, existing national AD guidelines, along with previously developed regional consensus, have largely excluded recommendations on advanced novel treatments such as biologics and Janus kinase (JAK) inhibitors, as they were authored prior to the availability of these newer treatment options in the region [6, 13–17, 20]. Consequently, physicians in these Asian countries may over-rely on nonregion specific disease management recommendations (such as those described in the 2022 EuroGuiDerm AD guidelines) to manage patients with AD, even though, ideally, treatment choices should take into consideration the barriers and limitations faced by patients in these countries [21, 22].

To address the unique challenges of managing patients with moderate-to-severe AD in Asia, specifically in Hong Kong, India, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam, a group of dermatology experts came together to review the current landscape of AD in the nine countries and territories across Asia and offered an updated group perspective on the management of moderate-to-severe AD, including the use of advanced systemic treatments, that would be appropriate and relevant to Asian patients.

METHODS

An expert panel comprised nine dermatological specialists from Hong Kong, India, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam was formed to review the current landscape of AD in these localities and discuss the optimal management approaches of moderate-to-severe AD in these Asian countries or territories. All experts in the roundtable were authors on the manuscript. The panel initially provided their individual input on country-specific disease landscape, patient journey, routine practices, and treatment challenges via a questionnaire. Subsequently, a scientific literature search was conducted using the PubMed search engine to review published literature on the management of moderate-to-severe AD. The search was limited to English articles published between January 2013 and 16 May 2023, using the following search terms: "consensus" or "recommendations" or "guidelines" or "position paper" and "atopic dermatitis" or "eczema".

The search returned 1641 articles, which were screened for mentions of AD-related diagnostic tools, assessment of disease severity, monitoring parameters and treatment selection, with a focus on Asian populations. Additionally, articles were only included for detailed review if they were treatment recommendations, consensus guidelines, position statements, or treatment algorithms on moderate-to-severe AD. Systematic reviews and meta-analyses were also included if they were used to derive treatment recommendations. All case reports, case series, summaries, editorials, clinical trials, cohort studies, protocols, analyses, letters and replies, or abstracts, as well as nonhuman-related treatment recommendations, were excluded. Guidelines from specific countries not found through the PubMed search were shared by members of the expert panel separately. A total of 128 articles were reviewed in detail eventually.

Relevant information from the literature review was compiled, summarized, and thoroughly scrutinized during a roundtable meeting held on 17 June 2023 in Bangkok, Thailand. At the meeting, the experts shared their opinions and perspectives on the subject matter and debated on the advantages and limitations of current management approaches for moderate-to-severe AD in their represented countries or territories. Differences in opinion were resolved through extended discussions to reach a collective agreement among members of the panel. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Unmet Needs in the Journey of Patients with AD

AD's burden on patient's quality of life, treatment adherence, and financial constraints have been identified as the top concerns when managing patients with moderate-to-severe AD. Table 1 provides an overview of the respective issues and their corresponding potential solutions.

AD's Burden on Patients' Quality of Life

The impact of AD on patients' quality of life is significant [23, 56]. A meta-analysis of various Asian studies reported that the average Children's Dermatology Life Quality Index (CDLQI) and Dermatology Life Quality Index (DLQI) scores of patients with AD ranged from 4.8 to 15.2 (CDLQI mean of means of 9.1) and 4.8 to 12.0 (DLQI mean of means of 9.1), respectively [23]. Meanwhile, a Taiwanese study showed that 89.2% of employed individuals with AD reported missing work or having impaired work, and 92.5% experienced restrictions in their regular daily activities due to AD [24]. There is a positive correlation between the severity of AD and the disease's impact on patients' work and daily activity; those with moderate and severe AD reported an 1.8- and 2.6-fold greater mean adjusted overall work impairment scores and 1.5- and 2-fold greater mean adjusted activity impairment scores, respectively, compared with patients with mild AD (all $p<0.001$) [24].

AD also affects patients psychologically [25–28, 57]. A cross-sectional study in Singapore found that 18% and 5% of patients with AD (aged 13–60 years) had symptoms of anxiety and depression, respectively [25]. Another Malaysian study of local patients with AD (aged 13 years or above) reported similar results, with a 12% prevalence of anxiety and 7.8% of depression, whereas around 29.2% of all Malaysians (aged 16 years or above) had mental health problems [57]. Moreover, a systematic review involving 310,681 patients revealed that patients with AD were 44% more likely to exhibit suicidal ideation and 36% more likely to attempt suicide compared with those without the disease [26]. A recent Taiwanese study also reported a higher risk of anxiety and depression in patients with moderate-to-severe AD than those with mild AD [28].

Treatment Adherence

Treatment adherence is a common issue in the management of AD [40, 45, 58]. A Japanese study of 3096 dermatological patients (of which 1327 had AD) showed that 66.3% and 75.5% of patients had low adherence to oral and topical medications, respectively, according to the Morisky Medication Adherence Scale-8 [40]. Another noninterventional, open-label Japanese study found that the adherence rate of dupilumab self-injection for AD was only 59.4%, which was significantly lower than that of patients with bronchial asthma or chronic rhinosinusitis with nasal polyps who were receiving the same treatment [58]. Analysis from the same study illustrated that adherence decreased with longer term use of dupilumab and not age, sex, underlying disease, or type of administration device (including self-injection syringe, syringe with an aid device, and prefilled pen) used, with the median duration of dupilumab use in patients with AD, bronchial asthma, and chronic rhinosinusitis being 604.0 days, 451.0 days, and 267.0 days, respectively [58].

Steroid phobia is also common among patients with AD and can lead to suboptimal treatment adherence [42, 48, 59]. In a large international study, Taiwanese patients with AD or their parents have a higher level of topical corticosteroid phobia than most of other countries included in the study, namely Australia, Belgium, Brazil, Canada, Denmark, France, Germany, Hungary, Japan, Mexico, Sweden, and the USA [60]. Factors that could have contributed to the differences in degree of corticosteroid phobia in each country include cultural attitudes, attitudes and messaging from doctors to patients, the time taken by the doctor to counsel patients, the healthcare system, existing education programs, involvement of nurses in the patient journey, socioprofessional situations of

Table 1 Top unmet needs in the journey of patients with moderate-to-severe atopic dermatitis (AD): experience from physicians practicing in nine Asian countries and territories

Unmet needs	Issues	Potential solutions
The burden of AD on patients' quality of life	• AD has a significant impact on patients' work productivity and psychological wellbeing (i.e., AD being a risk factor for anxiety, depression, and suicide attempts/thoughts) [23–31]	• Awareness campaigns should be launched to educate patients and their family about AD and the importance of treatment adherence [32, 33] • Psychodermatology clinics could be useful for some patients who are dealing with AD-related psychoemotional challenges [34–37] • A simple, easy-to-use, self-completed online app can be developed to enable patients to measure their quality of life as a function of treatment effectiveness [38, 39][a]
Treatment adherence	• Many patients do not follow their doctor's instructions when taking medications [40, 41] • Steroid phobia is a common issue [42–44]	• Simple treatment regimens that are easy to follow should be considered for most patients [45] • Patient counseling should be provided to inform patients about their treatment goals [50% reduction in Eczema Area and Severity Index (EASI-50) or 75% reduction in Eczema Area and Severity Index (EASI-75)] and prepare them for possible treatment-related adverse effects [46, 47][b] • A mobile app could be used to help monitor patients' adherence to their treatment [39] • It is also important to educate patients about the effects of indiscriminate steroid use and tachyphylaxis/tolerance, as well as steroid allergy and phobia [15, 48–50] • In AD clinics, more dermatology nurses should be recruited and trained to support patient education initiatives [51, 52] • In an outpatient setting, patient education can be delivered by partnering with nongovernmental organizations and patient support groups [32]

Table 1 continued

Unmet needs	Issues	Potential solutions
Financial constraints	• Newer systemic treatments are available, but not all patients can afford paying for the high cost • The cost of conventional therapies such as cyclosporine and phototherapy remains high in some countries • Health insurance coverage is currently limited across the region	• More patient assistance programs should be offered to patients to improve access to novel treatments • Healthcare professionals should actively provide input to industry partners and health policymakers on the cost and pricing of treatment • Biosimilars could be considered in cost-sensitive markets, but their efficacy and safety must be established first • Free-of-charge, industry-sponsored/subsidized testing and monitoring services should be made available to patients in need • Physicians and industry to lobby for an increase in government reimbursement for AD advanced therapies

AD atopic dermatitis, *ADCT* Atopic Dermatitis Control Tool, *DLQI* Dermatology Life Quality Index, *EASI-50* a 50% reduction in Eczema Area and Severity Index, *EASI-75* a 75% reduction in Eczema Area and Severity Index

[a]Dermatology Life Quality Index (DLQI) might be useful but is not specific for patients with AD, while Atopic Dermatitis Control Tool (ADCT) could be a potential tool that is simple and comprehensive for measuring the control of AD [53, 54]

[b]EASI-75 is still currently the treatment goal for available AD treatments, and EASI-50 is the criteria for treatment continuation under most subsidy schemes [55]. Patients should not expect complete skin clearance even when continuously on treatment. Physicians should provide patients with these exact figures to align patients' expectations, especially when patients are paying for their treatment out-of-pocket. Moreover, physicians should inform patients of the possible adverse events with their treatment(s) so they can monitor for any side effects immediately to help improve treatment adherence. Patients should also be educated that even the most efficacious drug could cause side effects, reassuring them the safety of their prescribed treatments

patients, and the system for dispensing medicine [60]. Another cross-sectional Malaysian study found that 98% of patients who had been treated with topical corticosteroid have a certain degree of steroid phobia, leading to an overall treatment nonadherence rate of 54% [48].

Financial Constraints

The cost of treatment is a major issue across many parts of the Asian region. A Taiwanese study in 2018 estimated that the costs associated with work productivity loss were NTD194,060 per year (around USD6346 per year) and NTD284,705 per year (around USD9,310 per year) for every patient with moderate and severe AD, respectively [61]. Another study involving 12 countries in the Asia–Pacific showed that working mothers missed an average of 13.5 days of work in 2010 to take care of their children who are affected by AD [62]. Moreover, an Indian study demonstrated that the costs of AD treatment amount to about 25% of patients' total earnings, thus creating a heavy burden on families [63].

Other Challenges

There is an uneven distribution of dermatology specialists across much of the Asian region. In Hong Kong, there are fewer dermatologists practicing in public hospitals; yet, the majority of patients with AD visits the outpatient clinics of public system, resulting in extended waiting time for dermatology services, ranging from 1 to 2.5 years (data as of March 2023). Meanwhile, most dermatologists in India, the Philippines and Vietnam are concentrated in big cities, and it is difficult for patients living in rural areas to access dermatology services. Access to newer treatment options such as biologics and JAK inhibitors specifically indicated for AD treatment also remains limited (Supplementary Table 2); even when these therapeutics are available, their approved age indications in the country may limit their use to selected patient groups only. Lastly, the scarcity of updated information on public health burden, disease epidemiology, and the various comorbidities of AD in Asia needs to be addressed urgently.

Experts' Perspective in Managing Patients with Moderate-to-Severe AD in the Nine Countries and Territories

Diagnosis of AD

The diagnosis of AD is mainly clinical and should be based on associated signs and symptoms. Patients should meet three out of four major and three out of 23 minor features listed within the Hanifin and Rajka's criteria to be diagnosed with AD [20, 64]. An alternative diagnostic tool that can be used is the UK Working Party's Diagnostic Criteria for AD, which had been developed based on the original Hanifin and Rajka's criteria [65]. For the diagnosis of AD, patients should have a history of pruritus plus three of the following five criteria: history of involvement in the skin creases; history of dry skin in the past year; personal history of asthma, hay fever, or atopic disease in a first-degree relative in children aged < 4 years; onset under the age of 2 years; or presence of visible flexural eczema. Blood investigations and biomarker tests are generally not recommended as there is currently no reliable biomarker available to diagnose AD.

Measurements of AD Severity

While many scoring tools are available for use in research, not all are commonly used in clinical practice. The Eczema Area and Severity Index (EASI) scale is commonly used to determine treatment reimbursement eligibility. Generally, patients with an EASI score of 16 are considered eligible for systemic treatments under the reimbursement schemes in Taiwan, and an EASI score of 21 in Hong Kong, Malaysia, and Singapore. Additionally, body surface area (BSA) measurement and the Investigator's Global Assessment (IGA) scale for AD are also routinely used in clinics [66, 67]. Meanwhile, the DLQI is recommended for assessing the impact of AD on patients' quality of life and the Peak Pruritus Numerical Rating Scale (NRS) and a simplified Patient Oriented Eczema Measure (POEM) scale can be used to measure patients' degree of

pruritus and other symptoms, including quality of sleep [68–70].

The Atopic Dermatitis Control Tool (ADCT) has demonstrated strong correlation with other patient-reported scales, ranging from a Spearman correlation coefficient of 0.76 (peak score)/0.79 (average score) with the Pruritus NRS to 0.82 with POEM and DLQI and is, thus, useful in evaluating AD control in clinical and non-clinical settings [54]. While the ADCT score is currently not a criterion for most government reimbursement schemes for systemic treatment, there should be more frequent considerations in using it as a measured outcome in clinical trials, and ADCT scores can potentially be used to simplify and hasten the clinical assessment process.

Monitoring Treatment Outcomes

EASI, IGA, DLQI, ADCT, and Peak Pruritus NRS can all be used to monitor treatment outcomes in patients with AD, while POEM and Scoring Atopic Dermatitis (SCORAD) may not be suitable for daily practice. Specifically, measuring itch intensity in patients with AD could help physicians understand whether a prescribed treatment is effective and physicians should also try to individualize the treatment of their patients as treatment response may vary across individuals.

In Asian populations, depression is more commonly seen in patients with moderate-to-severe AD than those with mild AD [25, 28]. A Taiwanese study showed an increased risk among patients with AD in developing major depression and any depressive disorders in later life than those without [71]. Hence, it is advisable to monitor patients' condition periodically using tools such as the Hospital Anxiety and Depression Scale (HADS) and Hamilton Depression Rating Scale (HAM-D) [25, 72–74].

Considerations for Systemic Treatments

Systemic treatments that are available to patients with moderate-to-severe AD include systemic corticosteroids, phototherapy, conventional disease-modifying antirheumatic drugs (DMARDs), biologics, and JAK inhibitors [14–16, 21]. Table 2 summarizes the role of each treatment type for moderate-to-severe AD, focusing on how they broadly fit into existing Asian healthcare systems.

Systemic Corticosteroids

Systemic corticosteroids can be used as a short-term treatment (1–2 weeks) for acute flares at a dose of 0.5–1 mg/kg/day of prednisolone for patients with moderate-to-severe AD [15, 16]. They can also be used to bridge treatments as phototherapy and medications, such as dupilumab and azathioprine, require time to elicit response [15, 21, 75, 85, 86].

Despite the regular use of corticosteroids in clinical practice, there are only a few studies involving patients with AD [21]. In two small clinical trials in children with severe AD, flunisolide and a combination of oral and nasal beclomethasone dipropionate were demonstrated to be more effective than placebo at 4 weeks and 2 weeks of treatment, respectively [87, 88]. Compared with cyclosporine, systemic prednisolone was less effective in achieving stable disease remission (SCORAD ≥ 50) ($p = 0.031$) at 6 weeks and higher incidence of relapse ($p = 0.043$) at 12 weeks in adults with severe AD [89].

Due to safety concerns with long-term use, it is important to communicate the risks with patients before prescribing systemic corticosteroids as many of them might have already taken corticosteroids prescribed by other physicians whom they have consulted previously [90].

Phototherapy

Phototherapy can be considered as the next treatment option for moderate-to-severe AD after patients experience failure with topical treatments, even though it might be challenging for individuals with mobility difficulties, working patients, or school-going children, as frequent visits to the hospital/clinic are required to optimize treatment effect [14, 20, 91–93].

When used for acute AD, the use of UVA1 has been shown to reduce SCORAD scores after 3 weeks of treatment, with results being evident after the first week of treatment [94, 95]. Meanwhile, narrowband UVB (NB-UVB) was found to reduce total disease activity, extent of dermatitis,

Table 2 Systemic treatments that can be considered for patients with moderate-to-severe atopic dermatitis (AD) in Asia: insights from physicians practicing in nine Asian countries and territories

Patient population	Systemic corticosteroids	Phototherapy	Conventional disease-modifying antirheumatic drugs (DMARDs)—cyclosporine (CsA), azathioprine (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF)[a]	Biologics (dupilumab)	Janus kinase (JAK) inhibitors (abrocitinib, baricitinib, and upadacitinib)
Adults	• Short-term treatment for acute flares [15, 16] • To bridge treatments [15, 75]	• The next treatment option after failure with topical treatments [14, 20] • An adjunct therapy to control itch [22] • For people with comorbidities and are not suitable for conventional DMARDs	• A third-line treatment option [14, 15], starting with the following priorities: CsA > AZA or MTX > MMF [15–17][b] • As maintenance therapy after achieving control with biologics and JAK inhibitors[c]	• A fourth-line treatment option [15, 76] • Consider after failing two out of four conventional immunosuppressive agents (CsA, AZA, MTX, and MMF) or if patients cannot tolerate them[c]	• A fourth-line treatment option [77] • Consider after failing two conventional immunosuppressive agents (CsA, AZA, MTX, and MMF) or if patients cannot tolerate them[c] • Consider abrocitinib or upadacitinib first, followed by baricitinib[d]
Children ≤ 18 years of age	• Can be used for a short duration under supervision [15, 76]	• Not contraindicated [14, 16, 78] • Parents can accompany their child into the phototherapy cabin during treatment[e]	• Can be used if biologics or JAK inhibitors are not indicated	• Can be considered if indicated for children in respective countries	• Can be considered if indicated for children in respective countries
Seniors ≥ 60 years of age [79]	• Can be used for a short duration under supervision • Osteoporosis is a concern [80]	• Same as the adult population	• Same as the adult population	• Same as the adult population	• Same as the adult population • Dose adjustment may be needed according to the licensed dosage of each drug in respective countries

Table 2 continued

Patient population	Systemic corticosteroids	Phototherapy	Conventional disease-modifying antirheumatic drugs (DMARDs)—cyclosporine (CsA), azathioprine (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF)[a]	Biologics (dupilumab)	Janus kinase (JAK) inhibitors (abrocitinib, baricitinib, and upadacitinib)
Pregnant women	• Can be used for a short duration under supervision [14, 15][a]	• ultraviolet B (UVB) phototherapy is considered relatively safe and may be used [14, 22, 81]	• CsA: may be used after careful evaluation as first-line systemic therapy for long-term control [15, 22] • AZA: generally not recommended but can be used if other alternatives are not available [15] • MTX and MMF: contraindicated and should be avoided [14, 15, 22]	• Not recommended owing to the absence of clinical trial data [22] • Physicians should discuss the benefits and risk of treatment with their patients if biologics are to be considered during pregnancy[a]	• Not recommended [22]

AD atopic dermatitis, *AZA* azathioprine, *CsA* cyclosporine, *DMARDs* disease-modifying antirheumatic drugs, *JAK* Janus kinase, *MMF* mycophenolate mofetil, *MTX* methotrexate

[a]This may be considered an off-label use. Physicians should discuss the risks and benefits with individual patients and the final decision should be made at the discretion of the treating physician

[b]CsA is recommended in young and fit patients [15–17]. In case of contraindications or treatment failure, physicians should then consider azathioprine or methotrexate, followed by MMF [15–17]

[c]Owing to cost considerations

[d]Baricitinib may be considered in patients with noncontraindicated comorbidities owing to its lower efficacy rates in clinical trials [82–84]

[e]This practice is common in Singapore. However, the accompanying parent is advised to wear appropriate clothing (long sleeves and pants) and apply sun protection while in the cabin

pruritus, and improved sleep in patients with chronic AD [96].

UVA1 phototherapy is currently not available in India, Indonesia, and Vietnam. In India, phototherapy is only available in referral centers while (NB-UVB) is limited to specific clinics or treatment facilities. In the Philippines, UVA1 and NB-UVB phototherapy devices are usually limited to bigger cities. At present, phototherapy is not reimbursed in India, the Philippines (though subsidized at public hospitals), and Vietnam, making it more difficult for patients to access treatment.

In patients who do not respond to phototherapy, they can be switched to conventional DMARDs, biologics or JAK inhibitors, or use a tapered dose of corticosteroids.

Conventional DMARDs

Conventional DMARDs can be used as a third-line treatment option in patients who failed phototherapy or when they have been on a few courses of corticosteroids [14, 15]. Cyclosporine was superior to placebo with a mean clinical improvement in AD severity of between 53% and 95% when used for short-term treatment (from 10 days to 8 weeks), while evidence for its long-term use is limited [97]. Azathioprine also demonstrated superiority against placebo with a mean improvement of 26–37% in the Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score at week 12 of treatment [97]. A study that assessed treatments for up to 16 weeks showed that the efficacy of azathioprine was comparable with that of methotrexate but lower compared with dupilumab and cyclosporine in clearing the clinical signs of AD [98]. Meanwhile, there is limited efficacy data in using mycophenolate mofetil for AD [21].

Baseline screening (including tests for tuberculosis and hepatitis) and treatment monitoring are important when patients are on conventional DMARDs. In Asian patients who are treated with azathioprine, they should be screened for the *NUDT15* gene and/or its activity instead of testing for thiopurine methyltransferase (TPMT) activity, as recommended by the European Academy of Dermatology and Venereology 2018 [76] and EuroGuiDerm 2022 [21] guidelines [77, 99, 100]. The prevalence of TPMT variants is exceptionally low (< 1%) in Asian populations [99], while the frequency of *NUDT15* polymorphisms is higher among Asians compared to individuals with European or African ancestry [101]. *NUDT15* polymorphisms are also found to be associated with azathioprine-induced hematological events in various studies of Chinese, Indian, and Korean populations, thus suggesting their usefulness in predicting azathioprine-related toxicities and guiding dose adjustment in clinical practice [100–104].

Biologics

Biologics should be considered as a fourth-line treatment option in the management of moderate-to-severe AD, and dupilumab is currently the only biologic agent available in many Asian countries [15, 76]. Compared with placebo, a study showed that more patients receiving dupilumab achieved at least EASI-75 ($p < 0.001$) at week 16 of treatment [86]. Improvement in pruritus, sleep, symptoms of anxiety or depression, and quality of life was also seen in significantly more patients treated with dupilumab than those on placebo ($p < 0.001$) [86].

A phase 3 Chinese study also demonstrated similar results, where 57.3% of patients in the dupilumab arm achieved EASI-75 versus 14.4% in the placebo group ($p < 0.001$) [105]. However, it may take a considerable amount of time for patients to develop a response to dupilumab, which could be more than a year [85, 86]. Two phase 3 clinical trials showed that between 44% and 52% of patients achieved EASI-75 with dupilumab at week 16 [86], while a post hoc analysis that included patients who did not achieve optimal response at week 16 with dupilumab in these two trials found that 91% of patients achieved EASI-75 by week 100 [85].

Unlike other systemic treatments, no laboratory monitoring is needed for patients receiving dupilumab treatment [21]. The level of immunoglobulin E is not a suitable biomarker for predicting dupilumab effectiveness [20]. Similarly, eosinophil count is also not a reliable biomarker as its level would usually increase within the first 3–6 months of using dupilumab [86, 106]. Although the Japanese Dermatological

Association recommended serum thymus and activation-regulated chemokine (TARC) level as a biomarker for treatment monitoring, tests for serum TARC level are not yet routinely available in most clinics and this limits the real-world use of the said biomarker [18].

If there is no barrier to affordability, biologics can be started and continued to maintain optimal disease control. For patients who do not achieve response with dupilumab, JAK inhibitors or add-on conventional DMARDs can be considered, depending on treatment risks and the availability of drugs in the respective countries. In situations where cost of treatment limits access to therapy, add-on conventional DMARDs may still be a feasible option, as the complete withdrawal of biologics may lead to relapse of AD symptoms [107].

JAK Inhibitors

JAK inhibitors are also an appropriate fourth-line treatment option for patients with moderate-to-severe AD [77]. The EuroGuiDerm 2022 guidelines strongly recommend biologics and JAK inhibitors in patients with severe AD [21]. Importantly, in countries where dupilumab is not available, patients may start on JAK inhibitors after considering conventional DMARDs.

All three JAK inhibitors (i.e., abrocitinib, baricitinib, and upadacitinib) that are currently available in most Asian countries have demonstrated higher skin clearance and itch relief responses in patients with moderate-to-severe AD compared with placebo. More patients on abrocitinib 200 mg achieved EASI-75 at week 16 of treatment [71% versus 30.6% (placebo)] and reported superior itch relief response compared with dupilumab and placebo at week 2 (49.1% versus 26.4% and 13.8% respectively, $p<0.001$) [108]. The superior itch relief afforded by abrocitinib 200 mg was evident from as early as day 2 of treatment (11% versus 4%, $p=0.0006$) [109].

Specific to baricitinib, more patients achieved EASI-75 compared with placebo at week 16 of treatment (21.1–24.8% on baricitinib 4 mg, 17.9–18.7% on baricitinib 2 mg, and 12.8–17.3% on baricitinib 2 mg versus 6.1–8.8% on placebo) [82]. Improvement in itch with baricitinib was observed as early as week 1 and week 2 for the 4 mg and 2 mg doses, respectively [82]. In a Chinese head-to-head trial, the efficacy of baricitinib 2 mg was shown to be similar to that of dupilumab at week 16 [104]. Moreover, improvement in pruritus was achieved significantly faster in the baricitinib group (seen within first 4 weeks) than in individuals receiving dupilumab [110].

All tested dose regimens of upadacitinib (7.5, 15, and 30 mg) showed significant improvement in EASI score at week 16 of treatment compared with placebo (39%, $p=0.03$; 62%, $p<0.001$; and 74%, $p<0.001$ versus 23%, respectively) [111]. A Japanese real-world analysis also reported a similar level of efficacy for the upadacitinib 15 mg dose (67.7% achieved EASI-75 at week 12) [112]. Around 80% of patients on upadacitinib 15 mg and 84% on upadacitinib 30 mg achieved EASI-75 at week 52 [113]. In a head-to-head trial, upadacitinib provided superior and more rapid skin clearance and itch relief compared with dupilumab—achieving EASI-75 at week 16 (71% versus 61.1%; $p=0.006$) and improvement in mean worst pruritus NRS as early as week 1 (31.4% versus 8.8%; $p<0.001$) [114].

A network meta-analysis showed that upadacitinib 30 mg was superior to all JAK inhibitor regimens (i.e., upadacitinib 15 mg, abrocitinib 100 and 200 mg, as well as baricitinib 1, 2, and 4 mg) in terms of IGA and EASI response [115]. Although the efficacy rates of baricitinib were lower in clinical trials compared with those of abrocitinib and upadacitinib, baricitinib—in combination with topical steroids—is effective in improving patient outcomes based on real-world, Asian clinical experience [115].

Despite its superior efficacy, upadacitinib is associated with more treatment-related side effects compared with placebo, followed by abrocitinib [115]. As JAK inhibitors are a relatively new class of drug for AD, it is important for physicians to be alert for any potential treatment-related side effects. When considering between choosing a JAK inhibitor and dupilumab for patients with AD, physicians should engage their patients in shared decision-making process to weigh the pros and cons of each treatment, including preferences for oral medications stemming from the fear of injections [116, 117].

In patients who do not respond to any JAK inhibitors, they can be switched to biologics or previous-lines therapies if patients have not attempted them previously. While there is currently no official indication for the combination of dupilumab and JAK inhibitors, studies have suggested that combining these treatments as rotational or maintenance therapy may result in better long-term efficacy and safety outcomes for patients [118, 119]. JAK inhibitors can be used to reduce itching (results evident within 1–2 weeks) and inflammation, followed by dupilumab monotherapy as a maintenance regimen (it usually takes more than 4 months for dupilumab to be effective) [82, 85, 86, 109, 114]. Alternatively, patients can also be considered for the clinical trial of new treatments, if available.

Other Treatment Options

Other potential treatments for moderate-to-severe AD are briefly summarized in Table 3.

DISCUSSION

In many parts of Asia, moderate-to-severe AD significantly impacts patients' physical and psychoemotional well-being, and many patients are nonadherent to treatment owing to multiple reasons. Nonetheless, patient education can help improve treatment adherence [32, 129]. For instance, physicians should remind patients to use corticosteroids judiciously and always follow prescriber's instructions to minimize the risk of treatment [75, 90, 130]. The cost of treatment, especially with advanced therapies, is also a substantial barrier. Financial support is often needed to help patients receive the most appropriate treatment. As universal health insurance coverage is currently limited in many countries across the region, a number of patients depend on nongovernmental support to access treatment. For instance, the Dermatological Society of Malaysia raises funds for patients who need financial support through a series of initiatives under the Malaysian Skin Foundation. Ideally, patients with AD should also be able to benefit from free testing and monitoring services provided by industry partners.

Both healthcare professionals and patients must be continuously educated about AD and its treatment options, particularly newer ones, that are available to them. Systemic corticosteroids can be used as short-term therapy for acute flares. When managing moderate-to-severe AD, phototherapy should be attempted first, followed by conventional DMARDs and subsequently, biologics or JAK inhibitors. Of note, when administering any systemic treatment, weight-adjusted dosing is particularly important in Asian populations as many individuals tend to be underweight [20, 131–133]. Prescribers should always refer to country-specific local prescribing information for guidance on appropriate drug dosing calculations.

To secure long-term resources for the AD community in Asian countries, there is a need to generate more real-world evidence on the outcomes of Asian patients who receive novel treatments. It is useful to investigate the different AD phenotypes among Asians and ascertain how each patient responds to the treatment prescribed. Notably, even advanced AD treatments are not necessarily effective in providing complete skin clearance [82, 85, 108, 113, 114]. Hence, the use of biomarkers to assist the selection of AD treatment may benefit Asian patients considerably, especially in situations where treatment options are limited [134–136].

AD management requires a holistic approach, not only providing appropriate treatment but also educating patients and their families on the long-term impact of the disease [32]. Resource permitting, patients should receive multidisciplinary team care that includes access to counselors and psychologists to improve their quality of life [34–37, 137]. The management of AD in Asia involves not only dermatologists but also pediatricians, family physicians, general practitioners and nurses, and additional healthcare practitioners [52, 138]. It is, therefore, important to continuously improve the knowledge and skills of all healthcare professionals who are involved in managing the disease [52, 138–142]. Comprehensive educational programs are practical approaches to disseminating information

Table 3 Other potential treatment options for patients with moderate-to-severe atopic dermatitis (AD) in Asia: Insights from physicians practicing in nine Asian countries and territories

Treatment options	Considerations
Antihistamines	• Antihistamines are not recommended for the treatment of AD [13, 16, 22, 120][a] Nonetheless, sedating histamines may be suggested in patients with sleep disturbance due to itch [13–15, 17][b] • Physicians should be mindful of the sedating side effects of any antihistamines and consider patients' profession[c] when prescribing antihistamines
Antibiotics	• Appropriate antibiotics (e.g., cloxacillin, cephalexin, and erythromycin) may be required when secondary infection occurs [13–17, 22] • The use of prophylactic antibiotic treatment in patients with AD is not recommended [13–17] • Bleach bath (sodium hypochlorite 0.005%) may be useful in patients with recurrent infections as it has anti-inflammatory effects and can help kill bacteria on the skin [13, 15, 22]
Allergen-specific immunotherapy (ASIT)	• The use of ASIT is not recommended due to limited scientific evidence regarding its effectiveness [13, 22, 121][d]
Traditional complementary and alternative medicine (TCAM)	• Although TCAM (e.g., Chinese herbal medicine and acupuncture) is often used by Asians, more clinical trial data are needed to establish its safety and efficacy [15, 22, 122, 123]
Vitamin D supplements	• While some data have suggested a potential link between vitamin D deficiency and an increased risk of developing AD, there is a lack of sufficient double-blind, placebo-controlled trials to conclusively demonstrate the efficacy of vitamin D supplementation in improving AD symptoms [13, 15, 16, 124, 125]
Avoidance of specific foods	• Food avoidance is not advocated unless there are concomitant urticaria, angioedema or gastrointestinal symptoms associated with specific foods [13, 14, 22][e] • If there is any proof of allergies, identified food allergens should be avoided to prevent the aggravation of patients' AD [22][f]

AD atopic dermatitis, *ASIT* allergen-specific immunotherapy, *JAK* Janus kinase, *TCAM* traditional complementary and alternative medicine

[a]Although often prescribed in daily practice, antihistamines are not effective in treating AD due to the complex pathophysiology of AD [13, 16, 22, 120]

[b]Based on the 2023 Indonesia Guideline of Systemic Treatment for Adults with Atopic Dermatitis, antihistamine-1 (sedative/non-sedative) and antihistamine-2 (cimetidine) are still part of the AD treatment in Indonesia

[c]Such as those who work as drivers, operate heavy machineries, or children who need to attend exams or schools

[d]A recommendation for ASIT in the 2020 Thailand clinical practice guidelines was limited to patients with respiratory symptoms rather than for all patients with AD [16]

[e]This is pertaining to low evidence, impracticality, and the potential result of malnutrition [126–128]

[f]If flares do occur despite the avoidance of potential food allergens, one possible explanation would be that the flareup could be due to airborne allergens, which are difficult to avoid completely

about AD to physicians in various practices and settings. Relevant topics include the selection of treatment, specialist referral, inappropriate use of steroids, and side effects of advanced therapies, as well as treatment costs. Some examples of ongoing local medical education initiatives with information specific to respective countries include an annual AD summit organized by the Pediatric Dermatology Society of the Philippines and a host of educational activities run by the Indian Society for Pediatric Dermatology.

Limitations

The treatments reviewed in this article are limited to systemic treatments for moderate-to-severe AD and do not include details of topical therapy or the management of mild AD. Moreover, the information cited in this article reflects practices as of June 2023 but may not include updates beyond this period. Of note, while our panel comprises dermatology specialists from nine countries or territories across Asia, we acknowledge that our experience may still not fully represent the whole spectrum of disease management practices in all of Asia. Readers are advised to interpret the information discussed carefully.

CONCLUSIONS

In Asia, moderate-to-severe AD significantly impacts patients' physical and psychoemotional well-being, and many patients are nonadherent to treatment owing to multiple reasons. The cost of treatment, especially with advanced therapies, is also a substantial barrier. To overcome these challenges, both healthcare professionals and patients must be continuously educated about the disease and treatment options, particularly newer ones, that are available to them. The diagnosis of AD should be based on clinical criteria outlined in either the Hanifin and Rajka's set of diagnostic features or the United Kingdom Working Party's Diagnostic Criteria for AD. In some Asian countries, disease severity scales such as EASI, BSA, and IGA are already commonly used to guide treatment decisions. Meanwhile, patient-reported outcome scales such as DLQI and ADCT can also be used alongside depression monitoring scales to monitor the treatment outcomes of patients with AD. Specific to AD treatment in Asian patients, systemic corticosteroids can be used as short-term therapy for acute flares. When managing moderate-to-severe AD with systemic treatments, the nine Asian experts consider using phototherapy first, followed by conventional DMARDs and, subsequently, biologics or JAK inhibitors.

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Declarations

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