Ann Acad Med Singap 2024;53:641-3
https://doi.org/10.47102/annals-acadmedsg.2024355

EDITORIAL

Evolving therapies for atopic dermatitis: Bridging guidelines and practice

Pawinee Rerknimitr[1] *MD*

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterised by dysregulated type 2 immune responses, skin barrier dysfunction and intense pruritus (itching). The disease burden of AD is substantial, affecting at least 171 million individuals worldwide in 2019, representing 2.23% of the global population.[1] Among skin diseases, AD ranks highest in disease burden, as measured by disability-adjusted life-years (DALYs).[2] Its profound impact on patients' quality of life, along with significant economic burdens, underscores its status as a major healthcare challenge.

The pathogenesis of AD is driven by the type 2 cytokine axis, which includes interleukins (IL)-4, -5, -13, -25, -31 and -33, along with thymus- and activation-regulated chemokine (TARC)/CC chemokine ligand 17 (CCL17) and thymic stromal lymphopoietin (TSLP).[3] Additionally, AD is highly heterogeneous, presenting diverse phenotypes differed by factors such as age, disease chronicity, ethnicity, filaggrin mutations and immunoglobulin E (IgE) status.[4] Advances in understanding the molecular mechanisms of AD have paved the way for promising therapeutic strategies. In recent years, biologics and small-molecule therapies have revolutionised the management of moderate-to-severe AD. Numerous guidelines have been updated to incorporate these novel treatments, reflecting their growing role in the evolving treatment paradigm.[5-7]

In this issue of the *Annals,* Yew et al.[8] present a study that updates the 2016 Singapore treatment guidelines for AD,[9] with a focus on biologics and oral Janus kinase inhibitors (JAKi) now approved and available for AD treatment in Singapore. Utilising a modified Delphi consensus approach, the updated guidelines[8] offer recommen-dations on disease assessment, treatment goals and the incorporation of new therapies including dupilumab, an immunoglobulin G4 monoclonal antibody against IL-4 receptor α (IL-4Rα) targeting IL-4/13 signalling pathway, and JAKi such as abrocitinib, baricitinib and upadacitinib, into treatment paradigms.

While the guidelines primarily focus on pharmacologic treatments for AD, they also stress the fundamental principle of managing the condition—primarily by enhancing the skin barrier. The use of emollients as a basic treatment is highlighted as an essential step, consistently reinforced in global guidelines.[5-7] Clinical studies have demonstrated that regular moisturisation, typically applied twice daily, significantly improves the skin barrier in both adults and children with AD. Long-term studies on flare-ups have shown that daily moisturisation reduces flare frequency and prolongs the time between flare-ups.[10] Furthermore, the importance of educational programmes and counselling for patients and their families is emphasised. A collaborative approach involving patients, caregivers and healthcare providers is crucial, with discussions regarding treatment objectives, expectations, options and plans being essential for effective management.

Yew et al. also emphasise the equal importance of incorporating clinical signs assessed by physicians, symptoms reported by patients, health-related quality of life and long-term control of AD into disease assessment. Tools that evaluate both symptom severity and the impact on quality of life are crucial for customising treatment plans to meet individual patient needs.[11] Their guidelines also emphasise the importance of a correct diagnosis prior to initiating systemic therapy. Life-threatening conditions, such as cutaneous T-cell lymphoma, which is a significant mimicker, should be ruled out. Therefore, dermatologists are crucial in ensuring an accurate diagnosis to prevent the use of inappropriate treatments.

According to the guidelines, dupilumab and JAKi are recommended as first-line treatments for certain patient populations with moderate-to-severe AD. Given that IL-4 and IL-13 are key drivers of type 2 inflammation in AD, which is a type 2 inflammatory disease, dupilumab targets IL-4Rα, inhibiting both IL-4 and IL-13 signalling. This dual action reduces type 2 inflammation and helps interrupt the itch-scratch cycle.[12] In addition to

[1] Division of Dermatology, Department of Medicine, Faculty of Medicine, Center of Excellence for Skin and Allergy Research, Chulalongkorn University, Thailand.
Correspondence: Associate Professor Pawinee Rerknimitr, Division of Dermatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand.
Email: pawinee.r@chula.ac.th
Accepted: 25 November 2024

clinical improvements, dupilumab has been shown to normalise intraepidermal nerve fibre density, restore skin barrier integrity, decrease *Staphylococcus aureus* abundance, and promote a healthier skin microbiome.[13,14] Approved for AD treatment in Singapore since 2019, this present guideline recommends dupilumab for children and adults aged ≥6 months, particularly those with concurrent type 2 allergic diseases, severe comorbidities or older adults (≥65 years). However, clinicians should ensure that age-appropriate vaccinations are given at least 4 weeks prior to initiating dupilumab, as live attenuated vaccines are contraindicated during treatment. Regarding adverse events, conjunctivitis is a potential side effect associated with dupilumab.

The JAK-signal transducer and activator of transcription signalling pathway plays a central role in the pathogenesis of AD, as it regulates the transcription of various genes following cytokine engagement (e.g. IL-4, IL-13 and IL-22) with their respective receptors. JAKi, which are small molecules that competitively block the phosphorylation of JAK proteins, include abrocitinib, baricitinib and upadacitinib—all of which were approved for AD treatment in Singapore in 2022. Clinical studies have shown that these inhibitors improve AD symptoms and induce skin lesions clearance compared to placebo. They offer an appealing option for patients seeking rapid relief, particularly from pruritus—one of the most common and burdensome symptoms of AD—as the clinical trials demonstrated their efficacy in quickly alleviating pruritus. Common reported side effects of JAKi are nausea, nasopharyngitis, acne and herpes infections.[15] The latest guidelines[8] recommend JAKi for adolescents aged 12–18 years old. Before starting therapy, screening and treatment for latent tuberculosis is essential. These inhibitors are contraindicated when used with immunosuppressive drugs and should be used with caution in patients aged ≥65 years, those at increased risk of major cardiovascular issues (such as stroke or myocardial infarction), smokers or former long-term smokers, individuals with cancer risk and those with factors predisposing them to venous thromboembolism. Regular screening for infections and laboratory monitoring is required to ensure patient safety during treatment.

In conclusion, this updated consensus highlights the importance of accurate diagnosis, patient education, skin barrier enhancement, and the judicious application of both conventional and innovative systemic therapies in managing AD. By embracing these principles, healthcare providers can significantly improve therapeutic outcomes, alleviate the disease burden and enhance the quality of life for patients with AD. As treatment options continue to advance, they bring renewed hope for a future where individuals with AD experience better-controlled symptoms, fewer complications and improved long-term health. Comprehensive and regularly updated guidelines like this one, which adopt a holistic approach addressing both the medical and psychosocial aspects of care, are vital for optimising treatment strategies and transforming the overall patient experience.

Declaration

The author declares there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. During the preparation of this work, the author used ChatGPT (OpenAI, version 2) to assist with language refinement. After utilising this tool/service, the author thoroughly reviewed and edited the content as necessary and take full responsibility for the accuracy and integrity of the publication.

Acknowledgement

The author thanks the Center of Excellence for Skin and Allergy Research, Chulalongkorn University for their support.

Keywords: *biologics, corticosteroids, dermatology, eczema, Janus kinase inhibitors*

REFERENCES

1. Shin YH, Hwang J, Kwon R, et al. Global, regional, and national burden of allergic disorders and their risk factors in 204 countries and territories, from 1990 to 2019: A systematic analysis for the Global Burden of Disease Study 2019. Allergy 2023;78:2232-54.
2. 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.
3. Nakajima S, Nakamizo S, Nomura T, et al. Integrating multi-omics approaches in deciphering atopic dermatitis pathogenesis and future therapeutic directions. Allergy 2024;79:2366-79.
4. Czarnowicki T, He H, Krueger JG, et al. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol 2019;143:1-11.
5. Chu DK, Schneider L, Asiniwasis RN, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. Ann Allergy Asthma Immunol 2024;132:274-312.
6. Davis DMR, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. J Am Acad Dermatol 2024;90:e43-56.

7. 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.
8. Yew YW, Alagappan U, Aw D, et al. Updated consensus guidelines for management of moderate-to-severe atopic dermatitis in Singapore: Integrating biologics, Janus kinase inhibitors and conventional therapies. Ann Acad Singap Med 53:670-82.
9. 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.
10. Hebert AA, Rippke F, Weber TM, et al. Efficacy of Nonprescription Moisturizers for Atopic Dermatitis: An Updated Review of Clinical Evidence. Am J Clin Dermatol 2020;21:641-55.
11. Thomas KS, Apfelbacher CA, Chalmers JR, et al. Recommended core outcome instruments for health-related quality of life, long-term control and itch intensity in atopic eczema trials: results of the HOME VII consensus meeting. Br J Dermatol 2021;185:139-46.
12. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med 2016;375:2335-48.
13. Simpson EL, Schlievert PM, Yoshida T, et al. Rapid reduction in Staphylococcus aureus in atopic dermatitis subjects following dupilumab treatment. J Allergy Clin Immunol 2023;152:1179-95.
14. Rothenberg-Lausell C, Bar J, Dahabreh D, et al. Biologic and small-molecule therapy for treating moderate to severe atopic dermatitis: Mechanistic considerations. J Allergy Clin Immunol 2024;154:20-30.
15. Kim RW, Lam M, Abuabara K, et al. Targeted Systemic Therapies for Adults with Atopic Dermatitis: Selecting from Biologics and JAK Inhibitors. Am J Clin Dermatol 2024; 25:179-93.