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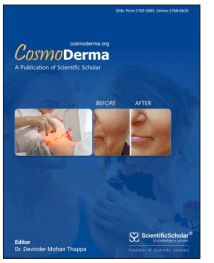

Review Article

Asian type atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder. Recent clinical and basic research has demonstrated that AD is an immune-mediated disease involving multiple inflammatory pathways and is considered a T helper (T_H)2-centered disease involving a common T_H22 component. Recently, some reports demonstrated that Asian patients with AD are more likely to present with clearly demarcated lesions with prominent scaling and lichenification and may exhibit distinct immune and barrier features compared with European American patients with AD. Besides T_H2 activation, patients of Asian descent (Japanese, Korean, and Chinese) with AD had strong T_H17 activation, overlapping clinically and molecularly with some hallmarks of psoriasis.

Keywords: Atopic dermatitis, Han Chinese, Lichenification, Psoriasis

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder, with a lifetime prevalence of 10–20% in children and 1–3% in adults.[1] Recent clinical and basic research have demonstrated that AD is an immune-mediated disease involving multiple inflammatory pathways and is considered a T helper (T_H)2-centered disease involving a common T_H22 component.[2] AD can be classified into different subtypes according to serum IgE levels (extrinsic or intrinsic), ethnicity (European American [EA], Asian, or African American), and age (pediatric or adult).[3-5]

Extrinsic and intrinsic AD

Extrinsic AD is associated with high total serum IgE levels and specific IgEs that target environmental and food allergens, whereas intrinsic AD presents with normal total IgE values and the absence of specific IgEs.[6] Increased IgE levels are detected in approximately 80% of AD cases (categorized as extrinsic), whereas normal IgE levels (categorized as intrinsic) are detected in 20% of cases.[6] Extrinsic AD is frequently accompanied by allergic bronchial asthma or allergic rhinoconjunctivitis, whereas intrinsic AD presents with normal serum IgE levels despite the development of skin lesions and distribution patterns similar to those observed in extrinsic AD. Patients with intrinsic AD are negative for *in vitro* tests that detect the presence of environmental or food allergens and are not associated with other atopic diseases.[7] However, metal allergy, which is common in AD, is more frequently associated with intrinsic AD than with extrinsic AD.[6] Intrinsic AD is also associated with a female predominance, the absence of other atopic diseases, Dennie-Morgan fold, later disease onset, and milder disease severity.[8] By contrast, palmar hyperlinearity, keratosis pilaris, pityriasis alba, and hand and/or food eczema are significantly less common in cases of intrinsic AD.[8] AD is associated with a decreased skin barrier function. Loss-of-function mutations in Filaggrin (FLG), which encodes the epidermal

barrier protein filaggrin, have been identified as the cause of ichthyosis vulgaris and serve as major predisposing factors for AD with allergic sensitization.[9-11] Filaggrin facilitates the terminal differentiation of the epidermis and the formation of the skin barrier, including the regulation of skin pH and epidermal hydration. The loss of filaggrin expression leads to the enhanced percutaneous transfer of allergens and epicutaneous sensitization to protein antigens.[12,13] AD patients who harbor *FLG* mutations have more persistent disease, a higher incidence of eczema herpeticum, and a greater risk of developing multiple allergies and asthma.[14]

Extrinsic AD is considered the prototypical form of AD, and an association between *FLG* mutations and extrinsic AD has been observed.[9,15] In a Japanese study, the incidence of *FLG* mutations was significantly lower (10.5%) in the IgE-low group (IgE < 200kU/L) than in the AD patients with IgE > 500kU/L (44.4%).[16] Palmar hyperlinearity and keratosis pilaris, which present more frequently in patients with extrinsic AD than in those with intrinsic AD, are phenotypic characteristics of ichthyosis vulgaris and are both highly associated with *FLG* mutations.[17,18] Patients with extrinsic AD show increased transepidermal water loss and reduced skin surface hydration, whereas no significant differences in these measures were observed in patients with intrinsic AD.[7]

Pathophysiology of extrinsic and intrinsic AD

Atopic dermatitis (AD) is well known as a T_H2-polarized disease, and both extrinsic and intrinsic AD show marked T_H2 activation (high expression levels of interleukin [IL]-4/IL-13). Extrinsic AD patients have elevated T_H2 cells and decreased T_H1 cells in peripheral blood, associated with elevated levels of IL-4, IL-5, and IL-13 expression and increased eosinophil counts. By contrast, intrinsic AD is associated with much lower IL-4 and IL-13 levels.[9,20] In mouse models, skin barrier damage drives the production of T_H2 cells and eosinophil-produced chemokines (C–C motif chemokine ligand [CCL]17, CCL22, and CCL5) and augments the expression of IL-4 and C–C motif chemokine receptor (CCR)4, leading to the dermal infiltration of eosinophils.[21] Keratinocytes that are differentiated in the presence of IL-4 and IL-13 exhibit significantly reduced *FLG* expression, even in patients without *FLG* mutations.[22] Atopic immune responses contribute to acquired skin barrier defects in AD, resulting in a vicious cycle. Another recent study showed similar increases in T_H2 cells in lesional skin from patients with both intrinsic and extrinsic AD, although the higher activation of T_H1, T_H17, and T_H22 cytokines was detected in patients with intrinsic AD.[16,23] Although IL-22 messenger ribonucleic acid (mRNA) expression increases significantly in lesional skin compared with non-lesional skin in both intrinsic and extrinsic AD, this increase is significantly higher in intrinsic AD than in extrinsic AD.[23] Intrinsic AD was also associated with Increased T_H1 signaling factors (interferon-gamma [IFN-γ], C–X–C chemokine motif ligand [CXCL]9, CXCL10, and MX dynamin-like GTPase 1 [MX-1]) and more pronounced T_H17/ T_H22 activation (IL-17A, IL-12/IL-23p40, CCL20, Elafin, and IL-22).[23] Patients with extrinsic AD showed strong correlations between disease activity and T_H2 cytokine levels (IL-4 and IL-5) and negative correlations with barrier products (loricrin, periplakin, and filaggrin). By contrast, disease activity in patients with intrinsic AD was correlated with the expression of T_H1/IFN-related genes (IL-1β and IFN-α) and the IL-17–related CCL20 chemokine.[23] In another study, the expression of IL22, IL36A, IL36G, CCL19, and CCL22 was upregulated in intrinsic AD and psoriasis but not in extrinsic AD. These findings suggest that the inflammation signature of intrinsic AD is more similar to that of psoriasis, than that of extrinsic AD.[24]

Epidemiology and clinical characteristics of Asian AD

Recently the heterogeneity of AD has become apparent, supported by the identification of clinical, molecular, and genetic differences associated with different racial backgrounds.[25] A high prevalence of AD has been reported in the Asian population. In the Asia-Pacific region, overall AD prevalence was 10.1% in children between the ages of 6 and 7 years, a higher level than reported for Western Europe (8.1%) or the total global prevalence of 7.9% reported by the International Study of Asthma and Allergies in Childhood Phase Three.[6,27] In the United States, Asians and Pacific Islanders are 7 times more likely to visit physicians for AD compared with whites.[28] There is a rising prevalence of both pediatric and adult AD in Asian populations worldwide, particularly in Asians living in urban areas. Potentially contributing to the evolving prevalence of AD is the rapid urbanization and increased pollution in many metropolitan areas in Asia.[29] A prospective cohort study in the United States found the adjusted odds ratio (OR) for risk of AD among infants born to Asian mothers in the first 6 months of life was 2.58, compared with infants born to white mothers.[30] Studies suggest that the children of Asian immigrants may be at higher risk for developing AD, potentially resulting from epigenetic phenomena unique to immigrant populations.[29]

Clinically, Asian patients with AD are more likely to present with clearly demarcated lesions with prominent scaling and lichenification compared with EA patients with AD, which is consistent with some molecular features of psoriasis in this patient population [Figure 1].[25,31]

Differences in skin barrier impairments in Asian AD

Several studies have found that up to 27% of Asian patients with AD harbor relevant *FLG* null mutations, whereas similar research in Europe reported one or more *FLG*

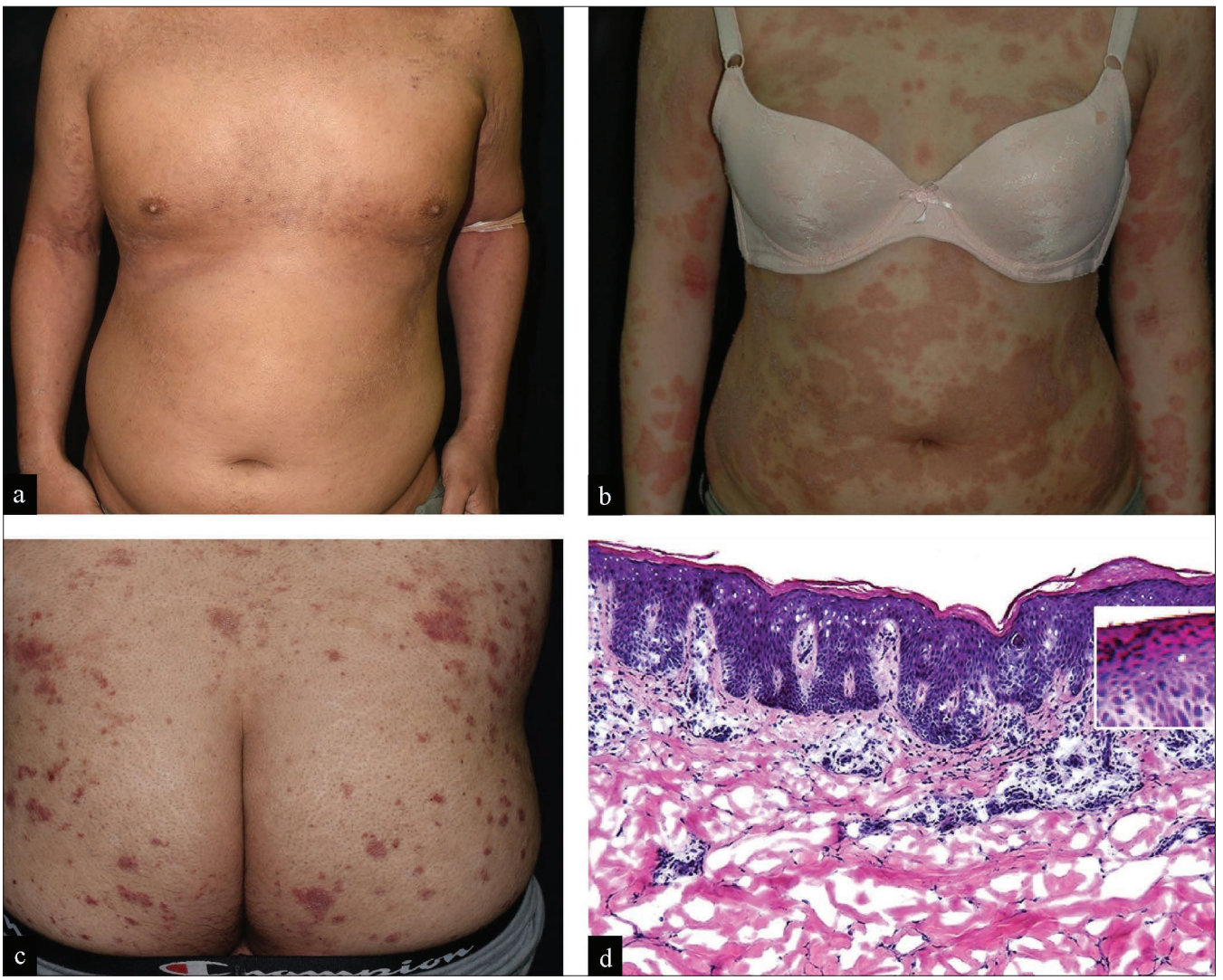

Figure 1: (a-c) Representative clinical images of Asian patients with AD, which characterized by clearly demarcated lesions with prominent scaling and lichenification. (d) Representative hematoxylin and eosin staining for lesional skin of an Asian patient with AD, characterized by epidermal hyperplasia, parakeratosis and hypogranulosis.

mutations in 50% of all AD cases.[31-33] The most frequent loss-of-function *FLG* mutations (R501X, 2282del4, S3247X, and R2447X) have been identified in 7–10% of the white European population; however, these mutations are usually absent in Asian individuals, who exhibit *FLG* null mutations that are unique to their respective ethnic groups.[34] In the white European population, two prevalent *FLG* mutations (R501X and 2282del4) account for over 80% of all *FLG* null alleles, whereas in the Singaporean Chinese population, seven different *FLG* null mutations have been identified (3321delA, 6950_6957del8, S1515X, S2706X, Q2417X, E2422X, and G323X), which account for 80% of the *FLG* mutation spectrum.[34,35] In another study, the *FLG* mutations K4671X and 3321delA were two of the most commonly identified *FLG* mutations of patients with AD in northern China (K4671X:11.2%, 3321delA:9.7%).[36] The OR for eczema was found to be higher for the R501X mutation than for the 2282del4 mutation in a meta-analysis, suggesting a possible differential risk effect associated with the *FLG* mutation site; however, an insufficient number of large studies have examined other uncommon recurrent null alleles, limiting the ability to explore this possibility further.[37] Serine protease inhibitor Kazal-type 5 (*SPINK5*) encodes lymphoepithelial Kazal-type related inhibitor (LEKTI), which is also involved in skin barrier function and AD development. LEKTI is a serine protease inhibitor that degrades corneodesmosome, leading to defects in barrier permeability. LEKTI polymorphisms are associated with common atopy and AD, especially in Eastern Asian populations.[38-42]

Different immunological status in Asian AD

Atopic dermatitis (AD) is thought to be associated with skin barrier dysfunction and adaptive immune responses to common environmental allergens mediated by T_H2 cells. Polymorphic differences among ethnic groups have been described in genes involved in innate and adaptive immunity, especially T_H2 signaling pathways. IL-4 polymorphisms are significantly associated with atopic AD in Egyptian, Japanese, and Chinese populations.[43-46] Several IL4R polymorphisms have been associated with AD in Japanese populations.[47] Linkage and association studies found that polymorphisms in the gene encoding signal transducer and activator of transcription 6 were significantly associated with allergic diseases, including AD, in Egyptian and Japanese populations.[44,48] IL-13 polymorphisms were significantly associated with an increased risk of AD in Japanese populations.[49,50]

Recent findings suggest that AD is more heterogeneous across more aspects than differences in T_H2-centric inflammation. In addition to T_H2/T_H22 pathways, T_H1 and T_H17 immune pathways have been implicated in AD pathogenesis. The epidermal hyperplasia response in chronic AD is likely driven directly by IL-22 produced by T_H22 cells.[51] Some AD subtypes are associated with T_H17, resulting in increased production of IL-17.[52] Intrinsic AD showed the stronger activation of T_H17 and T_H22 responses than extrinsic AD.[23] Early pediatric AD is associated with a significant increase in the induction of T_H17-related cytokines and antimicrobials (IL-17A, IL-19, CCL20, LL37, and peptidase inhibitor 3/elafin) compared with adult AD.[53] Although T_H2 activation has been described across all races and ethnicities investigated, studies in the Japanese population have demonstrated the expansion of IL-17$^+$ T cells in both skin and blood, suggesting that the Asian AD phenotype may exhibit distinct immune and barrier features compared with the EA AD phenotype. In additional to T_H2 activation, patients of Asian descent (Japanese or Korean) with AD had strong T_H17 activation, overlapping clinically and molecularly with some hallmarks of psoriasis.[31,54] Lesional epidermis derived from Japanese and Korean patients with AD showed greater acanthosis, higher Ki67 counts, frequent parakeratosis, focal hypogranulosis, and more elongated rete ridges but relatively preserved barrier proteins expression, including filaggrin and loricrin, compared with the EA AD population. Significantly higher T_H17 and T_H22 (IL17A, IL19, and S100 calcium-binding protein A12 [S100A12] in lesional and IL-22 in non-lesional skin) and lower T_H1/interferon (CXCL9, CXCL10, MX1, and IFN-γ in non-lesional skin) gene induction was observed in AD skin from Japanese and Korean patients.[31] IL-19 is induced by both IL-17 and IL-4/IL-13, which induces epidermal hyperplasia and amplifies many IL-17A effects on keratinocytes, and showed robust and significant increases in the Asian AD phenotype compared with the EA AD phenotype.[31] The psoriasis-like histologic features in the skin of the Asian AD population might be attributed to increased T_H17/T_H22 polarization and IL-19 induction.[31] Peripheral blood from these Asian patients with AD show significant increases in the T_H2/IL-13/CCL26 and T_H22/IL-22 axes, with decreases in T_H1/IFN-γ (IFN-γ, CCL2, CCL3, and CCL4) axis, which is highly correlated with the pattern found in the skin.[55] Decreased expression of T_H1 pathway genes in Asian patients with AD might be attributed to a negative regulatory effect of IL-17 on the IFN/T_H1 pathway.[31] Elevated IL-22 levels in Asian patients with AD are concordant with T_H17/T_H22 upregulation and the occurrence of more prominent epidermal hyperplasia and parakeratosis in the Asian AD population.[31,55] Similar to the results observed in Japanese and Korean populations with AD, skin lesions in Chinese individuals with AD show prominent hyperplasia, parakeratosis, and increased T_H17-skewing with decreased T_H1 activation compared with EA AD.[56] A positive correlation exists between IL-17A expression and severity (as measured using the scoring atopic dermatitis [SCORAD] scale) in Chinese patients with AD.[56] The T_H17-produced cytokine IL-17 is a key inducer of antimicrobial peptides and neutrophil chemoattractants.[57] Neutrophil infiltration has been described more consistently in AD patients of East Asian descent (Japanese, Korean, and Chinese) compared with EA patients with AD.[56,58] Interestingly, several T_H2 markers were significantly upregulated in Chinese psoriasis lesions from Chinese patients compared with those from EA patients. These data revealed overlapping tissue patterns between AD and psoriasis in the Chinese population, with variable degrees of T_H2 and T_H17 upregulation in both diseases. CCL26 was significantly upregulated in Chinese patients with AD and downregulated in Chinese patients with psoriasis and can be used to discriminate AD from psoriasis in the Chinese population.[56] The significant increase in CCL26 levels observed in Asian patients with AD is in line with reports describing increased circulating eosinophil counts in Asian patients compared with EA patients.[55] Thus, in the Asian population, AD is a disease with features observed in both EA AD and psoriasis (parakeratosis and increased neutrophils) and is characterized by a unique combination of immune dysregulation, including T_H17/T_H22 upregulation accompanied by comparable or even greater T_H2 activation (IL-13 and CCL26) and decreased T_H1/IFN-γ levels.[31,55,56]

Therapeutic implications for Asian patients with AD

Treatment of AD consists of initial assessment should include detailed history and the extent and severity of AD, followed by delivering basic care with emollients, therapeutic patient education and avoidance of irritants/allergens. Induction pharmacologic therapy is to provide immediate control of pruritus and inflammation by antihistamines and

topical corticosteroids (TCSs). If the signs and symptoms of the disease is inadequately controlled, treatment options such as burst use of systemic corticosteroids, phototherapy, or control of infections might be considered. Systemic immunomodulatory agents, potent TCSs, alternative medicine or psychotherapeutic approach might be helpful for severe recalcitrant disease. All patients may be switched to maintenance therapy once the disease is under control, and they may return to continuing basic care if the lesions achieve complete remission [Figure 2].[4]

Although Western medicine and ideas about AD have become popular in many Asian countries, local beliefs about the causes of AD and the types of treatment often prevail. Complementary and alternative medicine, traditional Chinese medicine, and integrative medicine usage are prevalent among the Asian population.[57] Despite its popular use in Asian societies, studies examining the safety and efficacy of traditional Chinese herbal mixtures in children with AD have reported inconsistent results.[58] Western medicine practitioners are often ignorant about complementary and alternative medicine. In addition, many of the cultural practices are preserved among the southeast Asian minorities residing in the United Kingdom and North America.[57] Parents are concerned about the potential side effects of Western medicine and are more likely to cause nonadherence to medication. Nonadherence to TCSs is associated with concern/fear of their side effects (TCS phobia or corticophobia). In a large international study evaluating levels of corticophobia by the validated Topical Corticosteroid Phobia score, Taiwan is among the top three counties with the highest levels of corticophobia.[59] Recognizing this phenomenon and providing accurate information are necessary for improving medication adherence and treatment outcome.[4]

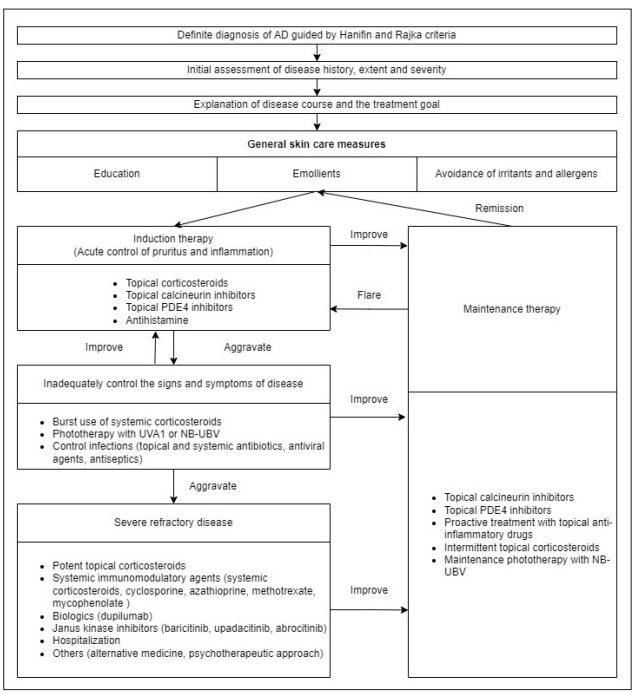

Figure 2: Atopic dermatitis treatment algorithm.

Given its key role in the pathway of T_H2 mediated immune response, IL-4 receptor subunit alpha (IL-4Rα) blockade was anticipated to represent a therapeutic approach to treating allergic diseases. Dupilumab is a fully IgG4 human monoclonal antibody that binds IL-4Rα and inhibits IL-4R signaling induced by both IL-4 and IL-13, and down-regulates T_H2 inflammation.[60] Although T_H2-skewing is common across all AD subtypes, as suggested by the efficacy of dupilumab across populations with AD, therapeutic targeting in AD is complicated by the contributions of multiple immune axes to different pathogenic disease features. Approximately 60% of patients attain a 75% reduction from baseline in the Eczema Area and Severity Index following dupilumab treatment, which suggests that AD is not a pure T_H2 disease.[60-62] Additional targeted therapies are likely to contribute to improved AD resolution across all subtypes. AD might be considered a multi-axis immune disease requiring the combined blockade of the T_H2, T_H22, and potentially T_H17 immune axes. Some AD subtypes with significant T_H17/T_H22 activation, such as intrinsic and pediatric AD and AD in Asian populations, may benefit from therapeutic agents that target the T_H17/IL-23 or T_H22/IL-22 axes. A randomized, double-blind, placebo-controlled trial examining monotherapy with intravenous fezakinumab (an IL-22 monoclonal antibody) showed improvements in SCORAD evaluations, body surface area involvement, and Investigator Global Assessment compared with placebo. IL-22 blockade only appears to elicit significant clinical effects in patients with severe AD.[63] Greater mean SCORAD improvements were observed following fezakinumab administration in the IL-22–high group than in the IL-22–low group.[64] Future studies may evaluate whether Asian patients with AD can benefit from IL-22 antagonism therapy.

Recently, a phase 2 randomized, double-blinded study examined the use of the IL-17–targeting agent secukinumab on intrinsic and extrinsic AD. The entire cohort of patients receiving secukinumab versus placebo was analyzed, with further analysis of patients with intrinsic AD versus patients with extrinsic AD. However, compared the secukinumab-treated with placebo groups, no significant differences were observed in either group in the primary outcome of changes in epidermal hyperplasia, clinical outcome measures, or secondary translational endpoints, as assessed by evaluating the mRNA expression of T_H17/IL-23–related products, even in in the secukinumab-treated patients with intrinsic AD.[65] Overall, 16 Asian patients were enrolled in this study, but no significant changes were found between secukinumab

Table 1: Characteristics atopic dermatitis (AD) in Asian and European American populations

	Asian AD	European American AD
Epidemiology	High prevalence (~10%)	~8%
Clinical phenotype	Clearer demarcation of lesions, with prominent scaling and lichenification.	Indistinct borders, wet and erythematous. In patients with chronic disease, lichenification, dry, and hyperpigmentation
Histopathology	Prominent hyperplasia, parakeratosis, hypogranulosis, and neutrophil infiltration.	Rare parakeratosis and rare neutrophils.
Epidermal barrier	Fewer *FLG* null mutations (27%), and *FLG* null mutations unique to ethnic groups.	Common *FLG* null mutations (~50%), especially R501X, 2282del4, S3247X, and R2447X.
Immune polarization	$T_H1\uparrow$ $T_H2\uparrow\uparrow\uparrow$ $T_H17\uparrow\uparrow$ $T_H22\uparrow\uparrow\uparrow$	$T_H1\uparrow\uparrow$ $T_H2\uparrow\uparrow\uparrow$ $T_H17\uparrow$ $T_H22\uparrow\uparrow\uparrow$

treatment and placebo in this subgroup. The outcomes of this study show that IL-17 may not represent a valid therapeutic target in patients with AD, including subsets of patients with higher T_H17 activation, such as those with intrinsic AD and Asian patients, in contrast to the hypothesis that IL-17A is a sole pathogenic contributor to AD. Janus kinase inhibitors (JAK inhibitors or jakinibs) inhibit signaling pathways through a variety of cytokine and hematopoietic growth factor receptors, including in the T_H1 (IL-2, IL-12, IFN-γ), T_H2 (IL-4, IL-5, IL-13), and T_H17 (IL-17, IL-22) axes, which may provide therapeutic relief for Asian patients with AD.[66]

CONCLUSION

The AD phenotype observed among patients of Asian descent might be associated with differences in epidemiology, clinical phenotype, histopathology, barrier defects, and immune characteristics than the better-studied phenotype in the EA population [Table 1]. Asian patients with AD present with a unique immune phenotype that combines the characteristics of AD and psoriasis and might require new clinical trials with specific cytokine antagonists, in addition to T_H2-specific therapies. Combination therapy with T_H2-targeting strategies and strategies that target the cytokines IL-17, IL-23, and IL-22 must be further evaluated and may lead to personalized or precision medicine approaches for the various AD subtypes.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflict of interest

Author Prof. (Dr.) Chia-Yu Chu is on the Editorial Board of the journal.

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