Atopic dermatitis endotypes and implications for targeted therapeutics

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Activity Objectives:

1. To describe the characteristics of intrinsic and extrinsic atopic dermatitis (AD).
2. To identify the phenotypes and endotypes across ethnic groups.
3. To distinguish the differences between AD in pediatric and adult patients.
4. To list the current endotype-based targeted therapeutic approaches for AD.

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Recent research advancements indicate that atopic dermatitis (AD) is a complex disease characterized by different subtypes/phenotypes based on age, disease chronicity, ethnicity, filaggrin and IgE status, and underlying molecular mechanisms/endotypes. This heterogeneity advocates against the traditional "one-size-fits-all" therapeutic approaches still used to manage AD. Precision medicine approaches, striving for targeted, tailored, endotype-driven disease prevention and treatment, rely on detailed definitions of the disease's variability across different phenotypes. Studies have shown that AD harbors different endotypes across different age groups and ethnicities and according to IgE levels and filaggrin mutation status. These include European American versus Asian patients, children versus adults, intrinsic versus extrinsic (IgE status) disease, and patients with and without filaggrin mutations. Therapies targeting different cytokine axes and other mechanisms involved in disease pathogenesis, which are currently being tested for patients with AD across the disease spectrum, will

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expand our ability to dissect the relative contribution of each of these pathways to disease perpetuation. (J Allergy Clin Immunol 2019;143:1-11.)

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Abbreviations used
AD: Atopic dermatitis
AMP: Antimicrobial peptide
EA: European American
FLG: Filaggrin
LOR: Loricrin
TEWL: Transepidermal water loss

Atopic dermatitis (AD) is a highly heterogeneous inflammatory skin disorder.[1] Skin and blood phenotyping and genotyping advancements, as well as the development of targeted therapeutics over the past few years, portray a complex disease profile.[2-6]

Endotype is defined as the molecular mechanisms underlying the disease's visible features/phenotype.[7,8] An example of an endotype that can control a phenotype is the presence of high IgE levels in patients with an allergic phenotype. AD is not only diverse phenotypically (children vs adults and white vs Asian patients) but is also characterized by a highly diverse endotype repertoire ($T_H1/T_H2/T_H17/T_H22$ immune activation with a compromised epidermal barrier, including terminal differentiation and lipid and tight junction abnormalities[9]). In patients with AD and other allergic disorders, few subendotypes comprised of several determinants with dynamic interactions can lead to a "complex endotype" that drives a specific phenotype.[10]

Despite these complexities, AD is generally managed according to a "one-size-fits-all" therapeutic approach, rather than adapting personalized, precision, endotype, and ethnicity-driven therapeutic strategies. Stratification of endotypes and definition of disease biomarkers specific to the different AD phenotypes might be important for developing personalized medicine approaches that can potentially improve therapeutic outcomes.

There are 2 major approaches for characterization and stratification of AD endotypes. The first encompasses endotyping based on molecular profiling across the entire AD spectrum.[11-13] Recent principal component analysis based on 147 serum mediators from 193 patients with AD and 30 healthy control subjects divided the AD population into 4 main clusters characterized by unique serum measures.[11] This approach does not differentiate between ethnic groups, the patient's geographic origin, or other clinical or demographic characteristics and in the United States has to be performed in a Clinical Laboratory Improvement Amendments–certified facility if used for therapeutic decisions. Conversely, the alternative methodology includes detailed endotyping based on specific clinical, ethnic, or demographic patient groups, assuming AD is not one spectrum but rather comprises different disease phenotypes. According to the second approach, in this review we will describe different endotypes of specific clinical and ethnic AD subsets (summarized in Fig 1) and will discuss how they translate into advancing precision therapeutic approaches for AD.

ACUTE VERSUS CHRONIC AD

AD is characterized clinically by acute and chronic stages. Acute (new onset, within 72 hours) lesions are usually erythematous, wet, and highly inflammatory, turning lichenified, dry, thick, and hyperpigmented in patients with chronic disease.[14-16] Comparing the skin profile of nonlesional, acute, and chronic AD skin[17] showed both barrier and immune disparities between disease stages. Chronic lesions are more hyperplastic and proliferative, with increased keratin 16 mRNA expression and Ki67 counts. The initiation of acute lesions is accompanied by marked increases in antimicrobial peptide (AMP) levels (S100A7/S100A8/S100A9) and T_H2 and T_H22 cytokine upregulation, with positive correlations between *IL22* mRNA levels and AD severity determined based on SCORAD scores. Lesser inductions of T_H17 markers are also observed in acute lesions. With disease chronicity, there is intensification of T_H2 and T_H22 cytokine axes, with significant increases in T_H1 markers in patients with chronic AD but no further increases in T_H17 markers.

INTRINSIC VERSUS EXTRINSIC AD

AD can be classified according to IgE levels into extrinsic and intrinsic subgroups. The classic (80%) extrinsic phenotype is characterized by high total and environmental serum IgE levels, eosinophilia, personal and family atopic background, and greater rate of filaggrin *(FLG)* mutation.[18-20] Despite a similar clinical presentation, patients with intrinsic AD (20%) have normal IgE levels; have female predominance; show delayed disease onset and preserved barrier function, as measured based on transepidermal water loss (TEWL)[20]; have increased metal contact hypersensitivity[20]; and lack any other atopic background.[21,22]

In blood the intrinsic endotype includes T_H1 but not T_H2 or T_H17 marker increases and low CCL17/thymus and activation-regulated chemokine levels.[23] We compared molecular and cellular measures in lesional and nonlesional skin of 42 patients with extrinsic and 9 patients with intrinsic AD. Both disease forms showed increased T-cell and dendritic cell cutaneous infiltrates along with epidermal hyperplasia in lesional compared with nonlesional skin; however, greater cellular infiltrates (T cells, myeloid dendritic cells, and Langerhans cells) were seen in patients with intrinsic AD. Nonlesional measures were overall comparable between the 2 groups. Contrary to past studies,[23,24] data did not show a bias toward T_H2 in patients with extrinsic AD, and T_H2 marker increases were grossly similar between intrinsic and extrinsic lesional skin. Increased T_H1 signal (IFN-γ, CXCL9, CXCL10, and MX-1) and more pronounced T_H17/T_H22 activation (IL-17A, CCL20, Elafin, and IL-22) historically linked to psoriasis[25] were significantly greater in patients with intrinsic AD. Parallel to these increases, levels of the antimicrobials S100A9 and S100A12, which are coregulated by IL-17/IL-22,[26] were greater in intrinsic versus extrinsic lesions. Although T_H2 markers in patients with extrinsic AD correlated positively with disease severity and negatively with barrier products (loricrin [LOR], periplakin, and FLG),

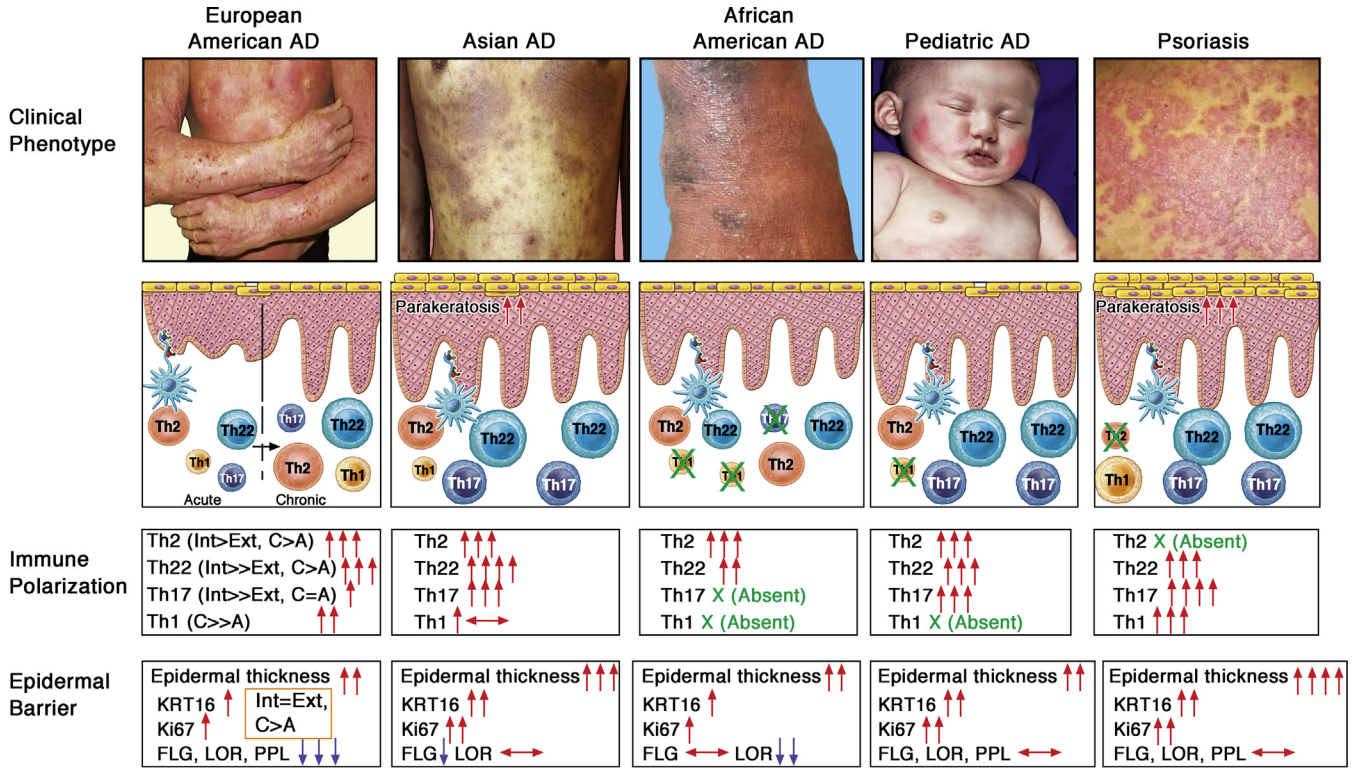

FIG 1. AD phenotypes and related endotypes. Presented are clinical phenotypes, polar cytokine activation cartoons, immune polarization of T-cell subsets, and epidermal barrier changes for each AD phenotype. Intrinsic *(Int)*, extrinsic *(Ext)*, acute *(A)*, and chronic *(C)* subtypes were characterized only in EA patients with AD and thus appear exclusively under this category. Epidermal barrier measures, including epidermal thickness, keratin 16 *(KRT16)*, Ki67, FLG, LOR, and periplakin *(PPL)*, were similar in patients with intrinsic and extrinsic AD but more evident in EA patients with chronic versus acute AD.

T_H1/interferon-related gene expression and levels of the T_H17 chemokine CCL20 correlated with disease severity in patients with intrinsic AD. Later reports showed an inflammatory (IL-22, IL-36α/γ, IL-36RN, and CCL22) and lipid metabolism pathway overlap between intrinsic AD and psoriasis, further supporting T_H17/IL-23 and IL-22 as common denominators of the 2 conditions.[27,28]

AD PHENOTYPES AND ENDOTYPES VARY ACROSS DIVERSE ETHNIC ORIGINS

AD in European American versus Japanese and Korean patients

Endotyping AD according to different ethnic backgrounds is critical for establishing disease biomarkers and nurturing precision therapeutic approaches. Although AD prevalence in European American (EA) adults is approximately 3% to 4%,[29,30] it is substantially greater in Asian countries (7% to 10%).[31-33]

Studying the Asian AD endotype, Koga et al[34] showed increased T_H17 frequencies in blood and acute lesions of Japanese patients with AD, both of which are associated with AD severity. These results are in contrast to skin and blood data from EA patients with extrinsic AD who did not show T_H17 axis activation.[2,19] A study comparing lesional and nonlesional skin of EA and Asian (Japanese and Koreans) patients with AD with that of patients with psoriasis and control subjects showed prominent epidermal hyperplasia and marked parakeratosis in Asian subject but relatively preserved barrier proteins (LOR and FLG). RT-PCR analysis revealed that although T_H2 markers (IL-13, CCL17, CCL18, and CCL22) were similar between Asian and EA patients with AD, T_H1 markers were significantly lower in lesional and nonlesional tissues of Asian patients with AD, possibly because of negative regulation by T_H17 marker increased.[35,36]

Importantly, greater expression of T_H17-related cytokines (IL-17A and IL-19) and related markers (CCL20), as well as IL-22 and the IL-17/IL-22–induced S100A12, were seen in lesional and nonlesional skin of Asian patients with AD. Levels of IL-19, which was induced by IL-4, IL-13, and IL-17 and augments IL-17's effects on keratinocytes,[37,38] were significantly greater in AD lesions of Asian versus EA patients. These data suggest that Asian patients with AD are characterized by a unique blended immune dysregulation and barrier feature phenotype between EA patients with AD and those with psoriasis. In line with their skin endotype, increased levels of T_H2 cytokines and related chemokines were similarly seen in sera of EA and Asian patients with AD, correlating with AD severity and IgE levels.[39]

Additionally, lower IFN-γ levels and levels of other T_H1-related markers were detected in sera from Asian patients. IL-17 levels were equally increased in sera of EA and Asian patients, but levels of the hyperplasia-inducing cytokine IL-22 were substantially increased in the blood of Asian patients compared with that of EA patients. Eventually, levels of a series of T_H2 markers and IL-22 in serum correlated positively with their mRNA expression specifically in nonlesional skin, supporting their potential as biomarkers reflecting overall rather than lesion-limited disease activity.[39]

AD in EA versus Chinese patients

Studies suggest that Chinese patients with AD have a unique clinical phenotype compared with EA patients with AD.[40] Our recent study[41] that compared Chinese patients with AD and patients with psoriasis versus control subjects showed that AD in Han Chinese patients is accompanied by remarkable epidermal hyperplasia, robust T_H2 cytokine and chemokine activation (IL-4, IL-13, IL-5, IL-10, IL-31, and CCL13/17/18/22/26), and T_H17/IL-23–induced (eg, IL-17F/IL-19/IL-21/CCL20) and T_H17/T_H22-induced (IL-22/S100As) marker upregulation. SCORAD scores correlated with IL-31, IL-5, and IL-17A levels. We also compared Chinese patients with AD with patients with the EA AD phenotype and found that lesional T_H17 expression was greater, whereas levels of IFN-γ and other T_H1-related markers were lower in Chinese patents compared with those in EA patients with AD. Altogether, these results establish a consistent T_H17/T_H2 or blended AD-psoriasis endotype across Asian patients with AD, supporting possible therapeutic approaches that benefit psoriasis in these populations.

AD in EA versus African American patients

AD is particularly common in African American patients (approximately 19%),[42,43] in whom the disease has a treatment-resistant lichenified phenotype,[44-47] but lack of studies limit therapeutic advancements in this population. Pathogenic differences were described between African American and EA patients with AD,[48] and genome-wide association study data identified some AD-associated gene polymorphisms.[49-53] Preliminary endotype data on this population, which compared African American and EA patients with AD with their respective control subjects,[54] found that African American patients with AD represent a distinct endotype. *FLG* loss-of-function mutations are not prevalent in African American patients with AD,[52,55,56] but FLG variations were associated with AD persistence in these patients.[57,58] African American patients with AD exhibited different barrier alterations compared with EA patients in parallel with T_H1/T_H17 attenuation and primarily T_H2/T_H22 skewing, as evidenced by molecular profiling.[59] Although T_H2 augmentation can be influenced by parasite pressure-driven genetic selection in African American patients,[60] upregulation of T_H22, which is reportedly associated with keratinocyte proliferation, epidermal hyperplasia, hyperkeratosis, and other barrier abnormalities,[61,62] might account for the atypical lichenified phenotype typically seen clinically in African American patients with AD, highlighting the potential of IL-22–targeted approaches in these patients.

Overall, defining disease biomarkers is an essential component in adapting precision medicine approaches, AD diagnosis, follow-up, and tailored drug selections. We have shown that integrated models of lesional and nonlesional skin and blood measures best reflect disease severity in both EA and Asian patients with AD.[39,63]

AD ACROSS DIFFERENT AGE GROUPS PRESENTS DIVERSE PHENOTYPES AND ENDOTYPES

Pediatric versus adult AD

Morphology and distribution of AD lesions differ between age groups, with face, trunk, and extensor limb inflammatory involvement in infants and young children and lichenified, chronic, dry, and flexural distribution in adults.[64] These changes might derive from background endotype skewing over time. Thus it is crucial to define those changes to tailor adequate treatments.[65]

Early life is a critical period for immune development. At birth, most T cells are naive, developing gradually into memory subsets, a process that is accelerated in children with AD.[66] Eighty-five percent of AD cases begin before the age of 5 years.[67,68] Studies have shown low T_H1 and high T_H2 levels in cord blood of neonates with AD.[69-71] This profile can be induced by various epigenetic factors, suggesting environmental influence on AD susceptibility.[72] High T_H2 with low or unaltered T_H1 signals in blood were subsequently reported in the toddler and young childhood age groups.[70,73-75] Results of flow cytometry in blood showed suppressed and delayed skin-homing T_H1 development in children with AD compared with control subjects or adults with AD.[66] Highlighting their role in disease initiation, persistence, and instigation of the atopic march, T_H2 frequencies were similarly increased in adults and children with AD within the skin and systemic compartments. IL-22, which is linked to disease chronicity,[66] and IL-9 and IL-17 frequencies in CD4/CD8 cells were similar between children with and without AD and lower than those in adults.[3] Given the selective activation of T_H2 in early-onset pediatric blood, we also demonstrated alterations in B-cell subsets and IgE allergen sensitization that increase with age in children with AD,[76] highlighting IgE and barrier integrity significance in early disease initiation.

Endotyping skin of patients with early-onset (<6 months) pediatric AD[77] showed profound epidermal hyperplasia and proliferation, with preserved FLG protein and mRNA expression. Parallel activation of the high-affinity receptor for IgE ($Fc\varepsilon RI^+$) and pattern recognition receptors, including Toll-like receptors, was implicated in allergen sensitization and AD initiation.[78-80] Indeed, although T-cell infiltration was similar to that in adults, $Fc\varepsilon RI^+$ counts were significantly greater in pediatric skin.

Although children lacked T_H1 signal in skin, levels of T_H2 cytokines and related chemokines (IL-13, CCL17, CCL18, CCL22, CCL26, OX40 ligand, and thymic stromal lymphopoietin receptor) were either similar or even greater in lesional and nonlesional pediatric AD skin compared with those in adults. IL-9/T_H9 expression was significantly greater in pediatric versus adult AD lesions. T_H17/T_H22-related marker (IL-17A, IL-12/23p40, CCL20, LL37, IL-19, and IL-22) and AMP (LL37, DEFB4B, and LCN2) expression increases were already seen in pediatric healthy skin, with further significant increases in AD skin to levels often comparable with those in adults with psoriasis. Similar to Asian patients with AD, who demonstrated a blended endotype between EA patients with AD and psoriasis, children with AD also showed a T_H2/T_H17-merged profile, as reflected by an increase in IL-19 expression. Overall, lesional and nonlesional pediatric profiles clustered around psoriasis and not their adult counterparts with AD, underlining the resemblance of this endotype to psoriasis and suggesting the possibility of entertaining different therapeutic approaches in young children with AD, particularly those that are successfully implemented in patients with psoriasis.

In their recent work Brunner et al[81] corroborated and expanded on these results. Tight junctions and lipid barrier genes were significantly downregulated in children with AD, possibly accounting for the compromised epidermal barrier function seen in pediatric patients with AD despite preserved FLG/LOR levels. Additionally, T_H17 activation (through IL-26) was

TABLE I. Targeted therapies and their applicability for specific AD endotypes and phenotypes

Agent	Target	Phase	Manufacturer	www.ClinicalTrials.gov	Endotype targeted	AD phenotype
Dupilumab	IL-4Ra	FDA approved, 2017, in phase II for pediatric AD	Regeneron, Eastview, NY	NCT01949311 NCT02407756 NCT02612454 NCT03054428	T_H2/T_C2	All AD phenotypes
Pitakinra/ Aeroderm	IL-4	Phase IIa completed	Aerovance, Berkeley, Calif	NCT00676884	T_H2/T_C2	All AD phenotypes
Mepolizumab	IL-5	In phase IIa	GlaxoSmithKline, Research Triangle Park, NC	NCT03055195	T_H2/T_C2	AD with increased eosinophil counts
Tralokinumab	IL-13	In phase III	MedImmune, Gaithersburg, Md	NCT02347176	T_H2/T_C2	All AD phenotypes
Lebrikizumab	IL-13	In phase III	Hoffmann-La Roche, Basel, Switzerland	NCT02340234	T_H2/T_C2	All AD phenotypes
QAW039/ Fevipiprant	CRTH2	Phase IIb completed (drug development program has been stopped)	Novartis, Basel, Switzerland	NCT01785602	T_H2/T_C2	All AD phenotypes
OC000459	CRTH2	Phase IIa completed (drug development program has been stopped)	Atopix, Carlsbad, Calif	NCT02002208	T_H2/T_C2	All AD phenotypes
AMG157/ tezepelumab	TSLP	Phase IIa completed	Amgen, Newbury Park, Calif	NCT00757042	T_H2/T_C2, T_H17 Affects sensitization pathways	All AD phenotypes/ prevention of atopic march?
MK-8226	TSLPR	In phase I	Merck, Whitehouse Station, NJ	NCT01732510	T_H2/T_C2, T_H17 Affects sensitization pathways	All AD phenotypes/ prevention of atopic march?
GBR830	OX40	In phase II	Glenmark, Mumbai, India	NCT02683928	T_H2/T_C2	All AD phenotypes
KHK4083	OX40	Completed phase I	Kyowa Hakko Kirin, Otemachi, Japan	NCT03096223	T_H2/T_C2	All AD phenotypes
QGE031	IgE	Phase II completed	Novartis	NCT01552629	Allergic sensitization	Extrinsic AD, AD in African American patients, AD in Asian patients, pediatric patients with AD
Tofacitinib	JAK1/3	Phase II published	Innovaderm, Montreal, Quebec, Canada	NCT02001181	T_H1, T_H2, T_H22, IFN-α IgE class-switching Keratinocyte differentiation and pruritus	All AD phenotypes
Baricitinib (LY3009104)	JAK1/2	Phase IIb completed	Eli Lilly, Indianapolis, Ind	NCT02576938	See above	All AD phenotypes
Upadacitinib	JAK1	In phase II	AbbVie, Lake Bluff, Ill	NCT02925117	See above	All AD phenotypes
ASN002	JAK/SYK	In phase IIb	Asana BioSciences, Lawrenceville, NJ	NCT03531957	See above plus T_H17	All AD phenotypes
PF-04965842	JAK1	In phase III	Pfizer, New York, NY	NCT03349060	See above	All AD phenotypes
Crisaborole/ Eucrisa	PDE_4	FDA approved, 2016	Pfizer	NCT02118766 NCT02118792	General anti-inflammatory	All AD phenotypes
Roflumilast	PDE_4	In phase IIa	AstraZeneca, Cambridge, United Kingdom	NCT01856764	General anti-inflammatory	All AD phenotypes
RVT-501	PDE_4	In phase IIa	Dermavant Sciences, Phoenix, Ariz	NCT03415282	General anti-inflammatory	All AD phenotypes
Apremilast/ Otezla	PDE_4	Phase IIa completed (drug development program has been stopped)	Celgene, Summit, NJ	NCT02087943	General anti-inflammatory	All AD phenotypes

(Continued)

TABLE I. *(Continued)*

Agent	Target	Phase	Manufacturer	www.ClinicalTrials.gov	Endotype targeted	AD phenotype
Ustekinumab/ Stelara	IL-12/23p40	Phase II published	Janssen, Beerse, Belgium	NCT01806662	T_H17, T_H1, T_H22	Intrinsic AD, Asian patients with AD, EA patients with chronic AD, pediatric patients with AD
CIM331/ nemolizumab	IL-31R	Phase II completed	Chugai, Tokyo, Japan	NCT01986933	Pruritus/T_H2	All AD phenotypes
BMS-981164	IL-31	Phase Ib completed	Bristol-Myers Squibb, New York, NY	NCT01614756	Pruritus/T_H2	All AD phenotypes
ILV-094/ Fezakinumab	IL-22	Phase II published	Pfizer	NCT01941537	T_H22, T_H17	Intrinsic AD, Asian patients with AD, adult EA patients with AD, African American patients with AD
Secukinumab/ Cosentyx	IL-17A	In phase II	Novartis	NCT02594098	T_H17 (and IL-22)	Intrinsic AD, Asian patients with AD, pediatric and elderly patients with AD
MOR106	IL-17C	In phase II	Galapagos NV, Mechelen, Belgium	NCT03568071	Th17	Intrinsic AD, Asian patients with AD, pediatric and elderly patients with AD

CRTH2, Chemoattractant receptor–homologous molecule expressed on T_H2 lymphocytes; *FDA*, US Food and Drug Administration; *IL-4Ra*, IL-4 receptor antagonist; *IL-31R*, IL-31 receptor; *JAK*, Janus kinase; *PDE_4*, phosphodiesterase 4; *TSLP*, thymic stromal lymphopoietin; *TSLPR*, thymic stromal lymphopoietin receptor.

positively correlated with the barrier measure TEWL, demonstrating the role of T_H17 in orchestrating barrier properties in patients with early AD.

AD in the elderly

Phenotype differences ("reverse sign" of lichenification) have been described for AD in older patients compared with the usual lichenification seen in the folds of younger adults.[82] AD prevalence is greatest in the younger population and decreases with age. We have recently compared the AD endotype among 3 age groups (18-40, 41-60, and ≥61 years old),[83] showing decreases with age in T_H2/T_H22 axes and parallel increases with age in T_H1/T_H17 axes and a less pronounced barrier defect. Thus targeted treatment approaches tailored for elderly patients with AD are needed. These data also support the notion that allergic sensitization through an impaired barrier likely plays a major role during early AD initiation, which precedes the atopic march, rather than in late disease stages, emphasizing the potential of barrier-targeted approaches in earlier rather than later disease stages.

AD FEATURES VARY ACCORDING TO THE PATIENT'S FLG STATUS

It is now recognized that AD pathogenesis is driven by a combination of immune dysregulation and impaired epidermal barrier integrity.[84-87] The primary defect that initiates the atopic cycle is still not clear; however, the general concept is that a skin barrier defect facilitates allergen penetration, leading to innate immune activation, Langerhans cells migration to regional lymph nodes, T_H2 production, and promotion of B-cell IgE switch, with T cells recirculating back to the skin and systemic organs to initiate AD and the atopic march.[79]

FLG (a filament-aggregating protein) is a key component of the epidermal differentiation complex, a cluster of more than approximately 70 genes located on chromosome 1q21 encoding for main terminal differentiation proteins involved in formation of the cornified envelope.[88] FLG is the major structural protein of the stratum corneum.[85,89] Its degradation products are essential for skin hydration, pH balance, and epidermal barrier integrity.[89,90]

FLG loss-of-function (LOF) mutations are the most common genetic susceptibility to AD[91] but are found in only 10% to 40% of patients.[52,92-94] However, regardless of its mutation status, FLG and other differentiation markers (eg, LOR) are decreased in AD lesional and nonlesional skin, likely because of IL-4, IL-13, IL-17A, and IL-22 upregulation.[95-97] The role of FLG in patients with AD is controversial because AD develops in only 42% of all FLG heterozygotes,[98] the majority of patients with AD with FLG mutations outgrow their disease,[98,99] and despite the disproportionally high prevalence of AD in African American subjects, only 3% have FLG mutations.[52] Nevertheless, AD associated with FLG LOF mutations has a distinct profile. It is characterized by reduced barrier function (measured by TEWL), increased allergic sensitization (eg, asthma and food allergy) and contact allergy, higher severity, protracted course, and frequent skin infections, particularly eczema hepeticum.[93,98,100-107]

Proof-of-concept FLG replacement therapy studied in model systems was shown to have a beneficial effect.[108] Otsuka et al[109] reported on a bioactive product (JTC801) that increased FLG expression in mice and keratinocyte cultures, attenuating AD-like skin inflammation in mice. The emollient petrolatum improved FLG synthesis in patients with and without AD in parallel with reducing skin inflammation and increasing AMP expression.[110] Amano et al[111] showed that application of the Janus kinase inhibitor JTE-052 on dry skin mouse models improved skin barrier function and increased terminal differentiation proteins, such as FLG. Dietary modifications[112] and engineered FLG monomer linked to a cell-penetrating peptide showed promising results in cultures and mice.[108] Liver X receptors are involved in epidermal barrier maintenance and suppression of inflammatory responses in model systems. The liver X receptor agonist VTP-38543 significantly increased FLG (and LOR) mRNA expression and reduced epidermal hyperplasia in patients with mild-to-moderate AD, with a nonsignificant effect on immune dysregulation.[113] Thus it might be that barrier-based approaches are more suited to prevent AD and the atopic march rather than for treating active disease, which necessitates direct targeting of immune dysregulation.

The value of most of these compounds in patients with active AD is yet to be determined, but if any, these approaches might prove beneficial in adults rather than in pediatric patients with AD in whom FLG expression levels were shown to be normal. Nevertheless, 2 pivotal studies indicated the potential of early skin emolliation to prevent AD in high-risk neonates.[114,115] However, once the cutaneous disease is overt and immune dysregulation predominates, systemic immune intervention (eg, dupilumab) might be mandated.

STAPHYLOCOCCUS AUREUS–COLONIZED PATIENTS WITH AD HAVE A UNIQUE PHENOTYPE AND ENDOTYPE

The vast majority of patients with AD are colonized and/or infected with *S aureus*, with emerging methicillin-resistant *S aureus* strains presenting a therapeutic challenge.[116-118] Complex interaction exists between *S aureus* and its related toxins and the immune dysregulation and barrier impairment seen in patients with AD.[119] Sequencing of the cutaneous microbial structure showed that although normal skin flora is characterized by a diverse collection of bacteria, patients with AD harbor a cutaneous dysbiosis that involves not only *S aureus* colonization[120] but also reduction of overall microbial diversity.[121] A recent study by Simpson et al[122] showed that patients with AD colonized with *S aureus* have a unique phenotype and endotype, including more severe disease, reduced barrier function, increased serum lactate dehydrogenase levels and allergen sensitization, increased IgE levels and eosinophil counts, and increases in levels of other type 2 immunity markers (CCL17/thymus and activation-regulated chemokine, periostin, and CCL26).

ENDOTYPE-BASED TARGETED THERAPEUTIC APPROACHES

There are multiple medications in the therapeutic pipeline for AD (Table I).[123] The recently US Food and Drug Administration–approved IL-4 receptor mAb that blocks IL-4 and IL-13, dupilumab, specifically targets the T_H2 AD endotype.[124,125] Disease improvement was accompanied by reversal of both immune and barrier abnormalities.[126-128] The efficacy of other T_H2 antagonists is yet to be determined (eg, anti–IL-13/tralokinumab and lebrikizumab/NCT02347176/NCT02340234 and anti-thymic stromal lymphopoietin/tezepelumab/NCT00757042). Because increased T_H2 levels are a common trait across the AD spectrum, targeting this axis should theoretically be beneficial for all AD phenotypes. Nevertheless, in recent phase III dupilumab trials (SOLO 1 and 2) the outcome of Investigator's Global Assessment score reduction to 0 or 1 only occurred in 36% to 38% of patients,[129] possibly reflecting the potential significance of axes other than T_H2 in driving different AD phenotypes.

Although both patients with extrinsic and those with intrinsic AD benefit from targeting the T_H2 axis, as recently evidenced by dupilumab treatment,[126,128] patients with intrinsic AD, patients with pediatric AD, and Asian patients with AD in whom there is a significant T_H17/IL-23 activation and in some cases also T_H22 activation might also benefit from targeting T_H17/IL-17/IL-23 or T_H22/IL-22 cytokine pathways. Future clinical trials that target different cytokine axes will have to determine whether dual targeting with bispecific or trispecific antibodies or small molecules are applicable in these patients. Targeting the IL-12/IL-23 common subunit p40 by ustekinumab (ClinicalTrials.gov: NCT01806662)[130] showed a limited effect on AD severity but improvement of the AD transcriptome and mRNA levels of general inflammation markers and T_H2-, T_H17-, and IL-22/IL-17–induced S100As. Although this study had few design limitations and subgroup analysis was not performed, this treatment harbors a therapeutic potential, particularly in groups with T_H17/IL-23/T_H22 axis dominance.

Two doses (45 and 90 mg) of ustekinumab (anti–IL-12/IL-23/p40) were recently tested on a group of Japanese patients with severe AD in a randomized, double-blind, placebo-controlled phase II study. Results showed that although well tolerated, nonsignificant improvements were seen, and neither 45 nor 90 mg proved effective in these patients.[131] Because of greater immune activation in patients with AD,[132] doses of ustekinumab in patients with psoriasis might be too low for AD treatment.

The increased T_H17 axis seen in the pediatric, Asian, intrinsic, and elderly AD cohorts make these groups potential candidates for IL-17/IL-23 targeting. The anti–IL-17 secukinumab, which is now being tested in clinical trials (ClinicalTrials.gov: NCT02594098), will possibly be able to delineate the effects of T_H17 blockade on each of these groups. AD is accompanied by an excessive systemic T-cell activation,[132] and the association with systemic comorbidities is now well established.[133,134] In patients with psoriasis, IL-17 was suggested as a main mediator driving the reported systemic comorbidities, including cardiovascular disease, obesity, and arthritis.[135] In patients with AD, although not yet clear, IL-17 might also play a key role in triggering associated systemic comorbidities. This hypothesis provides an additional rationale for targeting the T_H17 axis, particularly in patients with severe intrinsic AD and Asian patients, pediatric patients, and old patients with AD.

Antagonizing IL-22 (fezakinumab/ILV-094; NCT01941537) was shown, in a proof-of-concept phase IIa study, to be safe and effective at improving AD severity, particularly in patients with severe disease, whereas a strong placebo effect, as typically seen in patients with AD,[136] was documented in patients with milder disease and SCORAD scores of less than 50, in whom disease severity has more fluctuations.[137] Accordingly, ILV-094 (anti–IL-22 antibody) led to molecular improvement in T_H2-, T_H17/T_H22- and T_H1-related markers, particularly in patients with severe AD.[138] Improvements and transcriptomic changes were greatest among a subgroup of patients with high baseline IL-22 expression, providing a first example for a personalized medicine approach in AD and potentially beyond.[139] This study provides a proof for the pathogenic role of IL-22 in patients with AD. Anti–IL-22 treatment can be particularly efficacious among Asian and pediatric patients with AD and patients with intrinsic AD, in whom there is a blend with a psoriasiform T_H17/T_H22 endotype, and in African American patients with AD who are characterized by dominant T_H22 (but not T_H17) upregulation.

Despite ambiguous results with omalizumab IgE targeting in patients with AD,[140] given the positive correlation observed between SCORAD scores and IgE levels in patients with extrinsic AD, such an approach could be contemplated in patients with extrinsic AD (QGE031/anti-IgE/ClinicalTrials.gov: NCT01552629). Additionally, despite relatively low IgE levels in pediatric versus adult patients with AD, IgE plays a major role in allergic sensitization, possibly contributing to initiation of the atopic march, and thus its targeting might be beneficial in the younger AD cohort as a preventative measure.

Emerging approaches using antisense molecules to target T_H subset transcription factors improved inflammation in murine skin, possibly representing a new and promising strategy for treating inflammatory skin diseases.[141]

CONCLUDING REMARKS

Current inclusion criteria for AD clinical trials are mostly based on disease severity rather than AD phenotyping. An attempt to define the patient's endotype before treatment should be made to optimize therapeutic responses moving toward precision medicine based on the different clinical and molecular disease subsets. Although T_H2 axis activation seems to be a universal trait across the AD spectrum, it still might be the case that other or additional cytokine targeting will be highly effective for a particular subset of patients who present a distinct endotype.

AD pathogenesis is complex, and multiple genetic and epigenetic factors[142,143] orchestrate its phenotype. There are different ways to classify AD. Although a type 2 versus non–type 2 epithelial dysfunction classification was suggested for AD endotyping,[10,144] we here offer a wider perspective that encompasses age, ethnic origin, disease stage, IgE levels, and FLG expression status. Targeted approaches in selective AD subgroups will be able to potentially dissect the relative contribution of various cytokine axes/endotypes to disease phenotype in a given population.

What do we know?

- **AD is a heterogenous inflammatory skin disease characterized by different subtypes/phenotypes based on age, disease chronicity, ethnicity, FLG and IgE status, and underlying molecular mechanisms/endotypes.**
- **Endotype variances make the "one-size-fits-all" therapeutic approach irrelevant for patients with AD.**

What is still unknown?

- **Are there endotypes related to microbiome diversity or specific bacterial strains?**
- **Is there an allergic endotype related to specific allergens, such as food versus environmental antigens?**
- **Is there an endotype related to distinct autoantigens/T-cell autoreactivity?**
- **What is the relative role of different cytokine axis activation in driving disease pathogenesis across AD endotypes and phenotypes?**

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