Review article

Biomarkers in atopic dermatitis

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Atopic dermatitis (AD) is a complex and highly heterogeneous inflammatory skin disease. Given the highly heterogeneous character of AD, it is unlikely that every patient will respond equally to a particular treatment. The recent introduction of novel targeted therapies for AD has driven the need for patient stratification based on immunologic biomarkers. We have reviewed the use of different types of biomarkers as potential tools in the movement toward personalized medicine in AD, comprising different ways of endotyping patients with AD based on immunologic profiles and predictive biomarkers. The application of biomarkers will result in better characterization and stratification of patients and allow better comparison of current and new treatments. The ultimate goal will be to switch from the current generalized "one-drug-fits-all" management to more personalized "patient endotype–specific" management. (J Allergy Clin Immunol 2023;151:1163-8.)

Key words: *Atopic dermatitis, biomarkers, endotypes, T_H2 cell, IL-4, IL-13, IL-22, TARC/CCL17, CCL22*

Atopic dermatitis (AD) is a common though complex and highly heterogeneous inflammatory skin disease. Its pathophysiology is thought to be the result of both genetic and environmental factors, resulting in immunologic and barrier dysfunctions.[1] The current treatment guidelines for AD focus mainly on disease severity measured by using clinical scores; they do not take the individual pathogenesis of the disease into account. Given the highly heterogeneous character of AD, it is unlikely that every patient will respond equally to a particular treatment. The recent introduction of novel targeted therapies for AD has driven the need for patient stratification based on immunologic biomarkers. The increased use of biomarkers in AD research will result in objective outcome measures allowing better comparison of current and new treatments. Furthermore, biomarkers may provide us with a better understanding of the pathogenesis of AD and enable better characterization and stratification of patients with AD, further enabling more personalized clinical care.

Abbreviations used
AD: Atopic dermatitis
CCL: Chemokine C-C motif ligand
DPP4: Dipeptidyl peptidase-4

BIOMARKERS IN AD: DEFINITION AND TYPES

According to the US Food and Drug Administration, a biomarker is "a defined characteristic that is measured as an indicator of normal biologic processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions." Biomarkers can be broadly separated into 2 categories (Fig 1, *A*). The first category comprises biomarkers that are used to identify persons at risk of developing a disease (screening biomarkers), patients with active disease (diagnostic biomarkers), disease recurrence or progression in patients who have the disease (prognostic biomarkers), and the populations of patients that are most likely to benefit from a given therapy (predictive biomarkers). The second category includes biomarkers for monitoring treatment effects (disease severity biomarkers) and possible side effects (pharmacodynamics biomarkers) (Fig 1).

Biomarkers can be defined not only from genomics, transcriptomics, and proteomics (such as cytokines and chemokines) data but also from morphologic information (eg, immunohistochemical staining).[2] Moreover, they can be measured in different sample types, such as blood, saliva, and urine, or in tissue samples, including skin biopsy samples and tape strips. Although many different potential biomarkers have been identified for AD, none of them has yet been implemented in daily practice.

ENDOTYPES BASED ON BIOMARKER PROFILES OF PATIENTS WITH AD

Clinical characteristics such as age of onset, persistence of disease after childhood, and presence of other atopic diseases such as allergic rhinitis and asthma have been used to divide AD into different disease phenotypes.[3] However, clinical phenotypes do not necessarily relate to, or give insights into, the underlying disease mechanisms, and they might be less suitable than

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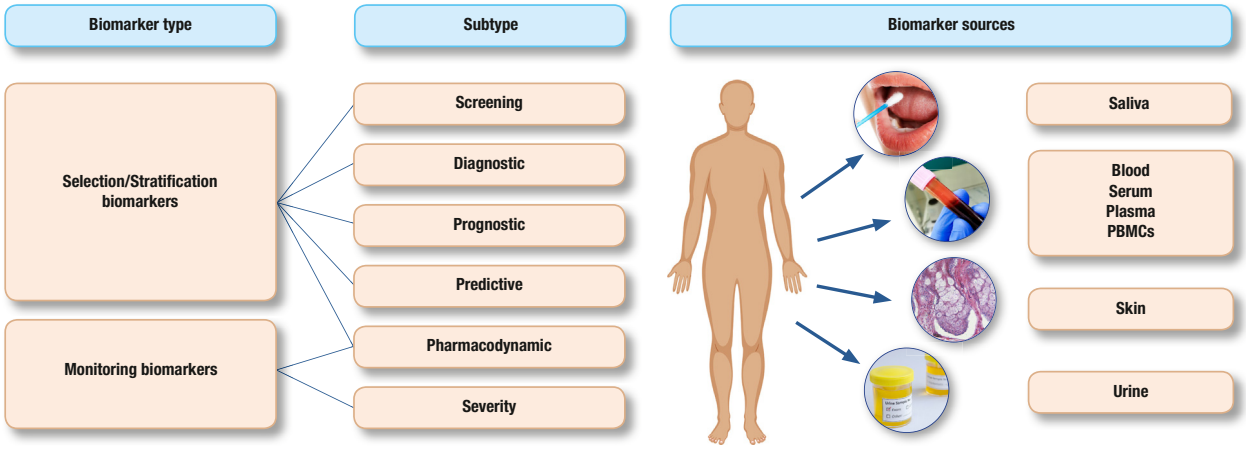

FIG 1. Biomarker types and sources. The different types of biomarkers and potential biomarker sources are summarized. Biomarkers can be broadly separated into 2 categories. The first category comprises biomarkers that are used to identify persons at risk of developing a disease, patients with active disease, and the populations of patients that are most likely to benefit from a given therapy. The second category includes biomarkers for monitoring treatment effects. Biomarkers can be obtained from biologic fluids such as blood, saliva, and urine or from tissue samples.

molecular markers for defining those subpopulations of patients with AD that are the best candidates for various treatments. It has become increasingly clear that not only is AD heterogeneous based on clinical characteristics but also that different underlying pathophysiologic processes can be seen in different subgroups of patients. Because of this heterogeneity, it is unlikely that newly developed biologic drugs targeting specific components of the immune system will be effective in all patients with AD. Thus, defining disease endotypes based on the most important pathophysiologic mechanisms at the cellular and molecular levels driving the disease has become an important development for stratification of patients with AD. Predictive biomarkers can subsequently be used to identify and select the specific endotype that will respond to a targeted treatment (Fig 2).

Several ways of endotyping patients with AD have been described (Table I[4-21]). Multiple studies have tried to endotype AD using a supervised approach, by characterizing the immunologic profile of predefined subgroups based on specific patient characteristics, such as treatment response,[17] intrinsic or extrinsic AD,[11,12] and ethnic or demographic patient groups (including pediatric versus adult patients with AD,[13,22] younger versus older adults,[8,9] and African versus Asian and European patients).[10,14,16] The main outcomes of these studies are summarized in Table I.

Thijs et al[4] were the first to encompass endotyping based on unsupervised molecular profiling across a broad spectrum of patients with AD. By using an unsupervised data-driven approach, they were able to classify adult patients with AD into 4 distinct patient clusters based on serum biomarker profiles. Of these 4 clusters, 3 could again be identified in a separate cohort, characterized as a "T_H1 cell/T_H2 cell/Th17 cell–dominant" cluster, a "T_H2 cell/T_H22 cell/PARC–dominant" cluster, and a "T_H2 cell/eosinophil–inferior" cluster.[5] Another unsupervised study by Sims et al[6] suggested the presence of 2 clusters of patients with AD based on a panel of 131 serum biomarkers: a low inflammatory subgroup and a high inflammatory subgroup. The high inflammatory subgroup was characterized by upregulation of diverse proinflammatory mediators spanning different T_H cell pathways and was associated with higher disease severity. Recently, Möbus et al[7] stratified 55 patients with moderate-to-severe AD into eosinophil-high and eosinophil-low endotypes based on significant differences in the expression levels of genes highly specific for eosinophils/eosinophil signaling. The eosinophil-high endotype was associated with increased global transcriptomic dysregulation. The eosinophil-low endotype, in contrast, was characterized by little transcriptomic dysregulation. As in the studies of Thijs et al[4] and Bakker et al,[5] no association between the 2 endotypes and clinical variables was found. In addition, the eosinophil-high and eosinophil-low endotypes remained largely unchanged during dupilumab treatment. Notably, validation in independent cohorts and longitudinal studies are needed to prove the stability of these endotypes among different cohorts and over time.

PREDICTIVE BIOMARKERS AND ENDOTYPE-DRIVEN THERAPEUTIC APPROACHES

In a recent Delphi survey of international experts in AD and psoriasis, the prediction of therapeutic response (predictive biomarkers) and progression of disease (prognostic biomarkers) were considered to be the most important purposes of a biomarker.[23] Biomarkers that have been identified as prognostic biomarkers for AD development include an altered stratum corneum lipid composition[24] and thymus and activation–regulated chemokine (TARC)/chemokine C-C motif ligand 17 (CCL17) in both skin strips and umbilical cord blood.[24-26] Lauffer et al[27] recently found that a low serum vascular endothelial growth factor level was associated with disease persistence in children at the age of 7 years. High serum IgE levels in adult patients with AD have been associated with ongoing eczema after 10 years.

The specific biomarker pathways distinguishing the different endotypes may be particularly meaningful for the application of molecularly targeted drugs and for defining the most optimal treatment for the individual patient, because different endotypes might respond differently to the particular treatments. For application in trials and clinical practice, the development of a single biomarker or a small set of representative biomarkers that can act as a surrogate marker for an endotype is very important for predicting response to a given therapy. Recently, baseline lesional

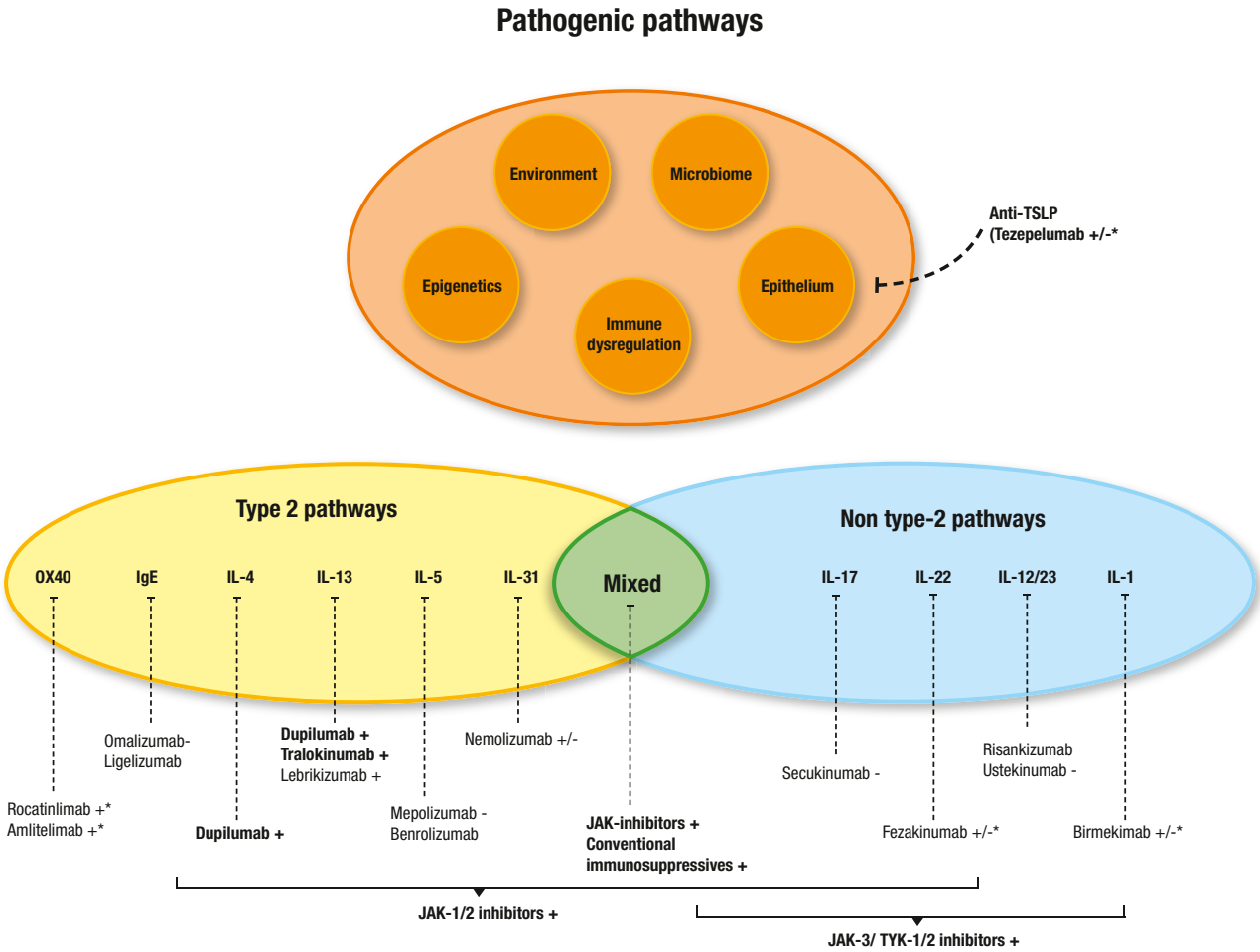

FIG 2. The complex and heterogeneous pathogenetic pathways involved in AD, disease phenotypes and endotypes, and the most important immunologic pathways with targeting treatments. AD endotypes can be roughly stratified into a type 2–dominant, a non–type 2– dominant, and a mixed endotype. In type 2–dominant AD, targeted therapies for 5 main pathways have been investigated: the IL-4/IL-13 pathway (dupilumab, tralokinumab, and lebrikizumab), the IL-5 pathway (mepolizumab and benrolizumab), the IL-31 pathway (nemolizumab), the IgE pathway (omalizumab and ligelizumab), and the OX40 pathway (rocatinlimab and amlitelimab). In non–type 2 AD, 4 targeting pathways have been investigated: the IL-17 pathway (secukinumab), the IL-22 pathway (fezakinumab), the IL-23 pathway (risankizumab), and the IL-1 pathway (bimerkimab). Janus kinase (JAD) inhibitors and conventional immunosuppressives are more broad-acting by targeting different pathways. Evidence for efficacy in AD has been depicted as follows: plus sign indicates efficacy proved in clinical trials and/or daily practice, plus or minus sign indicates moderate efficacy proved in clinical trials, and minus sign indicates no proven efficacy. *Data available only from phase II clinical trials. Drugs in bold are currently on the market for AD.

skin CCL22 expression was identified as the best biomarker to predict clinical improvement during multiple therapies targeting different pathways, including topical crisaborole, cyclosporine, and fezakinumab.[28] Additionally, baseline levels of the T_H17 cell–related cytokine CXCL2 showed strong predictive responses for dupilumab treatment.[28] Other attempts that have been made to predict response to targeted treatments in AD based on single biomarkers include the presence of high IL-22 skin expression for anti–IL-22 treatment with fezakinumab[17] and high serum concentrations of the IL-13–related markers dipeptidyl peptidase-4 (DPP4) and periostin for tralokinumab treatment.[29,30] Remarkably, recently published data from 3 large phase III clinical trials investigating tralokinumab in patients with AD do not report DPP4 or periostin analyses.[31,32]

To date, there are no data demonstrating that endotypes respond differently to different therapies, and current biomarkers are not yet precise in selecting the specific endotype that will respond to a targeted treatment. Compared with patients in the other 2 clusters, patients stratified into the "T_H1 cell/T_H2 cell/T_H17 cell–dominant" and "T_H2 cell/T_H22 cell/PARC–dominant" clusters in studies of Thijs et al[4] and Bakker et al,[5] representing about 40% of the included patients, showed particularly high levels of type 2 cytokines (including IL-4, IL-5, and IL-13). Similarly, by using minimally invasive skin strips, Dyjack et al found that 50% of patients with AD exhibited a type 2–high inflammatory signature.[18] These type 2–high patients could theoretically be the most ideal candidates for type 2–targeted treatments, including dupilumab[33] (anti–IL-4/IL-13), tralokinumab,[30] and

TABLE I. Overview of literature on endotyping AD

Source	Approach	Biologic material	Main outcomes	Reference
Blood				
Serum	Data-driven, unsupervised approach	Proteins	4 clusters of patients with AD with a specific signature of inflammatory markers	Thijs et al[4]
Serum	Data-driven, unsupervised approach	Proteins	Confirmation of 4 clusters of patients with AD with a specific signature of inflammatory markers	Bakker et al[5]
Serum	Data-driven, unsupervised approach	Proteins	2 AD clusters: high- vs low-inflammatory	Sims et al[6]
Blood	Data-driven, unsupervised approach	mRNA	AD can be stratified into eosinophilic and noneosinophilic endotypes	Möbus et al[7]
Serum	Supervised approach (age)	Proteins	Elderly phenotype had upregulated inflammatory markers	He et al[8]
Serum and biopsy samples	Supervised approach (age)	mRNA, immunohistochemistry	Decrease in T_H2 cell/T_H22 cell polarization during aging	Zhou et al[9]
Serum and biopsy samples	Supervised approach (race)	Proteins, mRNA	In Asian patients, AD displays a specific endotype (T_H2 cell/T_H22 cell)	Wen et al[10]
Skin biopsy samples				
	Supervised approach (intrinsic/extrinsic)	mRNA, immunohistochemistry	Higher activation of all inflammatory axes (including T_H2 cell) was detected in patients with intrinsic AD, particularly T_H17 and T_H22 cytokines	Suarez-Farinas et al[11]
	Supervised approach (intrinsic/extrinsic)	mRNA, immunohistochemistry	Increased expression of several inflammation-related genes (*IL22, S100A7-9, S100A12,* and *CCL22*) in intrinsic AD compared with in extrinsic AD	Martel et al[12]
	Supervised approach (age)	mRNA, immunohistochemistry	Children showed significantly higher induction of T_H17 cell–related cytokines and antimicrobials (IL-17A, IL-19, CCL20, LL37, and peptidase inhibitor 3/elafin), T_H9 cell/IL-9, IL-33, and innate markers (IL-8) than adults did	Esaki et al[13]
	Supervised approach (race)	mRNA, immunohistochemistry	In Asian patients, AD displays a specific endotype (T_H2 cell/T_H17 cell)	Noda et al[14]
	Supervised approach (race)	mRNA, immunohistochemistry	In Chinese patients, AD displays a specific endotype (T_H2 cell/T_H17 cell)	Chan et al[15]
	Supervised approach (race)	mRNA, immunohistochemistry	In African American patients, AD is characterized by attenuated T_H1 cell and T_H17 cell skewing	Sanyal et al[16]
	Supervised approach (treatment response)	mRNA, immunohistochemistry	Baseline IL-22 expression in patients with AD stratifies tissue responses to fezakinumab	Brunner et al[17]
Tape strips				
	Unsupervised approach	RNA, immunohistochemistry	50% of patients with AD exhibited a type 2 inflammatory signature (type 2–high endotype)	Dyjack et al[18]
Genetic variations				
		DNA	FLG deficiency is found in only 10%-40% of patients with AD	Palmer et al[19] Winge et al[20] Irvine et al[21]

lebrikizumab[34] (anti–IL-13), strengthened by the type 2–related biomarkers DPP4 and periostin as suggested predictive biomarkers for tralokinumab treatment.[29,30] Many groups are currently investigating differences in response to dupilumab treatment between the different endotypes.

Patients stratified into the non–type 2 endotypes might need a broader-acting drug, such as the emerging Janus kinase (JAK) inhibitors upadacitinib,[35] abrocitinib,[36] and baricitinib.[37] Patients in the eosinophil-high endotype found by Möbus et al[7] might benefit more from anti–IL5 treatments such as mepolizumab or

the anti–IL5RA antibody benrolizumab, which is currently in a phase 2a study (HIL-LIER Study [ClinicalTrials.gov identifier NCT04605094]).

A substantial part of the aforementioned studies used skin biopsy samples to investigate endotyping in AD. Because of their invasive character, skin biopsy samples are difficult to use in large-scale clinical trials and longitudinal studies, as well as in pediatric studies.[2] Although the skin is the target organ of AD, early signals of disease activity might be missed when looking only into skin biomarkers, and integrated blood-skin biomarker models might be a more holistic way to build a disease profile. Nevertheless, as AD leads to systemic inflammation,[38,39] the use of serum proteins has proved effective in identifying different immunologic endotypes of AD as well as in objectively scoring disease severity.[4,27,40-42] Because of their systemic representation, blood biomarkers might be useful to predict or monitor comorbidities and side effects.

CONCLUSION

As AD is currently moving toward an era of more targeted therapies, the application of biomarkers will result in better characterization and stratification of patients and allow better comparison of current and new treatments. Given the variety of (upcoming) treatments targeting specific cytokine pathways, it is important to stratify patients based on the most important immunologic drivers of their AD (endotypes) rather to subgroup them based on clinical phenotypes. To reach the ultimate goal of a biomarker-based tool for prediction of treatment response, it is essential to move forward to a validation phase in which a reduced number of biomarkers are linked to treatment response and can be standardized for use in daily practice. The ultimate goal will be to switch from the current generalized "one-drug-fits-all" management to more personalized "patient endotype–specific" management.

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