

Current and Future Biomarkers in Atopic Dermatitis



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KEYWORDS

- Biomarkers • Atopic dermatitis • Biologicals • Personalized medicine • Stratification
- Heterogeneity • Disease severity

KEY POINTS

- Technological advances now allow clinicians to determine large numbers of biomarkers in small volumes of body fluids.
- This enables better characterization and stratification of patients with AD and will result in objective outcome measures, allowing better comparison of current and new treatments.
- We hypothesize that in the near future patients with AD will be stratified based on biomarker expression levels in body fluids, tissue, genetic variants, or composite biomarker scores.
- This will lead to better identification of patients that can benefit from new highly specific, but expensive treatments.
- Biomarkers are essential in moving forward to predictive, personalized, preventive, and participatory medicine.

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease worldwide. It affects children and adults. Living with AD has a great impact on the quality of life of patients. AD is a complex disease, thought to be the result of genetic and environmental factors, resulting in immunologic and barrier dysfunctions.¹

AD is known to be a heterogeneous disease and many attempts have been made to define subsets of patients based on clinical characteristics. However, the current

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characterization of patients with AD might not adequately reflect the pathophysiologic diversity within patients with AD. Biomarkers may help in better defining heterogeneity and contribute to personalized medicine. This is one of many applications for biomarkers in AD.

Two main groups of biomarkers are discussed in this review: biomarkers for selection/stratification of patient groups and biomarkers for monitoring of patients (Fig. 1).

WHAT ARE BIOMARKERS?

The term “biomarker” is used in a broad sense to include almost any measurement reflecting an interaction between a biologic system and an environmental agent, which may be chemical, physical, or biologic. Two definitions of biomarkers are commonly used in literature. The World Health Organization definition of a biomarker is as follows: “any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease. Biomarkers can be classified into markers of exposure, effect and susceptibility.”² The other definition is largely overlapping and was proposed by the National Institutes of Health biomarkers definitions group, defining a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”³

BIOMARKER TYPES AND THEIR CLINICAL APPLICATION

Two biomarker categories with several subtypes are distinguished based on these definitions. The first category represents biomarkers that are used for selection or stratification of patients. Biomarkers in this category are used for screening and diagnosis, but also include the subcategory of prognostic and predictive biomarkers. Prognostic biomarkers help to estimate the likely course of disease and the patient’s future risks to, for example, clinical end points, such as hospitalization.⁴ A predictive biomarker identifies subpopulations of patients that are most likely to respond to a given therapy.

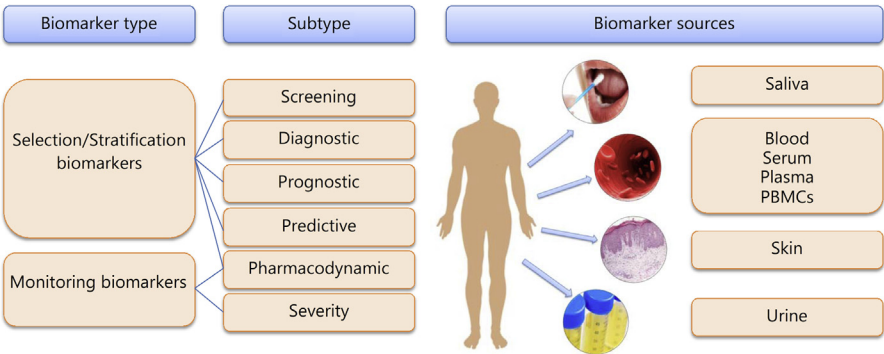


Fig. 1. Biomarker types and sources. This figure summarizes the different types of biomarkers and potential biomarker sources. Biomarkers can broadly be separated into two categories. The first category comprises biomarkers that are used to identify persons at risk to develop a disease, patients with active disease, and populations of patients that are most likely to benefit from a given therapy. The second category includes biomarkers for monitoring treatment effects. PBMCs, peripheral blood mononuclear cells.

The second category comprises biomarkers for monitoring the clinical response to a given therapy or intervention. This category includes biomarkers that measure disease severity and can function as a surrogate end point in clinical trials. This category also includes pharmacodynamic biomarkers. An overview of the different types of biomarkers is given in [Fig. 1](#).

WHY ARE BIOMARKERS NEEDED FOR ATOPIC DERMATITIS?

There are many possible uses for biomarkers. Three main reasons for using biomarkers in AD research and clinical trials are discussed in more detail.

Biomarkers for Stratification of Patients to Unravel Disease Heterogeneity

AD is highly heterogeneous with regard to clinical characteristics and natural history of the disease. Many attempts have been made to stratify patients based on clinical characteristics.^{5–7} Patients have been divided into clinical phenotypes based on age of onset, severity, and history of bacterial or viral infections. Classically, AD was divided into intrinsic and extrinsic, based on serum IgE levels. Despite high IgE levels in patients with extrinsic AD, suggesting increased expression of Th2-related genes, Suarez-Farinas and coworkers⁸ recently found that intrinsic and extrinsic AD patient groups showed similar expression levels of Th2-related genes. This suggests that intrinsic and extrinsic AD are more overlapping in terms of underlying pathomechanisms than was previously thought based on clinical characteristics. This confirms that current characterization of patients with AD does not adequately reflect the pathophysiologic diversity within patients with AD. Biomarkers may help in defining subsets of patients, also called endotypes, related to underlying disease mechanisms, as was previously suggested by the PRACTALL collaboration platform.⁹

Patients with AD are currently being treated with relatively nonspecific treatments, including (topical) steroids and cyclosporine A (CsA). So far, no correlation has been found between clinical phenotypes and treatment response, which may be explained by the relative broad immune suppression with these drugs. With new targeted biologic therapies (ie, dupilumab, anti-interleukin [IL]-4R; and lebrikizumab, anti-IL-13) becoming available, identification of patients with specific immune pathway polarity is of particular importance. This so-called precision medicine will not only be of benefit to the individual patient, but will also be of essence in controlling health care expenditures.

Predicting Treatment Response

Patients with severe, difficult-to-treat AD, not responding to topical treatments are currently being treated with several (mostly off-label) systemic immunosuppressants. In many European countries (but not in the United States) CsA is registered for the treatment of AD. Other off-label immunosuppressants that are frequently used when CsA treatment fails, or when there are contraindications for CsA, include methotrexate, azathioprine (AZA), and mycophenolic acid (MPA).

Besides their possible side effects, a major concern for patients and physicians is the high percentages of treatment failures with these systemic immunosuppressants.¹⁰ In daily practice, these treatments fail in 40% to 50% of patients.^{11,12} Feedback from patients with AD focus groups showed that the uncertainty if a patient will respond to a given systemic immunosuppressant is one of their major concerns (personal communication). Biomarkers predicting treatment response for these treatments have not been described so far.

Pharmacogenetics and therapeutic drug monitoring may be used to optimize treatment response to systemic immunosuppressive treatment. Pharmacogenetic biomarkers can play a role in identifying responders and nonresponders to treatment, but can also be used to avoid adverse effects, and to optimize drug dosing.^{13,14}

Biomarkers for prediction of therapy response may also be useful with the introduction of new targeted therapies for AD. Stratification based on a serum biomarker has already been proven to be useful in the treatment of asthma, where it was found that patients with asthma with high periostin levels showed a better response to anti-IL-13 (lebrizumab) treatment, compared with patients with low periostin levels.¹⁵ Periostin is an extracellular matrix protein that is induced by the Th2 cytokines IL-4 and IL-13 in airway epithelial cells and lung fibroblasts. This suggests that the Th2 immune pathway may be more predominant in periostin-high patients, explaining the better response to anti-IL-13 treatment in this subset of patients. Asthma, like AD, is also a highly heterogeneous disease, with many overlapping features to AD. We therefore expect that also in AD a biomarker-based stratification will be essential with the current introduction of new targeted therapies. A biomarker-based selection may even prevent new drugs from failing in early phase clinical trials because they may only be beneficial for a selected patient population as was shown for lebrizumab in asthma. This treatment effect may be underestimated in an unselected patient population.

Biomarkers as Objective Measures for Disease Severity

Currently, no gold standard for measurement of disease severity in AD exists, and more than 20 different composite indices have been described.¹⁶ A recent systematic review showed that most AD clinical trials used a severity measure (ie, SCORing Atopic Dermatitis; Eczema Area and Severity Index; or six area, six sign AD severity score), but that only 27% of these scales had been previously published.¹⁷ Another review assessed the validity and reliability of the 20 most commonly used severity measures, and found that only three performed adequately.¹⁶ To address these deficiencies in reporting, experts in the field have established the Harmonizing Outcome Measurements in Eczema initiative, an attempt to ensure that investigators use a core set of outcome measures to improve comparability between studies.¹⁸ The Harmonizing Outcome Measurements in Eczema initiative now recommends to use the Eczema Area and Severity Index in AD clinical trials.¹⁹ However, whether this score is preferable over the commonly used SCORing Atopic Dermatitis, even within the Harmonizing Outcome Measurements in Eczema group, is still a matter of debate.²⁰ The SCORing Atopic Dermatitis not only reports clinical signs, but also assesses subjective symptoms of pruritus and sleep loss with Visual Analogue Scales. We suggest that in addition to improve clinical outcome reporting, biomarkers for monitoring of disease severity would be of great added value. Biomarkers offer reliable and objective outcome measures, and may reflect objective and subjective signs and symptoms. Moreover, the use of biomarkers as a surrogate end point in clinical trials will improve comparisons across trials and facilitate meta-analyses.

CURRENT BIOMARKERS IN ATOPIC DERMATITIS

This section provides a brief overview of currently known biomarkers in AD. Biomarkers are summarized according to their subtype in [Table 1](#).

Table 1 Types of biomarkers	
Biomarker Type	Known Biomarkers in AD
Screening	Filaggrin gene ⁵² SPINK5 ⁵³ Cord blood IgE ²⁶ Infantile LT- α and Fc ϵ RI- β genotypes ²⁶ TSLP ²⁷
Diagnostic	No specific biomarkers currently available
Prognostic	Filaggrin gene ²³ IgE ^{54,55} Indoleamine 2,3-dioxygenase-1 ²⁸
Predictive	Not yet identified
Pharmacodynamic	CYP3A4/CYP3A5 tacrolimus ³⁰ CYP3A4/CYP3A5 cyclosporine A ³² UGT1A9 mycophenolic acid ³³ Thiopurine methyltransferase, 6-thioguanine nucleotides, 6-6-methylmercaptopurine ribonucleotides, azathioprine ³⁵
Monitoring	
Serum	TARC ³⁹ CTACK ⁴⁰ sE-selectin ⁴¹ Macrophage-derived chemokine ⁴² Lactate dehydrogenase ⁴³ Interleukin-18 ⁴⁴
Skin	Transcriptomic changes after treatment ⁴⁷
Itch	Interleukin-31, ⁵⁶ wearables ⁵¹

Diagnostic Biomarkers

AD is a clinical diagnosis, and there are no biomarkers needed to confirm the diagnosis. Classically, AD was divided into an intrinsic and an extrinsic subtype. Patients with the intrinsic subtype have normal total IgE levels, and are also referred to as nonallergic or nonatopic. Patients with the extrinsic subtype of AD show high levels of IgE and are often sensitized to multiple allergens.²¹ Because 20% of the patients have the intrinsic form of AD, without elevated total IgE levels, total serum IgE cannot be used as a diagnostic biomarker for all patients with AD. Moreover, total IgE levels can also be increased in patient with other allergic diseases, such as allergic asthma or allergic rhinitis.

Screening and Prognostic Biomarkers

AD is a highly heritable disease and the best known risk factor for the development of AD is having parents with AD. Because results from a recent trial in a birth cohort suggested that emollient therapy might be effective in the prevention of eczema,²² it might be helpful to use screening biomarkers to identify and treat the population at risk.

Many genome-wide linkage studies have identified several candidate genes associated with AD. The strongest association was found with filaggrin (FLG) gene mutations.²³ FLG gene mutations are found in about 30% of patients with AD, but not all FLG mutation carriers develop AD.²⁴ FLG gene mutations are more frequent in patients with severe disease and early onset AD. FLG mutations might therefore be

used as a prognostic biomarker,²⁵ in addition to a screening marker for early onset or severe AD.

We hypothesize that a composite score of genetic factors (ie, FLG) and serum or tissue biomarkers will increase the predictive value of prognostic biomarkers.

Other biomarkers that have been proposed as screening biomarkers include elevated cord blood IgE levels, infantile lymphotoxin- α , and Fc ϵ RI- β genotypes during pregnancy, which were shown to be associated with development of childhood AD.²⁶ Kim and colleagues²⁷ recently showed that epidermal TSLP protein expression may also serve as a screening biomarker in children at risk of developing AD. Indoleamine 2,3-dioxygenase-1 is a prognostic candidate biomarker for a specific phenotype (eczema herpeticum) that was proposed by Staudacher and colleagues.²⁸

Predictive Biomarkers

Although many attempts have been made to define subsets of patients based on clinical characteristics and biomarkers, such as total serum IgE levels or peripheral blood eosinophils, no predictive biomarkers have been identified so far.

Pharmacodynamic Biomarkers

Pharmacogenetics has been defined as the study of variability in drug response caused by heredity.²⁹ Pharmacogenetic research explores the effect of pharmacokinetics, pharmacodynamics, efficacy, and safety of drug treatments in relation to genome variations.¹³ The most common genetic variations that have been studied are single-nucleotide polymorphisms (SNPs), genetic copy number variations, and genomic insertions and deletions.¹⁴ All of these genetic variations can influence the response of a patient to a specific drug and can be used as biomarkers.

Pharmacodynamic markers are scarcely used in AD treatment. However, we recently showed that pharmacogenetic testing can be used to personalize and optimize treatment with systemic extended-release tacrolimus in patients with AD.³⁰ Tacrolimus is extensively metabolized by CYP3A4 and CYP3A5. The presence of a C > T SNP in intron 6 of CYP3A4 is associated with intermediate or poor tacrolimus metabolism, resulting in high tacrolimus blood levels. In addition, it was shown that carrying CYP3A5*3 (slow metabolism) and CYP3A5*1 (fast metabolism) alleles also affects tacrolimus metabolism. Expression analysis of SNPs in the genes for CYP3A4 and CYP3A5 now enables classification of patients with AD into poor, intermediate, or extensive metabolizers of tacrolimus.³⁰ This CYP3A4/CYP3A5 genotype cluster classification is used to tailor dosing of tacrolimus to the individual patient, and to avoid adverse effects.

CsA is frequently used in the treatment of severe AD.³¹ Bioavailability and systemic clearance of CsA is also mainly controlled by the isoenzymes CYP3A4 and CYP3A5.³² Therefore, pharmacogenetic testing of SNPs for CYP3A4 and CYP3A5 may also be of use in the treatment of patients with CsA and needs further investigation.

MPA is used off-label in treatment of patients with AD that failed CsA treatment. Unfortunately, MPA is only effective in around half of the patients.^{10,11} Pharmacogenetic biomarkers may be the key to optimizing MPA treatment. In kidney patients, low blood levels of MPA were found to correlate to lower efficacy and acute rejection of the graft.^{33,34} Low MPA blood levels also correlate to the presence of SNPs in the gene promoter region of UGT1A9.^{33,34} MPA is mainly metabolized by UGT1A9; therefore, increased UGT1A9 activity caused by SNPs could result in lower MPA blood levels. In patients with AD, UGT1A9 SNPs may be used as a pharmacogenetic biomarker to identify patients with nonresponsiveness to MPA. By prescribing higher MPA doses to these patients, the clinical efficacy of MPA in AD treatment may improve.

AZA is another second-line drug in the treatment of AD that also shows a good clinical performance in only half of the patients.¹¹ The performance of AZA is mainly limited by discontinuation of treatment because of side effects.¹¹ Studies in inflammatory bowel disease have shown that genetic polymorphisms in thiopurine methyltransferase influence the metabolism of AZA.³⁵ Genotyping of thiopurine methyltransferase before the start of AZA treatment allows identification of those at increased risk for adverse events.³⁵ During treatment, monitoring of the AZA metabolites 6-thioguanine nucleotides and 6-methylmercaptapurine ribonucleotides can be used for the risk assessment of myelotoxicity and liver toxicity.³⁵

Although pharmacogenetic biomarkers are currently scarcely used in AD treatment, we think that they are of great potential in optimizing and personalizing treatment in AD.

Monitoring Biomarkers

Total serum IgE is the most commonly measured biomarker in AD trials.³⁶ Although patients with severe disease tend to have higher total serum IgE levels, there is a group of patients with intrinsic AD that do not have increased IgE levels. This suggests that total serum IgE levels are not suitable as a biomarker for monitoring disease severity. In a recent meta-analysis it was shown that total IgE levels only weakly correlate to disease severity during follow-up of patients with AD.³⁶

Other serum biomarkers that have been frequently reported for monitoring disease activity in AD include eosinophilic cationic protein,³⁷ IL-2R,³⁸ and thymus and activation-regulated chemokine (TARC/CCL17).³⁹ In a meta-analysis on serum biomarkers for disease severity we found that serum TARC is the most reliable biomarker currently available.³⁶ Serum TARC levels have been determined in relatively large numbers of patients from different studies, showing pooled correlation coefficients of 0.60 (95% confidence interval, 0.48–0.70) and 0.64 (95% confidence interval, 0.57–0.70) in longitudinal and cross-sectional studies, respectively.³⁶ Additional biomarkers that showed promising results in this meta-analysis, but require additional research, include serum CTACK,⁴⁰ serum sE-selectin,⁴¹ serum macrophage-derived chemokine,⁴² serum lactate dehydrogenase,⁴³ and serum IL-18.⁴⁴

Although TARC strongly correlates with disease activity in individual patients during follow-up, TARC levels vary between patients within cross-sectional cohorts of patients that have similar disease severity scores.⁴⁵ The variation in TARC levels between these patients may be the result of the large number of biologic pathways involved in the pathogenesis of AD. The use of a panel of several biomarkers from different biologic pathways, representing different phenotypes/endotypes, may overcome this problem. Indeed, we recently demonstrated that a multivariate signature consisting of TARC, PARC, IL-22, and sIL-2R for serum biomarkers showed a correlation coefficient of 0.86 to disease severity measured by the six area, six sign AD severity score.⁴⁶ Even though this panel was designed in a small pilot study, it demonstrates that using a panel of biomarkers may be necessary in a multifactorial, complex disease, such as AD.

Although circulating inflammatory markers are much easier to investigate, most crucial information on the pathogenesis of AD probably has come from investigations of skin biopsies. The group of Emma-Guttman has shown for several treatments, including UVB,⁴⁷ CsA,⁴⁸ and more recently also for dupilumab⁴⁹ that there are large changes on the skin transcriptome. These studies are essential in reporting on differential disease-modifying effects of new treatments, and further contribute to the understanding of disease pathogenesis.

Itch is an important characteristic of the disease and has a great impact on the quality of life of patients. Although several questionnaires for measuring itch have been developed, there are no objective tools available to measure itch. IL-31 has been

associated with pruritus, and might be a potential biomarker for itch. Several studies investigated correlations between serum IL-31 levels and disease severity.⁵⁰ However, the correlation of IL-31 with pruritus has not yet been investigated. In the era of wearable fitness devices, one would expect that the introduction of a wearable scratching/itching device should not take much longer.⁵¹

FUTURE PERSPECTIVES

Technologic advances now allow clinicians to determine large numbers of biomarkers in small volumes of body fluids. This will result in better characterization and stratification of patients with AD and will also result in objective outcome measures that will allow better comparison of current and new treatments.

We hypothesize that in the near future patients with AD will be stratified based on biomarker expression levels in body fluids (blood/saliva/tears), tissue (biopsies/skin strips), genetic variants, or combined biomarker expression patterns (composite biomarker scores). With many new targeted therapies currently investigated in phase I to III clinical trials this will lead to better identification of patients that can benefit from these highly specific, but expensive new treatments. Biomarkers will be essential in moving forward to predictive, personalized, preventive, and participatory medicine.

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