

REVIEW ARTICLE

Atopic dermatitis: a candidate for disease-modifying strategy

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Abstract

The concept of disease modification has been introduced to define the therapeutic strategies aimed to break, stop, or reverse the natural course of a chronic invalidating disease. This strategy is tightly related to the biomarker-based stratification of affected patients using genetic and other biological markers. With regard to the progress in understanding the genetic background of atopic dermatitis (AD), its natural history and its pivotal role in the emergence of allergic asthma, the time is mature to foster the research field of biomarkers in AD and to consider the elaboration of disease-modifying strategies in the management of AD with the goal to stop or even reverse the atopic march.

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Atopic dermatitis (AD) is a chronic inflammatory noncommunicable skin disease for which progress in genomics and understanding of pathophysiologic events has led to a dramatic change in our view of how to approach this condition (1–3). Both the epidermal barrier dysfunction and immunoallergic events contribute to the particular inflammatory microenvironment of the skin. As for many other diseases, new insights into the genetic background of AD strengthened the concept that one given clinical phenotype may be the product of numerous distinct genetic variations interacting with a wide spectrum of environmental factors (4). A typical example for this situation is illustrated by the fact that only 30% of patients with AD have a mutation in the gene encoding for filaggrin (FLG) (5), leaving a substantial room for the identification of further genetic discoveries in this area such as the recently identified loci related to OVOL1 and ACTL9 (6). Most importantly, with regard to their potential predictive value for (i) the diagnostic; (ii) the natural history of AD (1); (iii) the therapeutic response; and (iv) the development of the atopic march (7–9), genomic and other biomarkers (BM) will have increasing significance for future disease management. It is expected that in the upcoming future, we will be able to stratify the large population of

patients with AD according to their genomic profile as well as to a number of either known or others yet-to-be-defined BM. This could lead to a new kind of subtle stratification of the disease and a refinement of the genotype–phenotype relationship. Thereby, BM will eventually allow to identify subgroups of patients who would have a substantial benefit from distinct therapeutic (10) and prevention approaches, potentially leading to a significant control if not cure of this disease at an early point of time. As a result of this progress, we are now entering the era of stratified medicine applied to AD with the potential of interfering in the ongoing pathophysiologic process by the implementation of disease-modifying strategies.

How is disease modification defined?

The regulatory definition of disease modification can be found, for example, in the guideline of the European Medicine Agency (EMA) for medical products for the treatment for Alzheimer disease and other dementias (11): ‘For regulatory purposes disease-modifying effect will be considered when the pharmacological treatment delays the underlying pathologic or physiopathologic disease processes and when it

is accompanied by an improvement of clinical signs and symptoms of the condition. Consequently a true disease-modifying effect cannot be established conclusively based on the clinical outcome data alone, such as clinical effect must be accompanied by strong supportive evidence from a biomarker program'. From this definition, we can extract three main aspects: (i) the treatment acts directly on the pathophysiological process; (ii) there must be an obvious improvement of the clinical signs; and (iii) disease modification must be substantiated by various validated BM tightly related to the pathophysiological progress of the disease.

With regard to the particular field of allergic diseases, disease modification has been mentioned in the *guideline of clinical development of products for specific immune therapy for the treatment for allergic diseases* (12) as one possible claim for efficacy of the treatment. In this guideline, a four-point scale is mentioned including (i) a short-term efficacy; (ii) a sustained clinical effect; (iii) the long-term efficacy, and disease-modifying effect is defined as a sustained significant and clinically relevant efficacy in the post-treatment years. The ultimate goal is defined as (iv) the cure of allergy with a sustained absence of allergic symptoms in post-treatment years. In this particular guideline related to allergen-specific immunotherapy, there is no mention of the prerequisite of BM as until today none has been definitely validated for this therapy.

Definition and value of biomarkers in disease-modifying strategies

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. According to this definition provided by the NIH biomarkers definition working group (13), every characteristic which has a kind of predictive value can be considered as a biomarker. Consequently, the spectrum of possible BM is quite wide including anatomical, histological, genomics, proteins, metabolites, and imaging technologies.

Beside markers obtained from genomics and pharmacogenomics approaches, a wide spectrum of other 'omics' (14),

such as proteomics, transcriptomics, metabonomics, epigenomics, or nutrigenomics, will largely complement the ever extending catalogues of putative markers which will be helpful in stratified and/or personalized medical approach and for the purposes of disease modification.

Endophenotypes are defined as measurable components unseen by the unaided eye along the pathway between disease and distal genotype (15). The endophenotype represents the collection of all kinds of BM between clinical phenotype and genotype. Ultimately, this individual biosignature which could also include data obtained from their environmental life will be steadily updated so that in contrast to the current 'snapshot situation' related to a particular phase in a given disease condition that corresponds to the current field of companion diagnostics, a more prospective and continuous picture will emerge for future therapeutic and most importantly preventive purposes. In the future, a virtual cloud of billions of data points including the clinical phenotype, the genotype, and the endophenotype is forecasted to surround each patient and will help to develop efficient and integrated workflows that predict the most suitable preventive and therapeutic strategy for each patient (16). One of the challenges of BM in AD is trying to identify from a mass of data which BM are the most informative and are a surrogate marker for numerous other BM. This is relevant all the way through the spectrum from genetic variant to clinical sign. Another important aspect of BM is the differences in reproducibility and how easy they are to perform, for example, the sum of 'filaggrin activity' in the skin has been looked at with techniques such as mass spectrometry which is expensive, time-consuming, and difficult. In contrast, NaPCA is a simple, cheap, and easy to perform assay.

Among the BM, so-called core-BM that are related to the fundamental disease mechanisms can be distinguished from the more downstream BM considered as secondary phenomena. This distinction could be important with regard to the value of a given biomarker in the context of disease-modifying strategy, but it seems currently too early to assign this status to a particular BM in any disease. On the other hand, BM can be classified at least into six main categories, which can include overlapping fields and BM. Table 1 summarizes

Table 1 Definition and purpose of biomarkers in stratified medicine. Examples for atopic dermatitis (AD)

Type of biomarkers (BM)	Purpose	Examples for AD
1. Screening/risk BM	Identification and stratification of patients at a preclinical stage	FLG (3), LEKT1/SPINK5, FCER1B (17), FCER1A (18), NaPCA and UCA (19, 20), IgE (17), FcεRI + DC (21)
2. Diagnostic BM	Confirmation of the entity once it is clinically expressed	
3. Severity BM	Implementation of the clinical scoring at an endophenotypic level	CCL17/TARC, CCL26/eotaxin-3 (22–26), IL-16, CCL22/MDC (27), IL-31, sCD-30 (28–30), NaPCA and UCA (19, 20), ECP (31), IgE (17), TSLP (32)
4. Prognostic BM	Stratification within a clinical phenotype suggesting higher risk of disease progression	FLG (3), IgE (17)
5. Predictive BM	Stratification on direct responsiveness to a given treatment	Not yet identified
6. Pharmaceutical dynamic BM	Stratification on metabolism and putative risk of serious adverse events	Not yet identified

the main purpose of the different BM types and gives some relevant examples for AD.

Current status of biomarkers in AD

Despite its high incidence, there are only a few reports providing validated data for a defined BM in AD, and no systematic review is so far available in this field. Among the candidate BM available (Table 1), the genomic marker FLG could be a reliable screening marker for early onset and severe forms associated with high IgE levels in infancy/childhood (33). As this particular form of AD is considered as the initial step of the atopic march (34–37) and FLG null mutations have been reproducibly associated with AD followed by allergic asthma (38, 39), it seems reasonable to suggest that FLG will represent the first important prognostic marker for atopic march in early infancy. However, we will certainly need a more complete ‘genotypic and endophenotypic profile’ to be able to proceed with a meaningful stratification of the complex AD phenotype in those subgroups, which may benefit from particular preventive or therapeutic strategies.

Biomarkers for severity have been widely explored in AD, mainly for the purpose of clinical trials. The correlation with the clinical scoring such as SCORAD was highest for IL-16, the ‘eosinophil cationic protein’ (ECP), and the ‘macrophage-derived chemokine’ (CCL22/MDC) (27). In the available literature, the ‘thymus and activation-regulated chemokine’ (CCL17/TARC) and the ‘thymic stromal lymphopoietin’ (TSLP) (32) belong to those markers which have recently been identified as available severity marker, but CCL22/MDC was also suggested as a potential marker for the course of AD in one single study (40). There is good evidence to consider AD as a disease with a marked systemic Th2 deviation, and total IgE seems a reliable BM for a stratification of patients with regard to the non-IgE-associated/‘intrinsic’ and IgE-associated/‘extrinsic’ genesis of the disease (41). This could be of particular interest in the context of new therapeutic approaches aimed to target IL-4 as a critical cytokine in the regulation of IgE synthesis. Moreover, a Th2 deviation seems favorable for the development of severe and dangerous viral infections such as eczema vaccinatum (EV). Eczema herpeticum represents a model disease for EV and is the subject of intense research during the last years (42), aiming to identify prognostic BM for the stratification of patients with AD.

The epidermal barrier dysfunction arising as a result of decreased levels of FLG protein and its metabolites may not only arise as a result of genetic changes in the FLG gene. The functional FLG protein, which binds keratin filaments together, is produced by proteolysis of the precursor protein pro-FLG by proteases such as matriptase (43, 44). One study has demonstrated increased protease inhibitory activity in suction blisters from patients with AD – leading to decreased proteolysis of pro-FLG to FLG (45). This provides an explanation for reduced FLG expression in AD that is not dependent on mutations in the FLG gene. Reduced expression of the FLG protein has also been found in the skin of patients who are not the carriers of known FLG mutations (46). FLG expression has been shown to be less in skin biopsies from

lesional AD skin compared to nonlesional AD skin. The Th2 cytokines IL-4 and IL-13 have been shown to downregulate FLG expression in keratinocytes (46). These observations indicate that the Th2 cytokine-mediated inflammatory response in active AD reduces FLG expression and contributes to the skin barrier defect. Natural moisturizing factor (NMF) is generated by the breakdown of FLG. NMF contains, among others, sodium pyrrolidone carboxylic acid (NaPCA) and urocanic acid (UcA), which are decreased in FLG mutations (19) and are somehow related to the severity (20). The NMF BM NaPCA and UcA can therefore be used as a measure of epidermal barrier dysfunction arising both as a result of genetic variants and of inflammation. Both can be used to measure epidermal barrier dysfunction both at phase 0 (genetic predisposition) and later in the disease owing to inflammation. This type of biomarker, which is affected by several events in the pathogenesis of AD, is potentially of great importance when assessing a therapy that has a disease-modifying activity. The pH of the surface of the stratum corneum may also represent an important and easy to measure biomarker which is regulated by genetic variants, the degree of inflammation, and environmental agents. It is therefore a biomarker that reflects a composite of events in the development of AD.

It is expected that not a single genomic/epigenomic or endophenotypic BM will suffice to properly stratify the AD population for a given purpose. Instead, a combination of several BM providing a distinct biosignature will be needed to address specific goals such as disease modifying or more targeted prevention and therapeutic concepts. Most of the candidate BM identified so far for AD still need to be replicated and validated in large cohorts. Thus, a consortial approach aiming to establish biobanks collecting genomic/epigenomic and biological material as well as detailed phenotypic information is urgently needed. Such an approach would be promising but represents one of the substantial challenges faced in the field of personalized (stratified) medicine (Bieber, personal communication).

Rationale for disease modification strategy in AD

Atopic dermatitis is highly heterogeneous with regard to the clinical phenotype and natural history. Thus, the various forms and onsets should be considered as an important aspect for the identification of those patients who may have a benefit from a disease-modifying strategy in AD. Based on the available epidemiological and genotypic data, it is assumed that early-onset AD represents the first step of the atopic march in patients carrying FLG null mutations. Several phases of the disease course could be identified (1) and potentially characterized by BM (Fig. 1). After a postnatal preclinical phase (phase 0), AD starts very early in infancy with chronic skin inflammation but without any evidence for IgE sensitization (non-IgE-associated infantile eczema)(phase I). This phase is more or less rapidly followed by the emergence of sensitization usually toward food allergen and other environmental factors leading to the classical IgE-associated AD phenotype (phase II). The role of a spreading and chronic inflammation of the skin and of the *Staphylococcus*

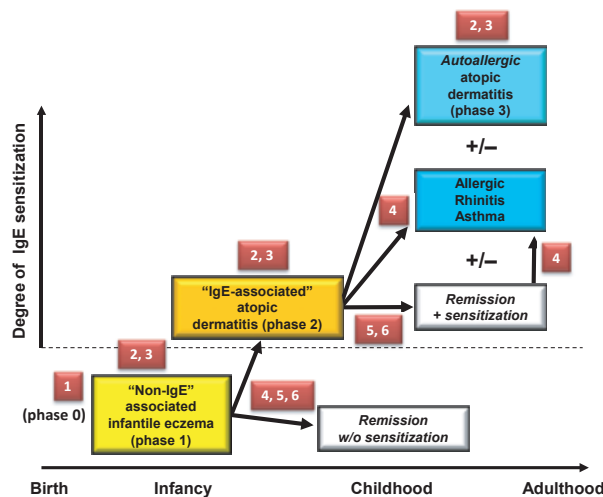


Figure 1 Cartography of the possible implementation of biomarkers in the natural history of atopic dermatitis (AD). (The numbers refer to the type of biomarkers as defined in Table 1, i.e. 1 = Screening BM for the identification and stratification of newborns and infants at a preclinical stage of AD. 2 = Diagnostic biomarker (BM) for the confirmation of AD once it is clinically expressed. 3 = Severity BM for the implementation of the clinical scoring of AD at an endophenotypic level. 4 = Prognostic BM for the stratification of AD with identification of a subgroup with higher risk for disease progression. 5 = Predictive BM for the stratification on direct responsiveness to a given treatment, for example, biologicals or other new systemic therapies. 6 = Pharmaceutical dynamic BM for the stratification on metabolism and putative risk of SAE in the context of a therapeutic procedure.

aureus colonization as catalyzers triggering IgE sensitization has to be considered in this context. Finally, a substantial proportion of these patients seem to have a high risk of developing allergic rhinitis and asthma and/or, further triggered by the chronic skin inflammation and scratching, to become sensitized to self-proteins ultimately leading to a kind of autoimmune form of AD (phase III) (47–49).

About 40–60% of the children suffering from AD (phase II) will experience a spontaneous improvement leading to complete remission until the age of 7 or latest at puberty (50), but 80% of them will have the new onset of allergic rhinitis and/or allergic asthma in childhood or in later life (51). This is of outmost importance as recent epidemiological studies have shown that childhood AD combined with allergic rhinitis provides a high risk (OR = 11.7) for allergic asthma in adulthood (36). It is assumed that at least a substantial proportion of the latter include patients with FLG mutations. However, there is currently no BM identified which would predict any of these possible courses of the disease. Hence, there is a great need for further studies identifying putative genomic and endophenotypic markers that would enable us to stratify the patients very early into those who may experience remission at the age of 7 without further atopic diseases in contrast to those who will go into the atopic march. For this latter group and with regard to the

substantial burden of allergic asthma, it would be worth to develop an adequate approach to eventually stop the progression of the atopic march or even try to reverse it.

Is there any current evidence for a disease-modifying effect in the management of AD?

The majority of intervention studies in AD have been of relatively short duration of <1 year. In ideal circumstances, a study should be controlled, and there should be a long-term control of both the inflammation and the barrier function of the skin. Such an ideal circumstance cannot be achieved with flare treatment only, as this does not control the subclinical inflammation present in AD. Therefore, the treatment for acute flares should be followed by a maintenance type of treatment (52, 53). At the present, there are no data available on disease modification with such a treatment only. However, we do have long-term studies with a treatment that differs from both flare treatment and maintenance treatment. In long-term studies with tacrolimus, ointment treatment was carried out until all signs of AD including the itch was controlled with a subsequent extra treatment for one more week (54). Treatment was started again after the first signs of eczema appeared. As a sign of effective treatment, both involved body surface area and use of treatment decreased over time for up to 10 years (55).

With the exception of three 1-year studies, all these long-term studies have been uncontrolled. Despite of this shortcoming, there are some signs of possible disease modification to be observed. Biomarkers of Th2 polarity seem to be predictive of staphylococcal colonization of the skin in AD. Such biomarkers include serum total IgE levels, eosinophilia, and allergic rhinitis (56). Effective treatment for AD resulted in the elimination of staphylococci, a shift in the inflammation toward Th1 dominance, and a normalization of the skin barrier function (57–59). Improvement of skin atrophy was also observed (60). Improved control of the skin inflammation may also have a positive effect to the airways and the overall atopic status (55, 61). Taken together these findings suggest that long-term effective treatment with good control of the inflammation of the skin and a proper barrier function, the inflammation of the skin can be reversed and this will have beneficial effects on airways as well. Earlier and more effective control of the disease symptoms results in better treatment results and will reduce the burden of the disease for both the individual and the society, as shown in asthma (62).

The putative future scenarios of intervention

Depending on the stage of progression of AD and the atopic march, several scenarios can be envisaged. The most evident goal of disease modification would be a treatment leading to a reverse of the established atopic march. Some preliminary results obtained upon the long-course treatment of such patients suffering from AD and asthma suggest that this kind of reverse is not excluded. Similarly, in the case of an established autoimmune form of AD (phase III), disease modification could be envisaged by a therapeutic approach, such as

specific immunotherapy, aimed to induce tolerance toward the putative self-proteins recognized by specific IgE in these patients. Thereby, BM such as autoantibodies providing information for a targeted desensitization and as well as for its success would be of great interest.

More upstream in the natural history, adequate therapeutic intervention during childhood could stop the switch from AD to asthma and thereby represents a true disease modification for these patients at high risk. Even more upstream, during the very initial phase of the disease in infancy (phase I), an early intervention with an optimized control of the underlying chronic skin inflammation could hamper the emergence of IgE sensitization and decrease the risk of the atopic march at a very early stage. BM able to predict the risk for the atopic march from phase I would allow to identify those patients which would greatly benefit from this kind of strategy. Finally at phase 0, BM allowing the identification of patients who are at high risk of developing an AD (and atopic march) could also serve as surrogate end points in adequate trials and preventive intervention strategies. Such approaches using newly designed products aimed to correct the disturbed epidermal barrier would represent the ultimate goal of stratified medicine combined to disease modification.

Conclusion

The recent progress in genomics and understanding of the pathophysiology of AD has revealed the heterogeneity of its

genotype, but attempts to establish genotype–phenotype relationship are rather scarce. On the other hand, these genetic findings have nourished the hope that we will be able in a near future to identify BM enabling us to stratify these individuals with the aim to develop new strategies such as disease modification including primary prevention in the population at high risk of developing AD and asthma. Whether this kind of strategy is already feasible with the arsenal of available medical products such as topical steroids or calcineurin inhibitors or whether the issue of safety, especially in infancy requires the further development of new and safe compounds for this particular approach need to be clarified. In any case, the scientific community will face a number of new challenges during this fascinating development ultimately leading to the reduction in the burden of AD and asthma.

Conflict of interest

Thomas Bieber has received a consulting fee from Astellas, Novartis, Intendis, he has also received Board membership and consultancy payments from Astellas, Intendis, and lecture payments from Astellas. Michael J. Cork has received research funding and/or given lectures for: Almirall, Astellas Pharma, Johnson & Johnson, Leo Pharmaceuticals, Reckitt Benckiser and Stiefel (a GSK company). Sakari Reitamo has received study grants from Astellas Europe, has acted as an Expert for Astellas and has been in the speaker's bureau of Astellas.

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