Chapter

Atopic Dermatitis: From Physiopathology to the Clinics

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Abstract

Atopic dermatitis is a chronic, pruritic, relapsing inflammatory disease with a complex etiopathogenesis. Alterations of the epidermal barrier function together with a predominantly type 2 altered immune response are responsible for the heterogeneous clinical manifestation. Although pruritic eczematous plaques represent the most frequent phenotype, several others are also characteristic. The diagnostic of the disease relies on clinical aspects, and no complimentary tests are needed. In the literature, we can find a significant number of diagnostic and screening biomarkers; however, severity ones are the most reliable and applicable. Patient-tailored treatment is mandatory, as not all the patients equally respond to the same drugs. The newly released therapies, as well as those under investigation, give hope to AD patients.

Keywords: atopic dermatitis, immunology, type 2 immune response, clinical features, eczema, biomarkers, risk factors, treatment, biological agents

1. Introduction

Atopic dermatitis (AD) is a common chronic, pruritic, relapsing, inflammatory systemic disease that affects both children and adults. Patients frequently have high levels of total immunoglobin E (IgE) and a personal or family history of atopic-related diseases.

AD is one of the most common inflammatory cutaneous diseases with an incidence that has tripled in the last 3 decades in industrialized countries. Prevalence in children population is approximately 15–20%, while it is much lower in adults, between 1 and 3%.

Several studies demonstrate that AD has a high impact on patients' quality of life (QoL). For some of them, the impairment in QoL is more significant than in some other chronic diseases such as hypertension, diabetes, or even psoriasis [1].

In this chapter, we will make a dual approach to AD. First, we will concentrate on the immunological mechanisms of AD and then will discuss the clinical and therapeutic aspects of the disease.

2. Immunological mechanisms of AD

2.1 Immunological mechanisms underlying atopic dermatitis

The immune system is a very complex and interactive network of cells and molecules to protect the host against potentially dangerous pathogens while

keeping at the same time a state of tolerance against self and innocuous non-self-antigens [2, 3]. The immune system employs a large number of molecular and cellular mechanisms that must be tightly regulated to perform this vital function. Alterations on these mechanisms lead to the appearance of immune-related diseases such as recurrent infections, autoimmunity, tumor tolerance, organ rejection, as well as allergic and skin diseases such as AD [2, 4–6].

AD is one of the most prevalent chronic inflammatory diseases of the skin affecting both children and adults [7, 8]. The clinical features that characterize the disease are dry and scaly skin, eczema lesions, and chronic itching. AD is a very complex and debilitating disease that should be considered as a systemic disease associated with different comorbidities. The development of AD depends on the integration of multiple factors such as genetic background, environmental exposure, skin barrier, and immune alterations [9–11]. All these factors cooperate and synergize leading to the clinical manifestations of AD. Over the last years, our understanding on the immunological mechanisms underlying AD has significantly improved [12]. Today, it is well accepted that the inflammatory component of AD is mainly driven by aberrant type 2 immune responses, which significantly contribute also to barrier defects and itching [5, 13]. Other immune responses including Th17, Th22, and, to a lesser extent, Th1 cells can also contribute to AD at different stages of the disease as well as in different subsets of patients and phenotypes [11, 14, 15].

2.2 Orchestration of type 2 immune responses

The immune system employs type 2 immune responses to combat parasites and helminths, as well as toxins and venoms [16, 17]. Parasites are pathogens very large in size that cannot be engulfed and eliminated by innate immune cells, and dangerous venoms/toxins might rapidly spread throughout the body. Therefore, the main aim of type 2 immune responses is to expulse away the pathogen from the body or destroy the toxins, thus avoiding their systemic dissemination and the lethal consequences for the host. Aberrant type 2 immune responses, due to different and sometimes unknown etiologies, might lead to the development of allergic diseases such as asthma or food allergy as well as to skin diseases such as AD [2, 4, 18]. Initially, AD was regarded as a Th2-mediated disease; however, recent findings showed that type 2 innate lymphoid cells (ILC2s) and other innate immune and effector cells also contribute to the orchestration of these responses. Therefore, the term type 2-mediate disease is more adequate according to our current knowledge [19, 20].

Different cell subsets from both arms of the immune system, as well as tissues and non-hematopoietic cells, directly contribute to the orchestration of type 2 immune responses, both locally and systemically [19]. Under normal conditions, the presence of helminths or toxic substances triggers the production of large amounts of alarmins such as TSLP, IL-33, or IL-25 by epithelial cells (ECs). Alarmins directly activate and expand ILC2s by mechanisms depending on IL-7 and condition the capacity of dendritic cells (DCs) to induce T helper (Th)2 and type 2 CD8+ cytotoxic T-cell (Tc2) responses by mechanisms depending on IL-4 [21]. Activated ILC2s, Th2, and Tc2 cells produce type 2 cytokines such as IL-4, IL-13, or IL-5, which contribute to the recruitment and activation of different effector cells such as eosinophils, basophils, and mast cells to the inflamed tissue. Type 2 cytokines also participate in the activation of non-hematopoietic cells and tissues, which in cooperation with the activated immune effectors' cells aim at eliminating the potentially dangerous invading pathogen/toxin, avoiding systemic dissemination.

2.3 Dendritic cells connect innate and adaptive immune responses

DCs are antigen professional presenting cells (APCs) that link innate and adaptive immune responses [2, 22]. They are localized in all peripheral tissues, circulating in the blood and lymphoid organs. Their primary function is to scan and collect antigens in the periphery (skin, airways, or gut), process these antigens into peptide fragments, and present them in the context of MHC molecules to naïve T cells. DCs express costimulatory molecules and produce polarizing cytokines, which, together with their migratory capacity, empower them as the essential APCs in the priming of T cell responses [15, 23].

Depending on the type of encountered antigen and the signals that DCs receive in the periphery and during the travel to the lymph node, they can generate different types of effector CD4+ T cells [24, 25]. When DCs encounter intracellular pathogens (viruses or bacteria), they produce large amounts of IL-12 and induce IFN-γ-producing Th1 cells that in turn activate NK cells and CD8+ T cells to combat these infections. Aberrant Th1 responses also associate other autoimmune diseases [25]. In contrast, extracellular pathogens (bacteria or fungi) condition DCs to produce large quantities of IL-23, IL-1β, TGF-β, and IL-6, thus promoting the generation of IL-17A-producing Th17 cells that contribute to neutrophilic infiltration to eliminate these pathogens. Alterations of Th17 responses have been associated with different autoimmune diseases and psoriasis [26]. Under certain circumstances, mucosal DCs can also generate IL-9-producing Th9 or IL-22-producing Th22 cells, which contribute to activate mast cells and to promote epidermal hyperplasia, respectively [24, 26]. As above discussed, the presence of parasites or venoms activates ECs and instructs DCs to polarize Th2 cells producing large amounts of type 2 cytokines such as IL-4, IL-13, IL-5, or IL-9. Aberrant Th2 responses are the main drivers of allergic diseases and AD [12, 25]. In addition to these effectors CD4+ T-cell responses, DCs can also generate regulatory T cells with potent suppressive capacity, which play a crucial role in keeping homeostasis avoiding excessive immune activation and tolerance induction [2, 3, 18, 27].

In humans, blood DCs are classified into two main groups: (i) myeloid dendritic cells (mDCs) and (ii) plasmacytoid dendritic cells (pDCs) [28]. According to the expression of specific markers, mDCs can be further divided into type 1 mDCs and type 2 mDCs [28–30].

pDCs are the primary producers of type I IFNs and are essential in antiviral responses, whereas different subsets of mDCs contribute to the orchestration of different types of immune responses. Both mDCs and pDCs are different phenotypic and functional DC subsets that cooperate to integrate and mount immune responses.

In the healthy skin, under non-inflammatory conditions, the number of DCs is relatively low with a clear predominance of epidermal and dermal Langerhans cells (LCs) [12, 31]. In contrast, the number and composition of DC subsets in the lesional skin of AD patients are altered with significant infiltration of inflammatory dendritic epidermal and dermal cells (IDECs and IDDCs, respectively) [12, 31]. DCs in the skin of AD patients express high levels of the high-affinity receptor for IgE (FcεRI), which might play a critical role in the priming and expansion of memory T cells. Besides, after IgE-FcεRI cross-linking, DCs produce a plethora of chemokines that add to the recruitment of Th2 cells and other inflammatory cells into the skin, thus enhancing inflammation. IDECs can also migrate to lymph node and polarize and increase the frequency of Th2 cells but also Th1, Th17, and Th22 as observed during the most chronic phases of AD [12, 31]. Overall, DCs play an essential role in the initiation and maintenance of type 2 immune responses in the

context of AD as well as in the generation of other Th cell subsets detected during the chronic phases and in different phenotypes of AD patients.

2.4 The immunopathogenesis of AD

The knowledge of the immunological mechanisms involved in the pathogenesis of AD has significantly improved over the last years. There are three phases in AD development involving different cytokines and cellular signatures that account for the clinical manifestations of the disease: (i) initial non-lesional stage, (ii) acute stage, and (iii) chronic stage.

2.4.1 Initial non-lesional stage

The structural integrity and permeability to environmental insults are severely compromised in susceptible patients displaying skin barrier defects [5, 10]. These skin alterations might be originated due to different factors including genetic susceptibility (mutations in filaggrin and/or other key genes for stratum corneum and skin integrity), alterations in tight junction proteins (TJ), dysregulation of skin lipid composition, changes in pH, altered microbiome, high transepithelial water loss (TWEL), or high susceptibility to infections and irritants. These skin barrier defects allow the penetration of large amounts of allergens, pathogen-derived antigens, and/or other environmental insults into the lower epidermal layers, leading to the activation of keratinocytes [7]. Skin DCs uptake the encountered allergens and migrate to the closer lymph nodes conditioned by keratinocyte-derived alarmins such as TSLP, IL-33, or IL-25. These alarmins also activate tissue-resident ILC2s, which produce large amounts of type 2 cytokines facilitating DC migration and recruitment of inflammatory cells into the skin [7, 10]. Under these circumstances, DCs polarize naïve CD4+ T cells into allergen-specific Th2 cells by mechanisms depending on IL-4. The clonal expansion and activation of Th2 cells significantly contribute to IgE class-switching at the B level. The generated IgE+ B cells differentiate into plasma cells that produce large amounts of allergen-specific IgE antibodies that bind to the surface of mast cells and basophils, leading to the allergic sensitization [2, 4]. The induced Th2 cells home back and infiltrate the skin through lymph and circulation, leading to the classical skin inflammation observed of this initial stage even in the absence of skin lesions.

2.4.2 Acute stage

During the acute stage of AD, activated Th2 cells and ILC2s produce large amounts of IL-4, IL-13, IL-31, and IL-5 [12, 24]. IL-5 favors eosinophil recruitment into the skin and IL-31 in cooperation with IL-4 and IL-13 play a critical role in itching, thus initiating the vicious circle of itching-scratching that contributes to increase the damage of the already altered skin barrier and to enhance inflammation [12]. IL-31 directly act on sensory neurons, but it also promotes the growth of sensory nerves and skin hyperinnervation [32, 33]. IL-4 not only contributes to increasing the expression of IL-31 [34] but also together with IL-13 to sensitize neurons to a large variety of pruritogens such IL-33 and TSLP that increase after scratching, thus potentially contributing to chronic itch [32]. IL-4 and IL-13 also directly act on keratinocytes by inhibiting their differentiation, the production of antimicrobial peptides (AMPs), and altering lipid metabolism, thus enhancing barrier disruption. Six IL-13-activated keratinocytes produce an extensive battery of chemokines such as CCL17 (TARC), CCL26 (eotaxin), CCL18, and CCL22. In cooperation with the increment of vascular permeability induced by IL-4 through

the increased of vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelial cells, a massive infiltration of different types of inflammatory cells and vascular leakage takes place [5, 7]. Collectively, all these mechanisms account for the typical clinical symptoms of the AD acute stage, including itching and eczema lesions characterized by edema and spongiosis.

2.4.3 Chronic stage

The perpetuation of this predominant type 2 inflammation might lead to the chronicity of the disease [5]. In this phase, inflammation increases and persists due to constant activation of keratinocytes, vascular endothelium, inflammatory cells, and chronic itching. Remarkably, in the chronic stage, other Th cell subsets including IFN-γ-producing Th1, IL-17-producing Th17, and IL-22-producing Th22 are also infiltrating the skin lesions [11, 15]. Depending on the AD subtypes, the relative frequency and contribution of these inflammatory Th cell subsets might vary significantly [11, 35, 36]. For example, in Asian AD patients as well as in some AD children subtypes, IL-17-producing Th17 cells might contribute to parakeratosis resembling typical features of psoriasis. In European-American, African American, and children AD patients, IL-22 produced by Th22 cells in cooperation with high levels of type 2 cytokines IL-4/IL-13 reinforce defective barrier function. It also enhances keratinocyte proliferation and promotes epidermal hyperplasia, leading to the lichenification and chronic itching typical of chronic stage [5, 10, 11, 35, 36].

3. Clinical features of AD

Although AD frequently appears during childhood and tends to subside as the patient grows, there is a considerable number of patients who persist in adulthood.

Recently, adult-onset and elderly onset phenotypes have been described [37, 38].

The essential features of AD are eczematous lesions and pruritus. Former can be acute, subacute, or chronic.

The clinical presentations, the lesion type and its distribution, are age specific, and this is a crucial aspect to consider when examining patients so as not to miss diagnose them.

AD phenotypes can be stratified according to multiple characteristics. One of the most used is the age-related clinical stratification, which classifies patients into four groups [39].

Infantile AD: Patients from 0 to 2 years present with an acute form of eczema, which typically affects cheeks, face, sparing nasal-labial triangle, scalp, trunk, and extensor surfaces of the limbs. The napkin area is typically respected.

Children AD: From 2 to puberty patients show subacute-to-chronic eczema that affects the flexural folds, dorsal aspects of the limbs, perioral area, and napkin area.

Adult AD: Adults typically present with a chronic or lichenified (**Figure 1**) and symmetric eczema that involves flexures, wrist, ankles, eyelids, and cheeks. In patients with a longstanding AD, a selective involvement of the neck and dorsal aspect of the hands is frequent, showing lichenified brown lesions that resemble dirt (**Figure 2**).

Elderly AD: AD in elderly presents with widespread chronic eczematous lesions with significant itch (**Figure 3**). It is usually misdiagnosed as cutaneous T-cell lymphoma, allergic contact dermatitis, or other types of eczema. Further information is needed regarding the exact clinical presentation so as not to underestimate its real prevalence.

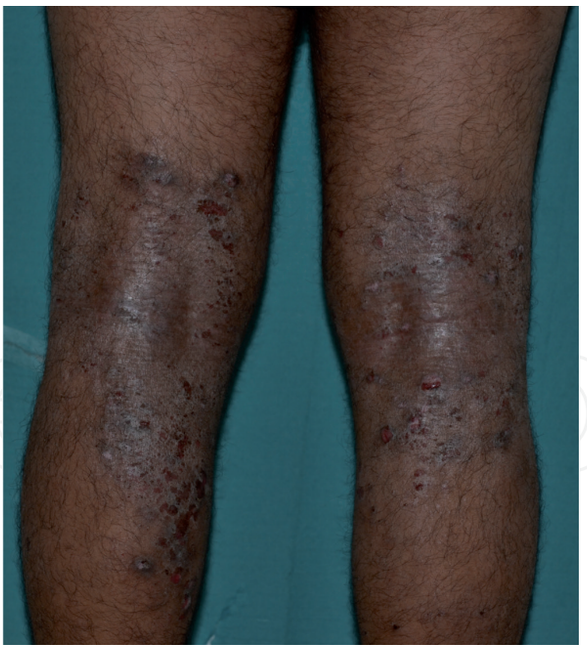

Figure 1.
Lichenified lesions on the posterior part of the legs.

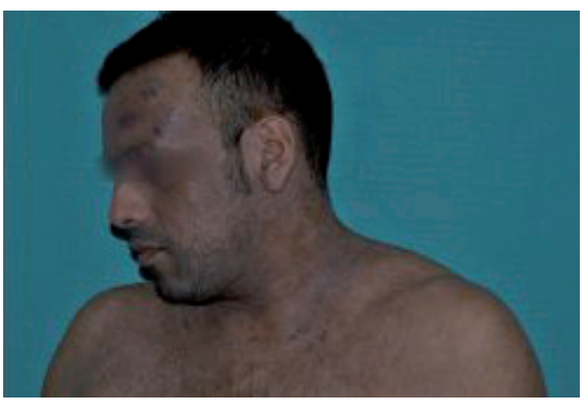

Figure 2.
Chronic eczema in an adult patient with lichenified brown lesions on the lateral aspects of the neck that resemble dirt.

Patients can also be classified according to the age of onset [39]. Bieber et al. proposed six phenotypes, which included very early-onset (3 months–2 years), early-onset (2–6 yeas), childhood-onset (6–14 years), adolescent-onset (14–20 years), adult-onset (20–60 years), and very late-onset (>60 years). The majority of patients fall into the first group; however, adult-onset is a recently identified group, which represents about 20% of all the cases. The latter group includes two subsets, those with AD in the past and a long period of remission and those with a very late-onset.

It is important to consider that patients can present not only with widespread lesions but also with localized or morphologically distinct phenotypes.

Localized variants include selective eczema of the nipples, hands, eyelids, periauricular area, cheilitis, subnasal region, and genital area. The head and neck type are typical of the adult group and show involvement of the upper trunk and scalp.

Morphological variants comprise the follicular type, which presents as aggregated follicular papules, the papulo-lichenoid variant, the prurigo variant that resembles a prurigo nodularis, the nummular variant, and erythroderma [5, 37, 40] (**Figure 4**).

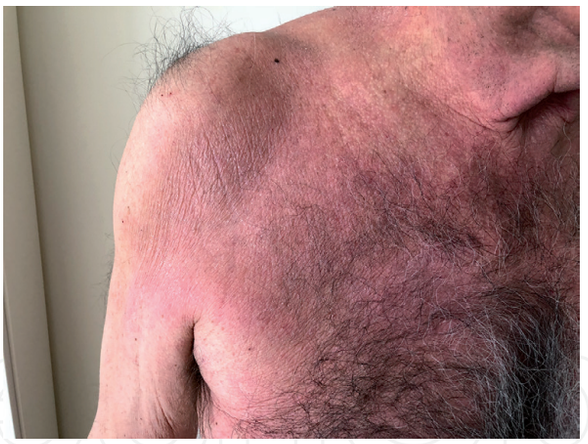

Figure 3.
Widespread eczema in an elderly patient.

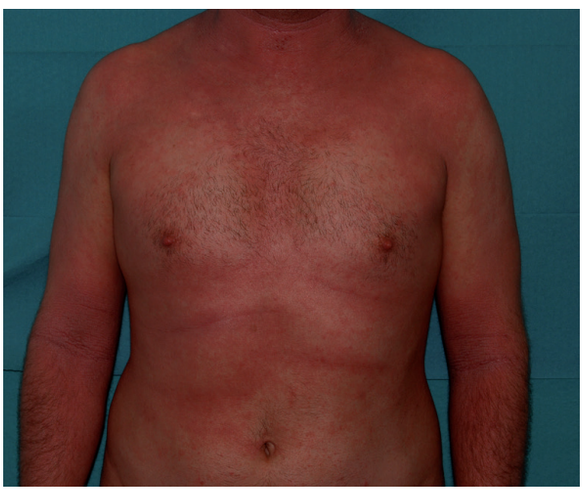

Figure 4.
Erythrodermic variant of AD.

Silvestre Salvador et al. [37] recently described and classified the clinical forms of presentation of AD in adult patients. They identified 11 groups: lichenified/exudative flexural dermatitis, head-and-neck eczema, seborrheic dermatitis-like dermatitis, portrait dermatitis, hand eczema, generalized eczema, prurigo nodularis, nummular eczema, erythroderma, psoriasiform dermatitis, and multiple lesions of lichen simplex.

3.1 Diagnostic of AD

The diagnostic of AD is based on clinical features since no specific biomarkers or histological hallmarks exist. It relies on the morphology and distribution of the lesions, clinical history, and other clinical signs.

Multiple sets of diagnostic criteria have been developed since 1980 when Hanifin-Rajka proposed the first, which included major and minor features. It requires 3 out of the four major and 3 out of the 23 minor criteria to establish a diagnosis. Later, the "United Kingdom Working Party" settled a set, which followed the essence of the Hanifin-Rajka's, but adapted it for epidemiological and clinical studies [5].

In 2003, Eichenfield et al. [41] revised the original criteria and elaborated a set dividing features into essential, important, and associated (**Table 1**). It also includes

exclusionary criteria to help with the differential diagnostic. Probably, these criteria are the most used in a clinical setting.

In 2016, Liu P et al. [42] proposed an easy-to-use set for adolescents and adults. They based the diagnostic on the presence of symmetric eczema for more than 6 months associated to one or more of the following: family or personal history of atopic-related diseases, eosinophilia, and elevated total or specific IgE.

Diagnostic criteria for SD			
Essential features (must be present)	Pruritus		
	Eczema (acute, subacute or chronic)	Typical morphology and age-specific patterns	Facial, neck, and extensor involvement in infants and children
			Current or prior flexural lesions in any age group
			Sparing of groin and axillary regions
		Chronic or relapsing	
Important features (seen in most of the cases, adding support to the diagnosis)	Early onset		
	Atopy	Personal and/or family history	
		IgE reactivity	
	Xerosis		
Associated features (help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD)	Atypical vascular response		
	Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis		
	Ocular or periorbital changes		
	Other regional findings		
	Perifollicular accentuation/lichenification/prurigo lesions		
Exclusionary conditions	Scabies		
	Seborrheic dermatitis		
	Contact dermatitis		
	Ichthyosis		
	Cutaneous T-cell lymphoma		
	Psoriasis		
	Photosensitivity dermatoses		
	Immune deficiency diseases		
	Erythroderma of other causes		

Adapted from Eichenfield et al. [41].

Table 1.
Diagnostic criteria proposed by Eichenfield et al. in 2003.

3.2 Approach to the patient with AD

When considering the diagnostic of AD, it is crucial making a thorough clinical history, which includes information regarding the chronicity of eczema, the presence of itch, and the personal and family history of atopy. In children, AD is one of the first diagnostics to consider, while in the adult population, probably due to a lack of familiarity with adult-onset disease and even when dealing with patients with a compatible clinical picture, the first diagnostic suspicion tends to be contact dermatitis. Physical examination is also mandatory to determine the morphology and distribution of the lesions, which can help to consider or even establish the diagnostic [37].

There are controversies regarding complementary tests, which are useful at ruling out differential diagnostics. According to the AAD guidelines, AD is a diagnostic of exclusion and should only be established after excluding other diseases [43].

Patch testing should be considered in patients with adult-onset disease, those with a chronic disease who fail to respond to adequate treatment, patients with atypical or changing distribution, as well as patients with patterns suggestive of allergic contact dermatitis. Patch test should always be assessed according to clinical history to determine the relevance of the results [37].

The utility of the prick test is somewhat controversial. A prick for airborne allergens could be useful in adults with an airborne pattern eczema involving the face, particularly eyelid area, neck, and exposed regions of upper limbs. Testing for food allergies might be of help in pediatric patients with generalized eczema that worsen when exposed to certain foods, but also in adult patients who are sensitized to pollen, as pollen-related foods can cause cross-reaction with airborne allergens and trigger flares. Ruling out a protein contact dermatitis could be indicated in patients with chronic hand eczema that flares when handling food [37, 44].

A blood test is not mandatory but can be useful at supporting the diagnostic of AD. High IgE levels and eosinophilia are frequent in these patients. Other parameters such as lactate dehydrogenase (LDH), serum thymic activation regulator chemokine (sTARC)/CCL17, CCL27, cationic eosinophilic protein (CEP), and antitransglutaminase antibodies may provide with information regarding the severity or helping in the differential diagnostic (see biomarkers).

Although the histopathologic picture of atopic dermatitis does not differ from other types of eczema, a skin biopsy may help rule out other diagnostics such as cutaneous T-cell lymphoma (CTCL), psoriasis, or drug reactions [37].

Including a simple blood test with hemogram, liver function, renal function, LDH, total IgE (and specific if the clinical history suggests it), IgA, and antitransglutaminase antibodies would be reasonable during the initial diagnostic workup. Indications for a patch test and prick test are those specified before.

3.3 Assessment of the disease severity and impact on the quality of life

After setting up the diagnostic of AD, it is essential to assess the severity of the disease and its impact on patient's quality of life.

3.3.1 Severity

Several scales evaluate the severity; some of them include just objective signs, while others also include subjective patient's symptoms.

Most of the scales are composite score systems, which assess different aspects of the disease (**Table 2**).

Severity				Quality of life			
Scale	**Score**	**Description**	**Msc**	**Scale**	**Score**	**Description**	**Msc**
SCORAD	0–103	<25 mild 25–50 moderate >50 severe	8.7	HADS	0–42 (A/D)	0–7 normal 8–10 borderline abnormal 11–21 abnormal	N/A
EASI	0–72	≤7 mild >7–21 moderate >21 severe	6.6	DLQI	0–30	0–1 no effect at all on patient's life 2–5 small effect 6–10 moderate effect 11–20 very large effect 21–30 extremely large effect	4
IGA	0–4	0 clear 1 almost clear 2 mild 3 moderate 4 severe	N/A				
			Symptoms				
POEM	0–28	0–2 clear or almost clear 3–7 mild 8–16 moderate 17–24 severe 25–28 very severe					3.4
VAS pruritus	0–10	The higher the score, the more severe the pruritus					2–3
VAS sleep	0–10	The higher the score, the more sleeplessness					2–3

SCORAD, scoring of atopic dermatitis; EASI, eczema area and severity index; HADS, hospital anxiety and depression scale; DLQI, dermatology life quality index; POEM, patient-oriented eczema measures for eczema; VAS, visual analogue scale; MSC, minimal significant change.

Table 2.
Scales of severity and quality of life.

The most used in European countries is the Scoring of Atopic Dermatitis (SCORAD). It first evaluates the body surface area (BSA) affected and then gives a score from 0 to 3 for each of the following clinical features: erythema, edema, excoriation, swelling/crusts, lichenification, and xerosis. Finally, the patient is asked to rank pruritus and sleeplessness from 0 (best situation) to 10 (worst situation), giving a total score that ranges from 0 to 103, being the latter the most severe. It is considered a score from 0 to 25 as a mild disease, 25–50 as moderate, and 50 and above as severe.

Eczema area and severity index (EASI) is a scale based on PASI score.

EASI is a more objective tool, which does not include the patient's symptoms, which is widely used in the US and also in the setting of most of the clinical trials. It divides the body into four parts, head and neck, trunk, upper limbs, and lower limbs. The first step is to assess the affected surface in each of the zones and then score erythema, edema, excoriation, and lichenification from 0 to 3. Each score is multiplied by a specific quotient, obtaining a final number that ranges from 0 to 72.

The patient-oriented eczema measures for eczema (POEM) is a symptom score that measures the subjective symptoms of the patient. The final result ranges from 0 to 28, being the latter the worst.

Investigator global assessment (IGA) is an easy-to-use scale that describes the overall appearance of the lesions and scores the severity from 0 to 3, 0 means a clear, 1 almost clear, 2 mild, 3 moderate, and 4 severe disease. Unlike the other three scales, it is not a validated score, but a global assessment of the disease.

3.3.2 Quality of life

Assessing disease impact on patient's quality of life is as important as evaluating the severity.

There are over ten disease-specific tests available for AD and more than 25 generic instruments that can be used in AD [45]. Each of these tools focuses on different aspects of the disease, not only regarding the patient but also their family or close relatives. **Table 2** shows two of the most used scales in assessing QoL.

There are also non-disease-specific questionnaires that study the school or work productivity, focusing not only on work absenteeism but also on presenteeism. One of the most known is WPAI (Work Productivity and Activity Impairment), which is composed of 6 questions regarding the effect of the disease on the ability to work and perform regular activities.

3.4 Biomarkers in AD

Biomarkers are an interesting matter of debate nowadays. Although there is plenty of literature on the topic, the utility and applicability of them still present some concerns.

A biomarker is a common term used across the atopic dermatitis literature. There are two definitions proposed by the World Health Organization (WHO) and by the National Institutes of Health (NIH) biomarkers definition group, which largely overlap. The WHO defines it as "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" [46], while the NIH definition 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." [47].

There are two types of biomarkers, those used for selection or stratification of the patients and those used for monitoring the clinical response.

The former includes screening, diagnostic, prognostic, and predictive biomarkers, while the latter comprises severity and pharmacodynamic markers [48].

Screening biomarkers: Several biomarkers could help in the screening. Mutations in the filaggrin gene are present in up to 30% of the AD patients. R501X and 2282del4 are the most frequent and are dose dependent. These may predict a higher risk of eczema herpeticum and an earlier onset of the disease [49, 50].

Other parameters, such as high levels of cord IgE, infantile a-lymphotoxin and FcεRI-β during pregnancy, as well as high TEWL and SPINK5/LEKTI, could also be useful as screening biomarkers [48].

Diagnostic biomarkers: Although the AD diagnostic is clinical, some biomarkers could help to decant the balance toward AD. Total serum IgE is a useful parameter for dividing patients into intrinsic and extrinsic phenotypes. Up to 20% of patients belong to the intrinsic group, with normal levels of IgE. Consequently, it is an unreliable biomarker for diagnostic purposes.

Filaggrin and leukotriene B4 serum levels could be two valuable biomarkers, as they have been shown to differ from healthy controls significantly. AD patients tend to present higher levels of the former and lower of the latter [51].

Prognostic biomarkers: The purpose of these markers is to estimate the course and evolution of the disease. The only known parameter in this group is the presence of some mutations in the filaggrin gene, which could determine a more severe course of the disease [48].

Predictive biomarkers: This group identifies patients that are most likely to respond to a specific therapy. Currently, as new targeted therapies are arising, there is an evident lack of such biomarkers that help to classify and assign a given treatment.

Recently, Wollenberg et al. described that higher levels of serum periostin and dipeptidyl-dipeptidase 4 (DDP4) conditioned a better response to anti-IL-13 therapies. On the other hand, the presence of single-nucleotide polymorphism (SNP) in the gene promoter region of UGT1A9 is related to low mycophenolate blood levels, and thus a worse response to the drug. Increasing the dose could solve this lack of response [48, 52].

Pharmacodynamic biomarkers: These biomarkers might be relevant when planning therapeutic regimens for AD patients. Although scarcely used, these may help to personalize and enhance efficiently of some systemic treatments.

Tacrolimus is metabolized by CYP3A4 and CYP3A5. CYP3A4*22 and CYP3A5*3 are seen in slow metabolizers, leading to high blood levels. CYP3A5*3 is associated with a fast metabolism, and it entails low blood levels.

Increased activity of UGT1A9 caused by SNPs can lead to a lack of response to mycophenolate due to low blood levels [48].

Azathioprine (AZA) adverse events can be predicted by genotyping thiopurine methyltransferase. The risk of myelotoxicity and liver toxicity can be assessed by monitoring AZA metabolites 6-thioguanine nucleotides and 6-methylmercaptopurine ribonucleotides [53].

Severity biomarkers: Most of the known biomarkers belong to this group. It is essential to distinguish between those biomarkers studied in longitudinal studies, which give information of the evolution of the parameter along the time and in response to the treatment and those derived from cross-sectional studies, which provide with an objective measure of severity at a given moment. Lately, most of the efforts on biomarkers are focused on identifying combinations of biomarkers, which better predict the severity of the disease [54]. Thijs et al. proposed two panels of biomarkers, the first of them [55] is made up of TARC, PARC, IL-22, and sIL-2R and correlates much better with the disease severity than each of the biomarkers alone. The same group elaborated a second panel composed of TARC, IL-22, and sIL-2R, which allowed to predict EASI with a sensitivity of 100% and specificity of 88.9% [56].

Table 3 summarizes these biomarkers.

3.5 Risk factors

Several factors have been associated with the development of AD. Some are regarded as risk factors, while others have a protective role.

Atopy family history and loss-of-function mutations in the gene of filaggrin are two clear risk factors for AD. About 70% of the patients have a positive family history of atopic diseases. The OR for children with one parent affected, compared to those without any, is 2–3, while those with the two parents affected it is 3–5.

FLG-null mutations condition a more severe, persistent and early-onset disease with a higher tendency to eczema herpeticum [43, 60].

Kelleher et al., have recently described that skin barrier dysfunction at 2 days and 2 months of life, as well as neonatal adiposity, increases the risk of AT during the first year of life.

Biomarker	Cross-sectional studies	Longitudinal studies	Conclusion
sTARC/CCL17	Yes	Yes	Potential biomarker for severity and evolution of the disease. Best characterized biomarker [54]
Total IgE	Yes	Yes	Could be a good biomarker for the severity but not for the disease evolution [54]
cTACK/CCL27	Yes	No	Potential biomarker for severity [54]
ECP	Yes	Yes	Questionable value as a severity and evolution biomarker [54]
EDN	Yes	No	Potential biomarker for the severity. Could be a predictor of relapse in severe AD [57]
LDH	Yes	No	Potential biomarker for severity [54]
Periostin	Yes	No	Good correlation with disease severity and chronicity [58]
IL-18	Yes	No	Potential biomarker for severity [54]
E-selectin	Yes	No	Potential biomarker for severity [54]
CD30	Yes	No	Potential biomarker for severity [54]
IL-2R, IL-4R, IL-31, and tryptase	Yes	No	May correlate with severity. More studies needed [54, 59]

ECP, eosinophil cationic protein; EDN, eosinophil derived neurotoxin; LDH, lactate dehydrogenase.

Table 3.
Severity biomarkers.

An increase in the transepidermal water loss (TWEL) at 2 days and 2 months of life conditions to a higher incidence of AD at 6 and 12 months, regardless of the FLG mutations, family history, or presence of itchy flexural rash at 2 months [61].

Besides, a fat mass of the 80th percentile or higher at day two might also be a predictor for AD at 6 and 12 months of age [62].

Risk and protective factors are summarized in **Table 4**.

3.6 Comorbidities

Compared to non-AD patients, patients with AD have a higher incidence of comorbidities that include not only the atopic march associated diseases but also other disorders. The sequential appearance, since early ages, of atopic dermatitis, allergic rhinitis, asthma, and rhinitis is known as the atopic march and is frequently seen together in patients with AD. Other diseases as chronic pulmonary disease, chronic rhinosinusitis, urticaria, autoimmune disorders, conjunctivitis, eosinophilic esophagitis, nasal polyposis, obesity, bacterial, fungal, and viral infections are also seen more frequently in these patients. Neuropsychiatric disorders including anxiety, depression, attention deficit hyperactivity disorder (ADHD), and sleep disturbances are also more prevalent in AD patients than controls.

In a study from the US, authors showed that not only these diseases are more frequent among AD patients but also that are more likely to occur in those with severe disease compared to less severe patients [64].

Finally, an increase in cardiovascular events has been reported in these patients. Andersen et al. showed that this higher incidence was due to an increased burden of comorbidities and detrimental lifestyle behavior [65]. Brunner et al., later suggested

Risk factors	• Family history • Loss-of-function mutations in FLG gene • Parents educations: higher education–higher risk • Urban zones • Domestic animals: cat increases the risk • Indoor exposition to chemicals • Environmental tobacco smoke • Traffic exhaust
Not risk factors	• Age at which food is introduced • Socioeconomical status • Type of delivery • Birth weight
Protective factors	• Hydrolyzed formulas or exposition to probiotics • Exposition to endotoxin, dogs and farm animals at early ages • Unpasteurized milk • Helminthic infections

Table 4.
Risk and protective factors for developing AD [43, 60, 63].

that inflammatory mediators involved in the atherosclerosis development such as CCL7, IL16, PI3, and E-selectin would be responsible for this increase in the incidence and that they were strongly related to the severity of cutaneous inflammation rather than obesity or lifestyle behavior [66].

4. Treatment

There is not a single approach to the treatment of patients with AD. It is a patient-tailored treatment, which depends on the patients' predominant symptoms and past medical history.

The therapy aims to control the skin barrier disruption, the altered immune response, and microbial infections, as well as pruritus [67].

4.1 Topical treatment

Baseline treatment for AD is moisturizers to help to prevent water loss and maintaining skin hydration. Emollients, humectants, or occlusive agents should be used as a maintenance treatment for all patients with AD. The recommended weekly amount is 250-500 g in adult patients and about 100 g in children.

The use of emollients in inflamed skin is poorly tolerated, it is advised to treat the inflammation first with topical treatments and then apply the moisturizer, at least twice a day [68].

According to the European guidelines for the treatment of AD, an "emollient" is a "topical formulation with vehicle-type substances lacking active ingredients," whereas "emollients plus" refers to "topical formulations with vehicle-type substances and additional active, non-medicated substances" and are meant to target specific lesions [68].

Simpson et al. showed that strict emollient therapy from birth in children at a high risk of developing AD (a parent or full sibling with AD, asthma, or allergic rhinitis) was a practical preventive approach [69].

It is also essential to keep optimal skin hygiene. There are some controversies regarding daily bath; however, a short bath of up to 5 minutes with bath oils or non-irritant and low-allergen formulas, to eliminate crusts and bacterial contaminants, is advised.

Adding antiseptics to the bathwater may be useful in cases that show bacterial superinfection [68].

4.2 Topical anti-inflammatory treatment and phototherapy

Topical corticosteroids and calcineurin inhibitors are the treatments of choice for flares in patients with mild disease (SCORAD <25/EASI <7). Moderate or recurrent cases (SCORAD 25–50/EASI 7–21) require proactive therapy with more potent corticosteroids, calcineurin inhibitors, or phototherapy. The proactive scheme consists of daily application of emollients to unaffected skin combined with intermittent use (twice weekly) of the anti-inflammatory drug in usually affected sites. Studies have proven long-term security and efficacy in reducing relapses [68].

The amount of topical anti-inflammatory drugs should follow the fingertip unit rule (0.5 g), which is the adequate amount for application to two adult palm area (approx. 2% of adult body surface area).

Phototherapy, UVA1 and narrow-band UVB, has shown its long-term efficacy in AD in multiple studies. Except for high doses of UVA1, it is not indicated during flares, but in pruritic and lichenified chronic forms. Most of the times, concomitant use of emollients and/or anti-inflammatory therapy is advised.

Severe patients (SCORAD > 50/EASI > 20) require a more aggressive approach with immunosuppressive agents or biologicals.

Crisaborole is a topical phosphodiesterase 4 (PDE4) blocker approved in the US for the treatment of mild-to-moderate AD in patients 2 years old and older, which has shown to be more effective than the vehicle alone. There are no comparative studies with topical corticosteroids or calcineurin inhibitors [67, 68, 70].

Topical Janus kinase inhibitors are still not licensed for the treatment of AD, but they are in the pipeline of multiple laboratories that are currently conducting phase II studies.

4.3 Systemic treatment

Antihistamines: Although the use of systemic antihistamines is widespread in the treatment of pruritus in AD patients, the scarce studies available have shown a minimal effect on decreasing pruritus. First-generation anti-H1 have a sedative effect that can help in decreasing nocturnal itch, but with impaired sleep quality.

Although there is not enough evidence to support the use of both first and second-generation anti-H1, the former should be used with caution in patients with AD and sleep disturbances.

Corticosteroids: Systemic corticosteroids have been widely used for the treatment of AD. Both European and American guidelines recommend to use them for short periods (up to 7–10 days), for treating acute flares, at a daily dose of 0.5 mg/kg. Long-term use is discouraged due to side effects. A possible rebound after withdrawal should be considered when treating these patients [71].

Immunosuppressive agents: These are the drugs of choice for most of the moderate-to-severe patients. Cyclosporine A (CsA) is the only approved systemic drug for the treatment of AD in Europe. It has shown its efficacy both in adults and children, although it is not approved under 18 years old. CsA is indicated in chronic, severe cases of AD for a maximum of 2 years in a row. Is a fast-acting drug with an onset of the efficacy within the first 2 months, but it has a rapid

relapse once stopped. The most used doses range from 2.5 to 5 mg/kg/day. There is no clear consensus on how to start, some authors opt for starting at low doses (2.5 mg/kg/day) and increase the dose 0.5 mg/kg/day every 2–4 weeks depending on the clinical response, up to a maximum of 5 mg/kg/day. Some others prefer starting at high doses and reduce the dose until the minimum efficacious dose. The main concerns regarding the use of this therapy are toxicities and interactions. Nephrotoxicity is the main side effect, which is more likely to occur in doses over 5 mg/kg/day, elderly patients and previous renal impairment. Patients under treatment with CsA are advised to take blood pressure regularly and monitor for renal parameters [71].

Other immunosuppressants such as methotrexate (15–25 mg/week), azathioprine (1–3 mg/kg/day), and mycophenolate mofetil (up to 3 g/day) are used off-label. These tend to have a slower onset of the effect, around 8–12 weeks, but with a more prolonged residual effect once the treatment is stopped [71].

No studies are comparing the efficacy of the three agents; however, Eckert et al. have recently shown that patients receiving mycophenolate mofetil required more oral corticosteroid than the other treatments, whereas those receiving CsA were the patients who needed the least [72].

Two studies compared the overall efficacy of methotrexate and azathioprine and concluded to be equivalent [73, 74].

It is essential to regularly monitor these patients for possible side effects, mainly liver toxicity.

Biological agents: Despite all the immunosuppressive armamentarium, some patients still show a lack of efficacy. Biologicals are highly effective therapies with an immunomodulatory effect that specifically target inflammatory cells or mediators. Most of the biologicals developed or in development for AD target cytokines of the T2 response.

Dupilumab is the first biological licensed for AD. It is a fully human monoclonal antibody that blocks a chain of the IL-4 receptor, which is common in the receptor for IL-4 and IL-13. It is approved as first-line therapy for adult moderate-to-severe AD who are candidates to systemic therapy. Clinical trials showed its efficacy and favorable safety profile on AD patients. Taking all the clinical trials together, about 70% of the patients achieved an EASI 75 or higher with a time-to-full-clinical-response of about 4 weeks. Pruritus showed a rapid response with an initial improvement at 2 weeks [71, 75].

Recent case series have observed a similar response [76].

It has been shown that dupilumab improves the AD inflammatory signature [77].

The main reported side effects were conjunctivitis and local reaction at the site of injection.

The recommended dose of dupilumab in adults is an initial dose of 600 mg followed by 300 mg every 15 days. There is no need for complementary studies before starting the treatment.

Only patients with previous helminthic infections should receive specific treatment before dupilumab.

Due to a lack of data, live and live attenuated vaccines should not be given currently with dupilumab. It is recommended to be up to date with immunization prior to the treatment. Contraindications include hypersensitivity to dupilumab or any of its excipients [78].

Currently, dupilumab is also licensed for asthma.

4.4 New treatments

Several other molecules are under investigation [70].

4.4.1 Biologicals

Tralokinumab and lebrikizumab are fully human monoclonal antibodies that target IL-13. They have shown sustained clinical improvement in moderate-to-severe AD patients in phase II studies with an acceptable safety and tolerability profile. Wollenberg et al. showed that patients with higher serum levels of periostin and DDP4 had a better response to tralokinumab compared to those with lower levels [52].

Tralokinumab has already begun phase III trials, whereas lebrikizumab has yet to start.

Nemolizumab, a humanized monoclonal antibody against the receptor A of IL-31, has also shown efficacy in phase II trials in patients with moderate-to-severe AD. IL-31 plays a role in the pathogenesis of AD and pruritus. The two phase 2 clinical trial showed not only a rapid and maintained effect on pruritus but also AD scores (EASI and BSA) [79, 80].

Fezakinumab is a fully human monoclonal antibody against IL-22. The phase 2a clinical trial showed a sustained clinical improvement in severe AD patients [81].

Tezepelumab is a fully human monoclonal antibody that targets TSLP. In the phase 2a trial, a non-statistically significant improvement over placebo at week 12 was observed [82].

There are contradictory papers regarding the efficacy of ustekinumab, a fully human monoclonal antibody against the p40 subunit shared by IL-12 and IL-23 [83–88].

4.4.2 Small molecules

There are several small molecules in development for AD.

Apremilast is an oral PDE4 inhibitor approved for the treatment of obstructive pulmonary disease, plaque psoriasis, and psoriatic arthritis [89]. Small series of cases have shown its potential as a treatment for AD [90, 91].

Baricitinib, a JAK 1 and 2 inhibitors, abrocitinib and upadacitinib, selective JAK 1 inhibitors, are currently running phase 3 trials. Phase 2 showed positive results regarding efficacy and safety for the three molecules [92].

Finally, delgocitinib, a small molecule that targets JAK 1, 2, 3 and TYK 2 demonstrated rapid improvement in clinical signs and symptoms with a favorable safety profile, in a phase 2 trial [93].

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