

## R E V I E W

## Atopic dermatitis

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**Abstract.** Atopic dermatitis (AD) is a common inflammatory skin disease, clinically characterized by recurrent eczematous lesions and intense itching, leading to excoriations and susceptibility to cutaneous infections. Although it is considered a pediatric disorder, mainly starting in infancy, it is also very common in adults. Etiology of AD is complex and multifactorial: interaction between genetic susceptibility and environment, but also cutaneous barrier impairment, change in microbiome composition and innate and adaptive immune dysregulation are the main factors involved in the pathogenesis of the disease. Originally, the disorder was considered mediated by an imbalance towards a T-helper 2 response and excessive IgE production to allergens, but now it is recognized as a lifelong disposition with variable clinical expressivity, where dysfunctions of the epidermal barrier, immune system and microbiome play a central role. AD leads to a substantial psychosocial burden on patients and their relatives and increases the risk of other allergic and non allergic disorders. The real economic impact of AD is difficult to measure due to the broad spectrum of disease severity and the multiple direct and indirect costs, but the overall medical expenses seem to be very high and similar to those of other diseases such as diabetes. Currently, a multiple therapeutic approach is aimed only at improving the skin state, reducing itching and keeping a stable condition. New safety and curative treatments may be developed only after enhancing our understanding on the pathogenesis of AD and the heterogeneity of its clinical manifestations. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** atopic dermatitis, prevalence, pathogenesis, economical-social burden, diagnosis, treatment

### Introduction

Atopic Dermatitis (AD), also called eczema, is a fascinating and heterogeneous disorder: every aspect, from the epidemiology, the pathogenesis, the clinical phenotypes to the different therapeutic approaches,

shows certain diversity (1). It is a complex polygenic disease, characterized by a wide range of clinical phenotypes based on the interaction between genetic susceptibility and environmental factors. Moreover, cutaneous barrier impairment, change in microbiome composition and innate and adaptive immune dys-

regulation play a significant role in the pathogenesis of AD (2-5). In fact, skin barrier, immune system and microbiome are connected since birth and their network is necessary to characterize onset, progression and maintenance of the disease.

### Natural history

AD has always been considered a typical pediatric disease. It occurs in 45% of cases within the first six months of life, in 60% within the first two years and in about 85% by the age of five (2). However, a very late onset and/or an ongoing course until adulthood have been recently reported especially for moderate-severe cases (6). A broad and heterogeneous spectrum of clinical phenotypes has been described with the main attempt to predict its specific natural history and implement personalized therapy (7). However, until now, none of the phenotypes described was characterized by a specific biomarker useful to predict the clinical evolution and contribute to the choice of the best treatment.

### Epidemiology

AD is the most frequent chronic inflammatory skin disease in children. In Italy, according to the latest available epidemiological data, its prevalence is around 16.5% (8), but in the world the prevalence is characterized by significant variations (9,10). A systematic review on epidemiological studies from 1990 to 2010 reports an increase in the prevalence of about 2.6-5% in Sweden, 5.1-10% in Mexico, Australia and some areas of Africa and more than 10% in Great Britain, Nigeria and South-Africa (11). These data underline the current heterogeneous distribution of the disease both in industrialized and rural environments. In the United States, data from the National Survey of Children Health describe a change in prevalence (from 8.7% to 18.1%) even between States and Districts (12), especially among black Americans, and a significant correlation between high prevalence and small family groups, life in urban and metropolitan environments and a high level of family education (13).

### Pathogenesis

Pathogenic mechanisms of AD are complex, widely involving many determinants such as genetic, epigenetic and environmental factors, including diet habit (breastfeeding, obesity), vitamin D levels, exposure to allergens, pollutants or antibiotics, cesarean section, immunological defects, skin barrier damage and microbiome.

The skin barrier defects, together with the dysregulation of both innate and adaptive immunity and the altered skin pH, play a central role in the pathogenesis, while the alteration of the skin microbiome has catalytic effect in the propagation of the immune defect (3-5,14, 15).

#### *Cutaneous barrier and immunity dysfunction*

The epidermis is an organ constantly renewed and at the same time it is a formidable physical barrier to the penetration of microorganisms, able to retain moisture and nutrients. Moreover, it is the first immunological defense and is composed by a complex ecosystem, known as "skin microbiome". The physical and chemical barrier damage involves, in a very complex network, skin microbiome and immune system, causing and amplifying skin inflammation (15,16).

Cutaneous barrier lesion leads to a significant increase in trans epidermal water loss (TEWL) and it is suggested that a high TEWL may correlate with a subsequent and earlier development of AD.

The skin also provides a "culture medium" for the growth of bacteria, which require water, carbon, nitrogen, macro and microelements to survive. Water is essential for their growth and the amount of water necessary is defined as water activity. *Staphylococcus Aureus* (SA) needs aw values up to 0.83 to replicate, while *Staphylococcus Epidermidis* (SE), less resistant requires aw value below 0.87. Therefore, dry skin in dermatitis promotes the survival and replication of potentially invasive staphylococci and inhibits the growth of commensal organisms (15,16). Also, decreased levels of natural moisturizing factor (NMF) in the stratum corneum (SC) are associated with more severe AD symptoms. Furthermore, AD is characterized by a reduced amount of proteins and lipids that stabilize the barrier.

In particular, we can observe an aberrant lamellar organization and an altered activity of the serine protease and the claudins, there are trans-membrane proteins forming the tight junctions (TJ). The loss of residual TJ could allow antigens and microbial pathogens to easily enter the SC, while low levels of sphingosines, which in normal conditions exert a powerful antimicrobial effect, reduce the defense towards the SA. In this way, SA can directly break down ceramides, through the release of a specific bacterial ceraminidases (17). The global decrease in the content of the three key lipids (cholesterol, free fatty acids and ceramides) occurs mainly due to a partial block in the secretion of the lamellar bodies, leading to a depletion of the SC interstices, and a high value of skin pH contributes to this process. (18,19). A further reduction of ceramides and a truncation of fatty acids, mainly two elongases (ELOVL3 and 6), occurs as a direct result of the cytokines production stimulated by Th2 cells. Barrier damage, in fact, stimulates the epidermal release of this kind of cytokines, such as TARC, TSLP and IL-33. Moreover, Th2 cells induce B cells to produce IgE, which are assumed to contribute to the progress of the atopic march (20). Also, IL-4 and IL-13 decrease the expression of filaggrin (FLG) in the epidermis, with consequent further barrier damage (21).

In 2006, Palmer et al. demonstrated loss-of-function genetic variants in the gene encoding FLG carried by approximately 9% of Europeans and showed a highly significant association with asthma and atopic dermatitis (22). In the context of skin damage, Th2 cytokines and histamine cause itching, which triggers the scratching and regional production of further itch-inducing cytokines, such as TARC, TSLP and Armin. The latter is produced by damaged keratinocytes and fibroblasts and leads to abnormal epidermis innervation of C fibers, amplifying an “itch-scratching” cycle that further impair the barrier (23).

In summary, since 80s the pathogenic mechanism of AD was considered mainly immunological, caused by a prevalence of Th2 lymphocytes and a related production of cytokines (IL-4, IL-5, IL-13) in the acute phase of disease, followed by a progressive Th1 polarization in the chronic phase and an increase in Th1 cytokines production (INF gamma and IL-22).

Recent studies confirm the importance of adaptive immunity but also consider the pathogenesis of

dermatitis as more complex relationship that involves especially the innate immunity system, the skin barrier and the skin microbiome.

### *Skin dysbiosis*

Various environmental factors (pH, temperature, dryness, antibiotics, hygiene practices) play a fundamental role in the correct stability of skin microbiome. Healthy skin actively regulates colonization of microbial organisms by producing different molecules, such as  $\beta$ -defensin, antimicrobial peptides, fatty acids and reactive oxygen species, which directly inhibit the growth of bacteria. The dysregulation of these systems alters the correct microbial composition, leading to a condition known as “dysbiosis”. It is characterized by reduced microbial diversity that promote the colonization of pathogenic organisms such as SA and the increased paracellular permeability (24). All patients with dermatitis are characterized by a skin dysbiosis. DNA/RNA sequencing technologies show skin microbiota changes are related to the worsening of the disease: severity and exacerbations are associated with reduced bacterial diversity (Streptococcus, Propionibacterium, Corynebacterium etc.) and increased colonization of SA while, during remission, bacterial diversity increases and tends to normalize. SE and SA play a decisive role. The first is the predominant gram-positive bacteria in the healthy microbiota and it is defined “good” because facilitates tissue repair, binding TLR2 to the keratinocytes. It also induces the T lymphocytes production of IL-17 and INF- $\gamma$ . Instead, SA is not a natural saprophyte and causes infection, worsening of the disease and development of chronicity, through multiple mechanisms: breakdown of epidermal integrity with its protease activity, down regulation of terminal differentiation markers and production of virulence factors such as cytolyisin, aureolysin, protein A and superantigens (24,25). Many factors can promote SA colonization, including a decrease in the lipid barrier mixture and inadequate production of catelicidine and  $\beta$ -defensins. Commensal germs are normally able to produce different AMPs, PSM $\gamma$  and PSM $\delta$  peptides, in order to limit the survival of pathogenic bacteria, to stimulate TLRs and to enhance the role of tight junctions in limiting

further penetration of germs and allergens. Most of the coagulase-negative staphylococcal strains (CoNs) that colonize healthy skin are able to suppress or decrease the survival of SA. On the contrary, eczematous skin is lacking of protective CoNS strains (26) and this condition during childhood seems to be associated with the development of AD at later ages. For all these reasons it would be useful to treat AD focusing on dysbiosis (27,28).

### *Role of pH*

Recent studies suggest that high values of pH are determinant in the pathogenesis of the disease due to the negative regulatory role towards antimicrobial defense, barrier homeostasis, inflammatory process and itching (18). Acidification of the skin occurs through three mechanisms: the breakdown of phospholipids by the secretory phospholipase A2, leading to free fatty-acids release, the transport of protons into the extracellular compartment through the action of the sodium-hydrogen exchanger protein, and the generation of free amino acids, through the catabolism of structural components of the SC. In particular, FLG is the main source of amino acids on the SC and it is important for a functional skin barrier, while skin in AD is lacking of this component (21).

### **Clinical features**

Dermatitis is a chronic condition characterized by intense itching, whose clinical course involves phases of remission and recurrence. Itching is mediated by complex signals that, starting from the skin, via the dorsal ganglia root, reach the spinal cord and the brain, coordinated by numerous molecules including substance P (29). Itching can be triggered by an increase in skin temperature that occurs during movement, sleep, emotions and various other stimuli. This symptom is clinically difficult to control, leading to scratching and then to sleep disturbances and worsening of the lesions (30). The skin is typically dry and hyper reactive, characterized by erythematous lesions generally distributed in typical sites according to age. In the acute phase, the lesions are exudative

while in the chronic phase they are more lichenified and desquamated (31). Depending on the phenotype, secondary bacterial, viral and/or fungal skin infections can occur in a recurrent or generalized way (31). The main bacterial infections are caused by staphylococci, which colonize the excoriated areas and produce exudative lesions (25,31). Viral infections are mainly caused by Herpes simplex (HSV). This virus is able to disseminate or lead to a Kaposi's varicelliform rash or herpetic eczema, characterized by vesicular lesions and pustules that can extend to large areas. In young children and adolescents, a greater susceptibility to molluscum virus infections is also reported (32). Fungal dermatitis of the neck and head is prevalent especially among adolescents. This form is linked to the *Malassezia* species, which could contribute to the genesis and maintenance of AD through stimulation of cell-mediated immunity and the production of specific IgE (33).

### **Diagnosis**

The diagnosis of AD is exclusively based on the clinical typical features, as there are no specific laboratory and/or histologic markers to date. Since the early 1980s, after the publication of the Hanifin diagnostic criteria, numerous tools have been proposed to assess the severity of dermatitis (34-37). Skin lesions are heterogeneous, they occur in alternating phases of quiescence and recrudescence, and are often associated with infections. In order to choose the best treatment, it is important to evaluate the clinical stage, which is classified as mild, moderate or severe. The main used tool so far is the SCORing Atopic Dermatitis one (SCORAD), which includes subjective and objective parameters for the evaluation: subjective criteria are itching and sleep disturbance, the objective ones evaluate the extent and intensity of the injuries (35). The more recently introduced Eczema Area and Severity Index (EASI), however, does not consider itching (36). Dermatitis is considered severe when the SCORAD score is > 50 or the EASI score is > 16-20. The Patient-Oriented Scoring Atopic Dermatitis index (PO-SCORAD) is a more recent variant (37).

## Atopic march

AD is not just an inflammation of the skin. The term “atopic march” in fact, is related to a sequential series of allergic diseases, starting from dermatitis, moving towards food allergy to culminate in allergic rhinitis and bronchial asthma manifestations (38). The concept of atopic march over the years has been gradually redefined and analyzed by numerous cross-sectional and longitudinal studies but, at the moment, it is still very controversial and certainly this complex and multifactorial progression occurs only in some phenotypes (39,40). The latest data suggest that genetics plays a more important role than environmental factors in atopic march and that the link between dermatitis, rhinitis and asthma is not driven by the influence of environmental factors in the first months of life (41).

## Comorbidities

AD can be considered a systemic disorder, as defined by Brunner et al. (42). In fact, although numerous recent studies are discordant and not conclusive, they all indicate that AD is often associated with non-allergic diseases and with a significant increase in cardiovascular damage risk, tumors, autoimmune diseases, smoking and psychiatric disorders (43–45). In children, several papers show a consistent association with attention deficit hyperactivity disorder (ADHD), although the mechanisms and time of onset are still unclear (46).

## Economic and social aspects

Atopic dermatitis has a huge economic impact on society and public health, whose costs generally exceed those of psoriasis and bronchial asthma and are similar to those reported for diabetes (47).

The largest American economic study conducted in 2004 estimated the national direct costs for AD at around 4,228 billion dollars, then amounting to 5,297 billion in 2015 (48). More recent studies show that additional costs, approximately 12 million dollars per

year, are attributable to the need of hospitalization for dermatitis and they identify a monthly expense per patient of approximately 274 dollars (49,50). The real cost of AD, however, is still underestimated due to the difficult evaluation of the direct costs (i.e., skin care therapies, specific clothing, environmental contamination, medical evaluation, laboratory tests), the indirect costs (i.e., work and school missing, transports, cleaning) and the associated comorbidities but also because of the psychological effects. Furthermore, only few studies assessed the economic value of AD, which is difficult to analyze due to the different methodologies used, the settings of patients analyzed and the type of public assistance and/or insurance existing in the various countries. To date, in Italy AD is not included in the list of chronic and disabling diseases entitled to exemption from participation to the cost (last update March 20, 2013) and exemption is only provided for some topical corticosteroids (note AIFA 88) and for a cycle of 12 thermal baths per year! Moreover it is important to consider the impact of this disease on quality of life, as it affects at least four essential functional domains: physical and emotional health, physical and social functionality (51–53).

It must be emphasized that starting from early adolescence, physical appearance constitutes a central element in determining self-confidence and appreciation. In fact, the skin is our social “business card” by which we can communicate our intentions and abilities, with a specific language that varies among different cultures. Our skin condition influences our sociability and self-reliance, impacting the stages of development to the adult age. Patients with AD often have to deal with social prejudice, based on the fear of contagion and on discrimination for aesthetic reasons. Moreover, since the onset of AD occurs mostly in the pediatric age, it can disrupt family relations and balances, at many levels. In this scenario, it could be difficult for these families to successfully face the disease and overcome the related psychological and quality of life difficulties (54). Sleep disturbances are reported in 60% of patients, together with itchy discomfort and in some cases painful skin lesions, and they contribute to a negative impact on the quality of life, causing attention and/or hyperactivity disorders, lack of school performance and/or anxiety and depression. Moreover,



it should be considered that a definitive therapy of AD currently does not exist and that the disease can last over time, being able to disappear for long periods and then reappear, with great discomfort for the affected person and his family members. Hence, in 2010, the WHO Global Burden of Disease survey considered AD at the first place among all skin diseases, in terms of grade and length of disability (55). It is clear how this disorder represents a considerable public health problem, although its actual and economic and social costs are still very underestimated.

## Treatment

Translating all current pathogenic theoretical knowledge into therapeutic practice would be particularly important in this disease, still without definitive therapy. Currently, the treatment is aimed at improving the skin state, reducing itching and keeping a stable condition. A multiple therapeutic approach can provide protection and restoration of the barrier, suppression of inflammation, control of dysbiosis and pH correction (31,56,57) However, it is important to take into account all possible associated symptoms (food allergy, asthma, urticaria, contact dermatitis etc.), comorbidities and the numerous psycho-social factors. In fact, mild-severe AD comprises several characteristics that need a combination of medical and pharmacological treatments with other forms of support. Patient(58) should be instructed to manage the disease and treat exacerbations.

### *Skin care*

The cornerstone of the first level treatment is the “skin care”, that is defined as a careful and daily attention to the restoration of the altered skin barrier using specific emollients and detergents (59). Skin care has strength of recommendation A and level of evidence I. The architecture of the SC is fundamental in maintaining a good level of hydration and in regulating the flow and retention of water. In particular, for the correct functioning of SC, some key elements must be respected:

- A good homeostasis between production/des-

quamation of the corneocytes, which represent the physical barrier of the SC and contribute to its elasticity.

- A correct lipid layers composition (ceramides and neutral lipids), which work as a humidifying barrier and, while preventing the entry of many substances, allow the penetration of most of the substances applied topically.
- Good natural hydration factors, such as amino acids derived from FLG and other hygroscopic molecules (i.e. urea, lactic acid, sugars and salts), which help to maintain the right level of pH and humidity within the corneocytes.

Products with an optimal ceramide-cholesterol-saturated fatty acid ratio of 3:1:1 have recently been developed. They represent a great nutritional mixture and are called third generation emollients-barrier repairers (16). These emollients can penetrate the skin, influencing its structure and function.

Dermatological cosmetics have also developed emollients with specific anti-inflammatory/ antipruritic/antibacterial action, by adding active ingredients in order to both improve the clinic manifestations and reduce the use of corticosteroids.

It may also be possible to “manipulate” the altered skin microbiome with a new therapeutic approach, by applying, for example, extracts from killed non-pathogenic gram negative bacteria, acting as pre-probiotics and symbiotics in order to modulate or balance the immune system (27,28).

In skin care, correct cleansing is essential to eliminate tissue debris, sebaceous secretions and environmental contaminants (59). It is a daily act performed with substances that mostly settle on the hydrolipidic film and it is important for the correct maintenance of physiological skin homeostasis. Cleansing with water alone is not able to eliminate lipophilic substances and at the same time cleansing with aggressive detergents can cause damage to the hydrolipidic film. In fact these products may remove ceramides, fatty acids, cholesterol and triglycerides of the surface sebum, altering the SC cement and worsening the conditions of the barrier. Thus, frequent washing and use of aggressive detergents are widely recognized as exacerbating dermatitis factors. Wet-dressing can be useful.

### *Topical corticosteroids*

Topical corticosteroids (CTS) represent the first-choice therapy (31,56,57). Their effectiveness has been widely demonstrated in numerous randomized controlled trials. A recent systematic review concludes that their correct use guarantees a good safety profile. Their anti-inflammatory action is particularly wide and is achieved binding specific receptors on adaptive immunity cells, with consequent inhibition of the release of pro-inflammatory cytokines. In order to obtain the greatest compliance and efficacy, it is fundamental to consider the kind of molecule to choose, the site to be treated, the AD stage and the length of the treatment. Generally, the CTS application once daily at night is recommended and, in case of acute forms, the use of medium-high power CTS is preferable for short periods, followed by a switching to less powerful preparations.

CTS should be used in early phases, up to the control of the acute inflammatory phase, and applied until they are completely absorbed. In subjects with frequent exacerbations, "proactive" therapy is suggested in order to reduce the number of relapses, i.e. the use, in exacerbation sites, of CTS once or twice a week even in the absence of injuries. The average monthly dose of a medium-high potency CTS that can be safely administered is 15 gr in a newborn, 30 gr in a child and 60-90 gr in an adult.

Even today, "corticosteroid phobia" represents the greatest limitation to the use of CTS and it is a real considerable problem in the therapeutic world of AD, already very limited. Therefore, it is important to explain to the patients the differences on the several types of CTS, clarifying how and when to apply these molecules and reassuring them about their excellent safety profile (60).

### *Topical antibiotics*

*Staphylococcus Aureus* and *Streptococcus Pyogenes* are the main bacteria involved in the colonization of AD. The superantigens and exotoxins released by the SA promote the chronicity of the lesions and the development of tachyphylaxis, therefore it is recommended to promptly act in case of bacterial superinfection. Fusid-

ic acid and mupirocin are the most suitable topical antibiotics and require 2-3 applications per day for 7-10 days. More recently, in case of very frequent bacterial recurrences, therapies with mupirocin intranasally (2 applications for 4-5 days) or baths with sodium hypochlorite 6% at the final concentration of 0.005% are recommended.

### *Calcineurin inhibitors*

Tacrolimus, derived from the bacterium *Streptomyces Tsubaensis* and pimecrolimus, the chemical derivative of ascomycin, were approved in 2000 and 2001 respectively for second-line treatment of AD, in adults and children from two years of age (61). These substances inhibit the activation of T lymphocytes, eosinophils, mast cells and basophils, through an immunological mechanism that guarantees good disease control and a low risk of side effects, especially when used in more sensitive areas (e.g. eyelids and genitals) and for long periods. In fact, compared to CTS, their high molecular weight (822 Da) allows only a low penetration in healthy skin, preserving the formation of TJs (62).

Tacrolimus ointment is indicated in moderate/severe forms, in the formulation 0.03% for patients aged 2-15 years and in the formulation 0.1% for patients  $\geq$  16 years, while Pimecrolimus cream 1% is indicated for mild/moderate forms, already from 2 years of age. The treatment requires two applications per day for 2/3 weeks and therefore one application in the evening, until the resolution of the lesions. Calcineurin inhibitors can be successfully used with a "proactive" approach, similarly to CTS. The most common side effects, always transient, are itching and burning. These sensations can be reduced by applying cold drugs or by preceding an application of CTS. It is important to point out that their potential carcinogenicity, reported by the Food and Drug Administration in 2006, has been largely overcome by multiple drug surveillance studies (63).

### *Systemic antimicrobials*

Barrier defect and innate immunity dysregulation predispose patients to frequent infectious complica-

tions. However systemic antibiotics should be used only in case of clear signs and symptoms of bacterial infection and not for simple colonization. Betalactam, flucloxacillin, amoxicillin and clavulanic acid or cephalosporins active towards SA, such as cefuroxime and cefixime, represent the first-choice antibiotics (64). Acyclovir therapy is required in case of herpetic eczema due to HSV.

Neck and/or head injuries in adolescents, who do not respond to the usual therapy, must suggest *Malassezia* infection and therefore require oral antifungal therapy, such as itraconazole.

#### *Systemic corticosteroids*

A recent document on systemic CSs does not recommend its use, which is to be restricted only to the most serious cases with poor symptoms control (65). In fact, despite their clear anti-inflammatory activity, systemic CSs do not act positively on barrier alterations or on innate immunity defects and can instead cause side effects. In addition, a rebound effect after their suspension is often reported. Short cycles can be used in cases of severe and extensive recurrence with intense itching, before starting therapy with immunosuppressive agents, or in case of concomitant severe exacerbations of bronchial asthma (65).

#### *Systemic immunosuppressants*

These agents, such as cyclosporine, azathioprine and methotrexate, can be prescribed in specialized centers and are a valid therapeutic option in severe AD, which does not respond to first and second-line therapies. Their administration should be considered especially when the disease has a physical but also psychological strong impact (64).

#### *Biological drugs*

Recently, scientific attention on AD treatment has been addressed to the use of biological drugs, able to act more selectively on some key molecules in the pathogenesis of AD. Considering the possible refractoriness to standard therapy in moderate to severe forms, clinicians and researchers are hopeful on the ef-

ficacy and safety of these potential therapies, but most are currently still in phase 2 or 3 of experimentation (66,67).

#### *Anti IL-4 -IL 13 (Dupilumab)*

Dupilumab is a monoclonal IgG4 antibody directed against the alpha receptor of interleukin 4.

This drug, binding to the IL-4 receptor, inhibits the signal of IL-4 and IL-13, Th2 type cytokines that play an important role in inflammation, epidermal barrier dysfunction and susceptibility to infections in patients with DA. In March 2017, Dupilumab has been approved by the FDA for its use in the treatment of adults with moderate-severe and not adequately controlled AD. The Official Gazette of 18 September 2018 also authorized the marketing and reimbursement of this drug in adult Italian patients who did not respond to cyclosporine. More recently, the US FDA in March 2019 and the EMA in August 2019 approved the use of Dupilumab in adolescents aged 12 to 17 years, suffering from moderate-severe dermatitis. The numerous phase 3 studies have in fact extensively demonstrated that this biological can significantly reduce the extension and severity of the disease and the intensity of the itching, therefore improving the quality of life of adolescents affected by this disease (68).

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