South African Family Practice 2018; 60(6):26-33

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

Atopic Dermatitis

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Abstract

The aetiology of atopic dermatitis is multi-faceted and affects our first line host defence, the skin. Atopic dermatitis has a significant influence on a patient's social and occupational functioning and can have long-lasting effects. The signs and symptoms of AD includes pruritus, erythema, fissuring, and lichenification – these are reduced by the use of moisturizing agents. Guidelines on how to manage atopic dermatitis aims to improve symptoms and achieve long-term disease control. Patient education remains as important as other treatment strategies and the pharmacist plays an integral role in educating patients on the management of their condition and adherence to therapy.

Keywords: Atopic dermatitis, pruritus, filaggrin, FLG gene, microbiome, Th2 cells

Introduction

The skin is our largest organ and acts as a protective barrier between the host and its external environment. Except for preventing entry of pathogens and allergens, water loss from the body is also minimised.[1] Atopic dermatitis (AD), also referred to as eczema, is a chronic inflammatory skin disease that commonly affects children younger than five years, but onset can be at any age.[2] Characteristics of AD include chronic cutaneous inflammation, dry skin and epidermal barrier dysfunction with intense pruritus as the major symptom.[3] Skin lesions are mostly localised to the flexural surfaces of the body. The areas mainly affected include the face, scalp and extensor surfaces, especially in infants and its onset is usually from 3 months of age[2,4]

Atopic dermatitis is the first manifestation of allergy to present in the "atopic march" and precedes food allergy, asthma, and allergic rhinitis.[7] A family history of AD, asthma or allergic rhinitis often prevails.[2] The disease is debilitating and a patients' quality of life is often impaired.[6] Not only does AD impact on health-related quality of life, but also on patients' mental health, and on their social and emotional functioning.[8] Atopic dermatitis is recognised as a lifelong disposition with variable clinical manifestation and expressivity, in which defects of the epidermal barrier play a pivotal role.[9]

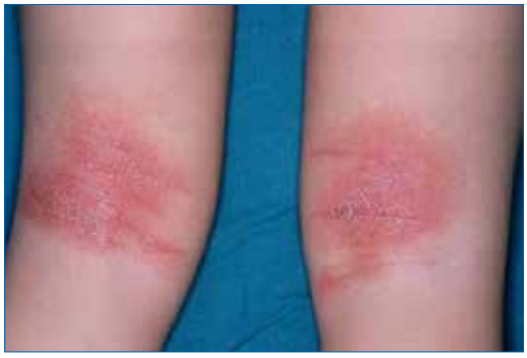

Figure 1. Atopic dermatitis – flexural areas [5]

Figure 2. Common sites of AD outbreaks[6]

Types of atopic dermatitis

The clinical manifestation of AD is distinct, but due to numerous differences in other aspects, AD can be categorised in two forms: intrinsic (non-allergic) and extrinsic (allergic).[10,11] An intrinsic form of AD not associated with IgE mediated sensitization contradicts the classic definition of an atopic disease and is better referred to as non-atopic AD.[25]

Epidemiology

Atopic dermatitis is the most common chronic inflammatory skin disease. In developed countries, the prevalence of AD has plateaued at 10–20% but continues to increase in low income countries.[9,12,13]Although the disease can become apparent at any age, it manifests at an early age in approximately 60% of cases, with 10–20% lifetime prevalence in children.[9,14]According to a 2013 report, the worldwide incidence of AD averaged at 7.9% in

Table 1. Categories of atopic dermatitis[10,11]

Types	Non-atopic	Atopic
Onset	Later onset	Early childhood
Frequency	15% – 30%	70% – 85%
IgE serum levels	Normal	High
Specific IgE	Absent	Present for aeroallergens and foods
Skin prick reactions	Negative	Positive
Cytokines: IL-4, IL-13	Low levels	High levels
Skin barrier	Normal	Defect
Filaggrin gene mutations	No	Yes
Other atopic diseases	Absent	Present

the six to seven year age group but varied a lot between regions; from 3% in the Indian subcontinent and 4.8% in the Eastern Mediterranean to 10.2% in Asia-Pacific and 10.3% in North America.[15] In South Africa the prevalence of AD in children was found to be around 17%.[16] Adult AD has been recognised with a prevalence of between 2–10%.[17]

The prevalence of AD among different races is not known, but due to AD being a heterogeneous disorder with its different genetic mechanisms, some races may be more prone to develop the disease. Asians have increased Th17 and Th22 responses when compared to Caucasians, while the immune response in the African population still needs to be determined.[18]

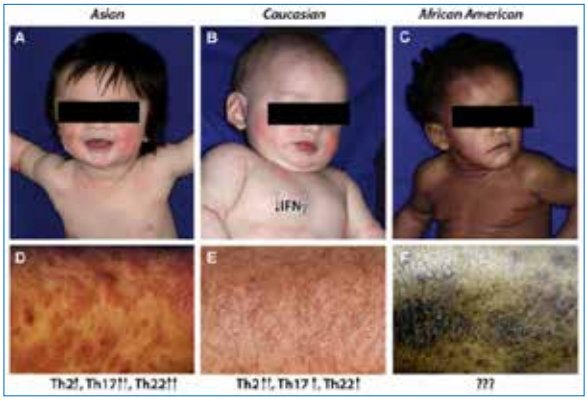

Figure 3. Different races and AD[18]

Concerning gender, various studies show the difference to be either insignificant or male preponderant in preschool children, while more females suffer from AD in adulthood.[19]

Pathogenesis of AD

An interaction between genetics, immunologic and environmental factors contributes to the pathogenesis of AD.[15] Genetic studies have mainly focused on immunological mechanisms, but a defect in the primary epithelial barrier has been reported.[14] It is important to have a good understanding of the interaction between the various factors to enable effective management of the condition.

Genetics

Genetic factors play an important role: monozygotic twins showed a consistent higher concordance rate (0.77) compared to dizygotic twins (0.15). A positive parental history is furthermore the strongest risk factor for AD; if the disease is present in one parent, the incidence rate doubles, and should both patents suffer from AD, the incidence rate triples.[20]

Filaggrin (FLG), a key protein in terminal differentiation of the epidermis and development of the skin barrier, protects the body from the entry of foreign environmental substances that can otherwise trigger immune responses. It is synthesised as a giant precursor protein, profilaggrin. The latter is found within the granular layer of the epidermis and is encoded by the FLG gene. This gene is located within the epidermal differentiation complex on chromosome 1q21.[1] It has been shown that two independent loss-of-function genetic variants (R510X and 2282de14) in the FLG gene are important predisposing factors for atopic dermatitis.[20] Based on a patient's ethnic background, several differences have been noted in AD phenotypes. Loss-of-function FLG mutations are different in European, Asian and African countries and become evident when compared amongst the different populations.[21]

Several other candidate genes have been suggested to play a role in AD, e.g. chromosome 5q31-33, the locus containing genes for the Th2 cytokines IL-3, IL-4, IL-5, IL-13, and granulocyte macrophage colony stimulating factor.[14] Variants of an encoding region or functional mutations of promoter regions could be linked to the incidence of non-atopic dermatitis. Furthermore, polymorphisms of the IL-18 gene may be the cause of the dysbalance between Th1 and Th2-immune responses, resulting in Th2 predominance.[22]

Another possible contributing factor to the genetic susceptibility for AD is a genetic variant of mast cell chymase, a serine protease secreted by skin mast cells, which may have organ specific effects.[14]

Environmental factors

The worldwide incidence of AD and the variations thereof suggest that environmental factors play a pivotal role in the expression of AD. Some of the environmental factors implicated include climate, diet, obesity, smoking rate, and microbial exposure.[15]

Skin microbiota are involved in the homeostasis as well as pathogenic conditions of the skin. Both *Staphylococcus aureus* and *Staphylococcus epidermidis* significantly increase during exacerbation of AD.[15] These bacteria release allergenic compounds and superantigens (toxins)[23] and can act as effective immunological adjuvants for increased IgE response to aeroallergens. Intense pruritus is a hallmark of AD, and skin damage due to scratching enhances the progress and continuance of the disease.[24]

Gut microbiota might also be involved in the pathogenesis of AD as it has been shown that children who present with AD

later on in life have different early gut microbiota compared to children who do not develop AD, referring both to composition and diversity. Furthermore, systemic antibiotic treatment was reported to increase the risk of AD.[15] No evidence has however been reported in favour of AD management with regards to probiotics, dietary supplements, botanical extracts and homoeopathy.[9]

Figure 4 depicts factors such as temperature, indoor heating, humidity, and UV-light exposure influencing the prevalence of AD. A combination of high humidity and precipitation are associated with an increase in the disease, while high temperatures and exposure to UV-light has shown to have protective effects specific to AD.[26]

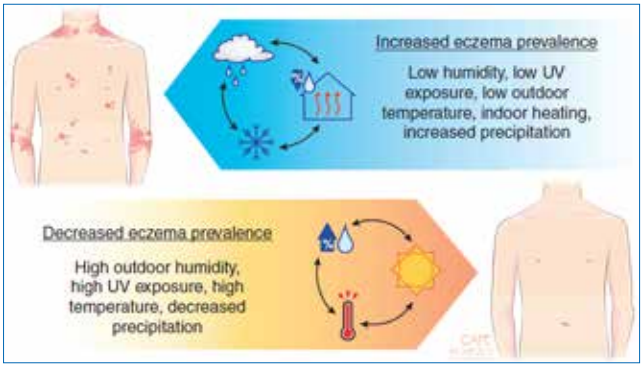

Figure 4. Impact of climate on AD prevalence during childhood[26]

The acidic environment of the skin contributes to its barrier function as it has a strong antibacterial effect and controls the desquamation of corneocytes. Soaps and other detergents are common environmental agents that increase the skin pH. In addition, these agents emulsify skin surface lipids, change skin proteases, and consequently thin the stratum corneum.[15]

Immunology

Although recent studies have proposed interleukin (IL)-22-producing T cells (Th22) to play a significant role in the initiation and progression of the disease and to a less extend IL-17-producing Th17 cells, AD is currently considered as a biphasic T cell mediated disease. A Th2 signal predominates the acute phase, whereas the chronic phase is promoted by a Th2 to Th1 switch.[3]

> The functions of Th2 cytokines include increased epidermal thickening, sensitization, inflammation, pruritus, decreased expression of antimicrobial peptides and the barrier proteins filaggrin, loricrin and involcrin.[25]

Both the adaptive and innate immune systems are implicated in the development of AD. A complex interaction of immune cells mediates AD skin lesions. T cells play a major role in adaptive immunity and pathogenesis of AD. Atopic dermatitis lesions contain an increased amount of Th2 cytokines during both acute and chronic phases of the disease compared to normal skin. Chronic lesions are however associated with a reduced production of IL-4 and IL-13 and an increased production of IL-5 and IL-12.[15]

Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) are two types of epidermal dendritic cell populations that are crucial elements of the immune system, bridging innate and adaptive immunity. These cells express increased levels of IgE high affinity receptor, FcεRI, on their surface and have the potential to respond to numerous antigens in an antigen-specific manner. It was shown that Langerhans cells, activated by FcεRI, drive naïve T cells into Th2 cells. They further highly express the receptor for thymic stromal lymphopoietin (TSLP). The latter plays a critical role in Th2 skewing and mediation of AD development.[15]

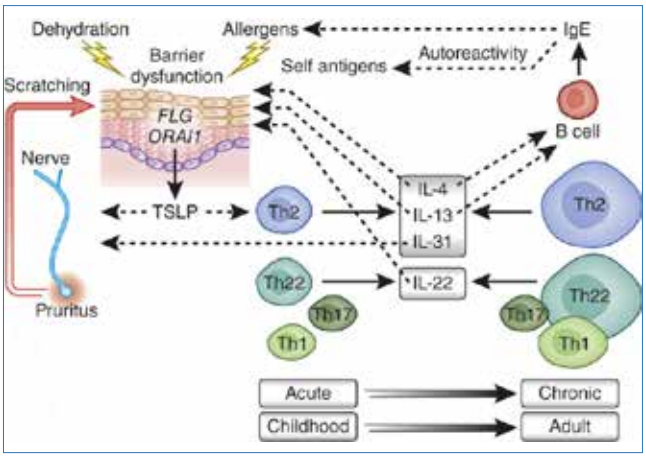

Figure 5. Pathogenesis of AD[3]

TSLP, thymic stromal lymphopoietin
FLG, filaggrin

Figure 5 represents a schematic illustration pertaining to Th2 cytokines and AD: genetic mutations in FLG cause barrier disruption and dehydration, allowing external allergens to penetrate. The barrier-disrupted epidermis releases TSLP and triggers the Th2/Th22 immune response. These reactions are the fundamental abnormality in AD. During the disease progression, e.g. from acute to chronic or childhood to adult AD, the Th2/Th22 deviation is further accelerated. Th1 but not Th17 is involved in the chronic phase of AD. β-cells are stimulated by Th2 cytokines (IL-4 and IL-13) to produce IgE antibodies toward allergens. Elevated IgE is likely to be engaged in the development and severity of AD by manifesting IgE autoreactivity. Approximately 80% of AD patients present with elevated serum IgE levels.[3] In addition, IL-4, IL-13 and IL-22 supress FLG expression, leading to a defective skin barrier.

Mechanical injury, e.g. scratching, activates keratinocytes. The release of TSLP from keratinocytes is dependent on calcium influx regulated by the ORAI1 channel. Pruritus is evoked by TSLP and Th2-derived IL-31, and the subsequent scratching exacerbates the inflammation by accelerating cellular damage in the lesional skin.[4] Inflammatory AD skin furthermore contains, except for LC, IDEC and various T cell subsets, vast numbers of neutrophils, basophils, eosinophils, innate lymphoid cells, natural killer cells and fibroblasts.[27]

Skin barrier

Although not an inherent factor in patients suffering from AD, ceramide is a lipid that is important for water retention in the stratum corneum. The significance of ceramide is evident, as an inversed correlation exists between transepidermal water loss (TEWL) and the level of ceramides in the stratum corneum of AD patients. A decreased level of ceramide in patients with AD is thought to be a post-inflammatory effect.[15]

Human kallikrein-related peptidases are key proteases for desquamation of corneocytes. The activity of these proteases is pH dependent with enhanced activity when the pH in the stratum corneum is elevated. Activation of epidermal proteases and subsequent increased corneocytes desquamation can induce AD-like dermatitis.[15]

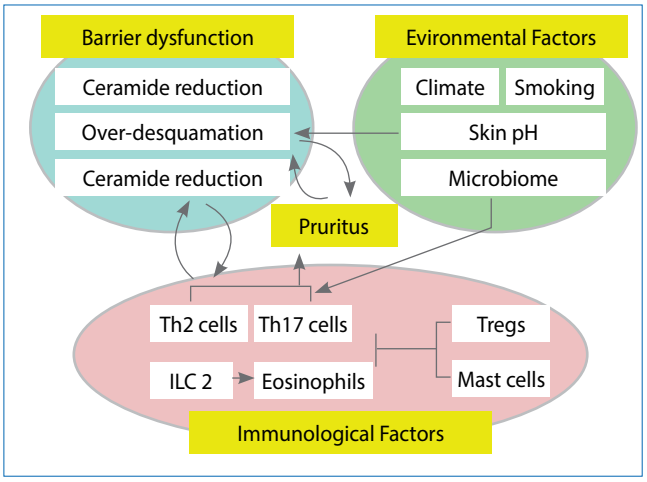

Figure 6. Interplay among contributing factors[15]

AD and its management

Atopic dermatitis is considered by experts to be an incurable skin condition.[28] Contrary to this, some experts conclude that approximately half of children affected by AD reach disease resolution into their adult phase.[29] Guidelines on how to manage AD aim to improve symptoms and achieve long-term disease control. A multistep approach has included avoidance of trigger factors, continuous epidermal barrier repair with emollients, and anti-inflammatory therapy with topical corticosteroids or calcineurin inhibitors. The use of phototherapy or systemic immunosuppressant therapy is indicated in severe and refractory cases.[9] Alternative options to consider in the management of AD include novel treatments, e.g. dupilumab.[30] The management of AD should however always be adapted according to disease severity. Health care providers should not neglect patient education which remains as important as other treatment strategies.[22]

Non-Pharmacological management

Avoidance of trigger factors

Several factors can trigger or worsen the symptoms of AD – these factors are usually individualised and based on a previous reaction to an identified provoking agent.[31] Based on clinical experience, the following factors are widely assumed to worsen the disease: food, inhalant or contact allergens, detergents, wool fabrics, climate, infections and stress. Based on evidence, aeroallergens (e.g. dust mites) and food allergens (e.g. cow's milk) worsen the symptoms of AD in both children and adults.[9] Avoiding these factors has shown to contribute to the long-term and effective management of AD.[31]

Moisturising

The main aim of using moisturising agents is to combat xerosis, the cardinal clinical feature of AD that results from a dysfunctional barrier layer. Moisturising agents predominantly reduce TEWL and have shown to lessen symptoms and signs of

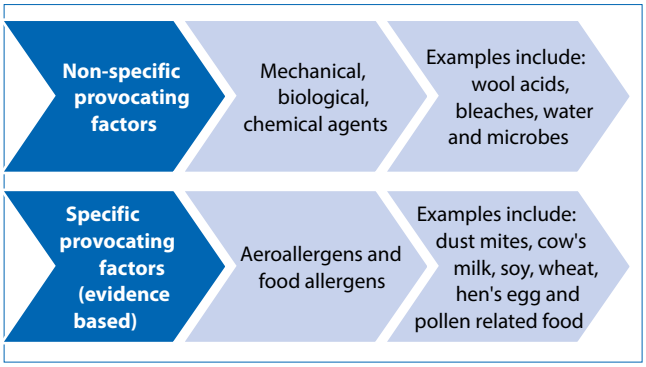

Figure 8: Different factors causing AD flare-ups[31]

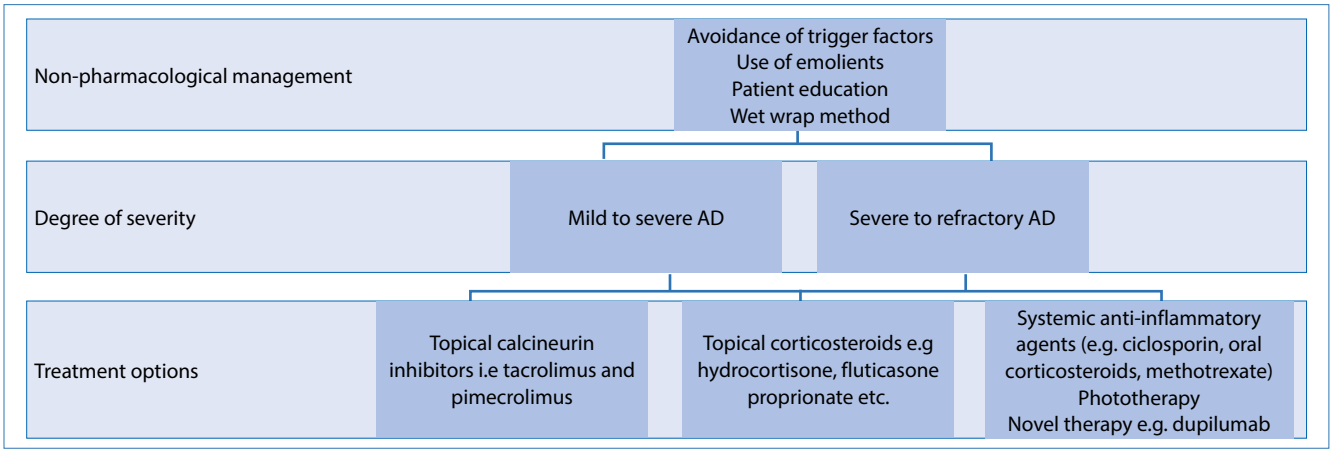

Figure 7: A summary of major management options for AD

AD, including pruritus, erythema, fissuring, and lichenification.[31] The various available products include emollients, humectants and other miscellaneous agents. Frequent use of emollients is of key importance in maintaining homeostasis of the epidermal barrier. Emollients supply exogenous lipids and thereby soften the skin and reduce water loss by forming an occlusive layer. Emollients are mostly composed of different ingredients, such as glycerol, petrolatum, mineral oil, purified water (e.g. Dexeryl®). These products ensure that the skin is softened and lubricated.[32] Humectants such as urea (note: avoid in infants; ≤ 4% in children; up to 10% in adults), glycerine, and lactic acid added to the emollient, further increase water binding in the stratum corneum.[9,22]

Products containing perfumes, colourants, etc., could induce an allergic reaction or act as an irritant and are best avoided. Non-soap fragrance free cleaners with a neutral to low pH are highly recommended for patients suffering from AD. The use of wet-wrap therapy, with or without a topical corticosteroid, has also been seen as a favourable alternative in the management of AD. The latter is recommended for patients with moderate to severe AD in an attempt to decrease disease severity and water loss during flares.[9]

It is important to note that Aqueous Cream BP®, commonly prescribed to relieve skin dryness, contains sodium lauryl sulphate (SLS). This surfactant is an irritant and affects the effectiveness of the skin barrier. Studies have shown that SLS significantly reduces the thickness of the stratum corneum with an overall increase in baseline TEWL.[33] The use of ointments is recommended to relieve skin dryness as they provide more effective treatment with the added benefit of having a lower risk of allergic reactions as they contain fewer preservatives.[34]

Phototherapy

In cases where AD cannot be controlled with topical treatment, short-term phototherapy should be considered. Narrow-band ultraviolet B radiation and medium-dose ultraviolet A1 radiation have shown to be the most effective. This therapy should not be used in combination with topical calcineurin inhibitors and systemic cyclosporin treatment due to a potentially increased cumulative risk of skin cancer.[9] The long-term effects of phototherapy include an increased risk for developing skin cancer while the short-term adverse effects include itch and acute burns.[28]

Pharmacological management

Anti-inflammatory therapy

Topical corticosteroid therapy

Topical corticosteroids are the mainstay anti-inflammatory treatment to control acute outbreaks of AD and have a low risk profile when used appropriately and intermittently.[9] The mechanism of action of this class of medicine is linked to their potential to affect various immune cells. The latter include T lymphocytes, macrophages, monocytes and dendritic cells interfering with antigen processing and the suppression of pro-inflammatory cytokines release.[31] Low-potency corticosteroids are preferred to use on the face, on areas with thinner skin, and in children. Short-term treatment of severe exacerbations is an exception.[9] Thicker-skinned areas should initially be treated with moderate to high potent steroids followed by a dose reduction or an exchange to a lower potency preparation.[22]

Table 2. Different topical corticosteroids used in AD, including their potency and trade names[29]

POTENCY	TRADE NAMES
Weak	
Hydrocortisone 0.5%	Dilucort®, Skincalm®
Hydrocortisone 1%	Procutan®, Mylocort ®, Biocort®
Moderate	
Betamethasone Half-Strength 0.05% (as valerate)	Sekpharma®
Potent	
Beclometasone dipropionate 0.025%	Beclate®
Betamethasone 0.1% (as valerate)	Sekpharma®, Lenovate®, Persivate®
Betamethasone 0.05% (as dipropionate)	Diprosone®
Fluticasone propionate 0.05%	Cutivate®
Hydrocortisone butyrate	Locoid®
Methylprednisolone aceponate 0.1%	Advantan®
Mometasone	Elocon®
Very potent	
Clobetasol propionate 0.05%	Dermovate®, Dovate®, Xenovate®

Calcineurin inhibitors

Calcineurin inhibitors, for topical application, include tacrolimus (not available in SA) and pimecrolimus and are regarded as second-line for short term and intermittent treatment.[9] These agents selectively inhibit the production and release of pro-inflammatory cytokines and mediators by T cells and mast cells.[35] The advantage of calcineurin inhibitors is that they do not cause skin atrophy and are therefore of particular value in areas with delicate skin, e.g. the face and groin. Topical corticosteroids and calcineurin inhibitors should be applied proactively for two consecutive days per week to help reduce exacerbations of the disease.[9]

The calcineurin inhibitors are often associated with a transient burning sensation of the skin, less observed with pimecrolimus than tacrolimus.[34] Safety has not been established in children younger than 2 years of age and treatment is therefore recommended for patients above the age of two. The use of pimecrolimus and tacrolimus is not recommended in pregnant and breastfeeding patients.[34]

Systemic immunosuppressive therapy

Several immunomodulatory agents investigated for their use in AD include cyclosporine, azathioprine, methotrexate, oral corticosteroids and mycophenolate mofetil. The immunosuppressive agents are usually reserved for refractory

cases where treatment failure with topical and phototherapy options have been observed. Most of these agents are used off-label with the exception of cyclosporine and oral corticosteroids.[9]

Novel therapy

Dupilumab is a novel therapeutic option approved for use in AD and is a full human monoclonal antibody. It exerts its action through binding to interleukin 4Ra, which is a component of the IL-4 and IL-13 receptors. Binding to these receptors inhibits their signaling and downregulates type-2 immunity[30] The breakthrough of dupilumab was achieved during 2012 when results from a phase 2 trial showed safety and efficacy as monotherapy in moderate-to-severe AD.[36] The US Food and Drug Administration (FDA) approved dupilumab, the first biological therapy for use in AD, in March 2017. The use of dupilumab has enhanced confidence in the long-term control of AD, especially in patients with resistant, extensive disease.[30]

Conclusion

Atopic dermatitis affects people of all ages and children are sometimes able to outgrow the condition. The physical effects of AD are unpleasant, but even more worrisome is the link to psychological and emotional distress. Treatment focuses on the use of topical therapies such as corticosteroids and/or calcineurin inhibitors to reduce the immunological response. The use of systemic therapies is usually reserved for AD resistant to conventional therapy. Exciting new treatment options for the long-term control of AD, especially in patients with resistant extensive disease, have recently become available and need to be considered.

It is important to remember that histamine has little relevance in the pruritic pathway of AD and is therefore poorly effective in the management of the disease. First generation antihistamines are indicated for their sedative effect in order to facilitate sleep which might be impaired due to itching.[37] Second generation antihistamines seem to have little or no value in the treatment of AD, as concluded by most studies.[22]

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