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REVIEW ARTICLE

Targeting therapeutic approaches and highlighting the potential role of nanotechnology in atopic dermatitis

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Abstract

Atopic dermatitis is a chronic as well as widespread skin disease which has significant influence on the life attributes of affected people and their families. Systemic immunosuppressive drugs can be utilised for effective care of disease, although they are often prescribed for rigorous disruption or disease that is complicated to manage. Therefore, topical applications of corticosteroids are considered the primary pharmacologic therapies for atopic dermatitis, and research recommends that these medications might be helpful in preventing disease flare-ups. However, topical medicine administration to deeper layers of skin is challenging because of the skin anatomic barrier that restricts deeper drug permeation, and also due to barrier function abnormalities in atopic dermatitis skin, which might result in systemic drug absorption, provoking systemic consequences. Hence, effective management of atopic dermatitis needs new, effective, safe and targeted treatments. Therefore, nanotechnology-based topical therapeutics have attracted much interest nowadays because of their tendency to increase drug diffusion and bioavailability along with enormous drug targeting potential to affected cells, and, thereby, reducing the adverse effects of medications. In this review, we mention different symptoms of atopic dermatitis, and provide an overview of the different triggering factors causing atopic dermatitis, with emphasis on its epidemiology, pathophysiology, clinical features and diagnostic, and preventive measures. This review discusses existing therapeutics for treating atopic dermatitis, and the newer approaches as well as the current classical pharmacotherapy of atopic dermatitis against new nanoparticle skin delivery systems. This review has also briefly summarised the recent patents and clinical status of therapeutic modalities for atopic dermatitis.

Keywords Atopic dermatitis · Food allergy · Filaggrin · Topical corticosteroids · Emollients · Topical calcineurin inhibitors · Wet wrap therapy

Abbreviations

AD	Atopic dermatitis
LOF	Loss-of-function

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FLG	Filaggrin gene
UVB	Ultraviolet light B
TCIs	Topical calcineurin inhibitors
TEWL	Transepidermal water loss
GCR	Glucocorticoid receptor
UVA	Ultraviolet light A
TrkA	Tropomyosin receptor kinase A
NGF	Nerve growth factor receptor
JAK	Janus kinases
PDE4	Phosphodiesterase 4
IL	Interleukin
REM	Rapid eye movement
SPINK5	Serine peptidase inhibitor Kazal type 5
LEKT1	Lympho-epithelial Kazal-type-related inhibitor

Introduction

Atopic dermatitis (AD), commonly known as atopic eczema, is a prevalent chronic or recurrent inflammatory skin disease that affects 15 to 20% of children and 1 to 3% of adults around the world. Severe flare-ups of eczematous pruritic wounds on dry epidermis are the hallmarks of this condition (Garg and Silverberg 2015). So even though the name eczema is commonly used to define this type of dermatitis, AD is a more specific term. The term 'atopy' (originated from the Greek atopia, which means 'different' or 'out of place') was first coined in 1923 to describe asthma and allergic rhinitis; however, in 1933, AD was included to the list of atopic illnesses due to the link between this type of eczema and asthma and allergic rhinitis. In fact, AD is frequently the initial indication of the atopic triad (Spergel and Paller 2003). According to recent research, atopic dermatitis is a basic epidermal barrier deficiency which contributes to an onset of various eczema problems (Luger et al. 2021; Elias 2018; Kraft and Prince 2019; Dinakar et al. 2018). AD frequently begins in infancy and may be the first step in the so-called atopic march, which is defined by a characteristic succession of atopic conditions in childhood before the onset of several different allergic ailments afterward in lives. Within the first year of life, 50% of people with AD have additional allergy symptoms, and up to 85% of those with the disease develop symptoms before the age of 5. Patients commonly outgrow the condition by late childhood, with roughly 70% of individuals having a disease commencement amid childhood experiencing a sudden absolution preceding adolescence. Early childhood AD, on the other hand, is frequently the first sign indicating that youngsters might develop asthma and/or allergic rhinitis (hay fever) later in life (Dharmage et al. 2014; Yang et al. 2020). The condition causes severe illness and has a negative impact on quality of life (Na et al. 2019). Patients are afflicted not just by the social disgrace of having a visible epidermal problem, but also by the disease's extreme itching, which can cause skin damage and sleep difficulties. In addition, emollients (preparations which soothe, moisturise and soften the skin) and topical treatments must be applied often, as well as physician visits (Reed and Blaiss 2018; Handa et al. 2015). The clinical manifestations of atopic dermatitis vary; however, they can be divided into three categories of diagnostic features: essential, important and associated. Early atopic dermatitis may possibly have a role in the development of food allergies (Roerdink et al. 2016). Atopic dermatitis affects the flexural parts of the body, as well as the buttocks and cheeks. The prognosis is generally good as most children outgrow the illness by initial adolescence. Recurrent cases are linked with initial disease commencement, life-threatening, widely spread disease, accompanying asthma or hay fever, and a family history of atopic dermatitis. Atopic dermatitis is caused by a number of reasons, the most common of which are genetics, environment and a relatively weak immune system (D'Auria et al. 2016). Recent research suggests that AD is substantially inherited, with monozygotic twin pairs having higher phenotype concordance (0.72 to 0.77 versus 0.15 to 0.23) than dizygotic twin couples (Morar et al. 2006). If both parents have AD, the children have a 70% chance of developing it as well. The skin of atopic patients has infiltrates of activated T-helper cells (Faergemann 2002). Individual genetic variables or genes that lead to the trait's cause are similar to those seen in other complicated genetic illnesses (Hoffjan and Epplen 2005). There are significant information that environmental and food allergies are key triggers for AD flare-ups. Particular IgE antibodies towards food or environmental allergens have been found within serum of 80% of people having AD (Breuer et al. 2001). In comparison of normo-IgE and non-allergic intrinsic AD individuals, extrinsic AD individuals having higher IgE levels are related to greater disease severity, FLG gene alterations and reduced skin barrier function (Furue et al. 2017). Recent research on AD suggests that both skin structural defects and immunological dysfunction play an essential part in the pathophysiology of atopic disease. Thus, the best treatment for atopic dermatitis involves a multidisciplinary approach that focuses on repairing and conserving the skin barrier as well as addressing the complicated immunopathogenesis of the disease (Werfel et al, 2006; Anderson and Dinulos 2009; Lipozenčić and Wolf 2007).

In this review, we mention different symptoms of atopic dermatitis, and provide an overview of the different triggering factors causing atopic dermatitis, with emphasis on its epidemiology, pathophysiology, clinical features and diagnostic, and preventive measures. This review discusses familiar therapeutics for treating atopic dermatitis as well as the newer approaches. For this purpose, an extensive search of the literature was conducted using the PubMed, Google Scholar and ScienceDirect databases. Literature review was

done from the papers published in peer-reviewed journals from the year 2000 to year 2021. This review has also briefly summarised the recent patents and clinical status of therapeutic modalities for atopic dermatitis.

Epidemiology of atopic dermatitis

Atopic dermatitis impacts approximately one-fifth of all people during their lives; however, frequency of the disorder differs widely around the world (Somanunt et al. 2017). The frequency of atopic dermatitis is expected to be 15 to 20% in children and 1 to 3% in adults, and the incidence has been rising by 2- to threefold in industrialised areas over the previous decades (Spergel 2010). In various so-called industrialised nations, the frequency of allergies increased dramatically from 1950 and 2000, towards the point where many refer to it as an 'allergic epidemic'. However, available evidence suggests that eczema indications have generally levelled out or even declined in certain nations with historically higher incidence, like the United Kingdom and New Zealand. This suggests that this allergic disorder epidemic is not growing at a constant rate globally. However, atopic dermatitis is a severe medical problem, and in various nations, especially in the developing world, the condition is still on the increasing (Thomsen 2014). AD is among the most prevalent chronic disorder globally as well as the most frequently reported inflammatory skin condition in the industrialised world; affects males and females of all ethnicities, children and adults; and is frequently found in families having other atopic disorders (bronchial asthma and/or allergic rhinitis) (Torres et al. 2019). It has been found that the incidence of atopic dermatitis is continuously rising. The rapid growth in occurrence shows that environmental factors, probably linked to lifestyle Westernisation, are driving the development instead of genetic alterations (Mayba and Gooderham 2017).

Pathophysiology

Although the pathophysiology of atopic dermatitis is unknown, the disease is believed to be caused by a complicated interaction between impairments in epidermal barrier function, immunological dysregulation and exposure to environmental and infectious pathogens (Sandeep et al. 2018).

Skin barrier disorders have seemed to be linked with mutations or diminished expression of the filaggrin gene, which produces a structural protein required for the development of the skin barrier. Furthermore, dysregulation of lipid metabolism and ceramide depletion are significant variables that result in trans-epidermal water loss and enhanced penetration of irritants, allergens and microorganisms into the skin (Chovatiya and Silverberg 2019). The skin barrier deficiency in AD also makes it easier for pathogenic bacteria (such as *S. aureus*) to colonise or infect the skin, which can further disrupt the skin barrier with exogenous proteases (Malik et al. 2017). There is an indication that a disrupted skin barrier may permit allergens to enter deeper into the skin, causing allergic sensitisation, asthma and hay fever (Pyun 2015).

The epidermis is disrupted by a genetic deficiency in the filaggrin protein, which is believed to be the main reason for AD. As a result of this disturbance, antigens from the external environment come into contact with immune cells in the dermis, causing acute itching, scratching and inflammation. The itch-scratch cycle describes how scratching can cause more damage and inflammation of the epidermal skin barrier (Berke et al. 2012; Silverberg and Silverberg 2017). Loss-of-function (LOF) mutations in the FLG gene are regarded as the greatest common underlying genetic risk factor for AD. The existence of two homozygous mutations in the FLG gene has been linked to more recurrent diseases (Fuxench 2017). Filaggrin is an important component of the skin barrier and a key epidermal protein that is required for corneocyte development and production of intracellular metabolites that keep the stratum corneum hydrated and the skin's pH stable.

The immune response seen during AD is described by a biphasic inflammation (Ezzedine and Kechichian 2017). IL-4, IL-5, IL-13, IL-25 and IL-31-rich type-2 T-helper cell (Th2) signals predominate in the acute infection, while a Th2–Th1 transition enhances disease chronicity. Moreover, IL-22-secreting Th22 cells, as well as IL-17-secreting Th17 cells to a lesser extent, play a significant function in the onset and maintenance of AD (Renert-Yuval and Guttman-Yassky 2018). Furthermore, the innate immune system and regulatory T cells in the skin are affected. The first line of defence for infections is the innate immune system. A reduction in antimicrobial peptides (a constituent of the skin's innate immune system) has been seen in AD patients, which could explain their susceptibility to infections (Taieb 2012) (Fig. 1).

The condition is divided into three stages, i.e. onset, acute and chronic. Abnormalities in the skin barrier allow antigens to penetrate the epidermis, where they are received by Langerhans and dermal dendritic cells, which stimulate Th2 cells and produce IL-4 and IL-13. IgE class switching and enhanced Th2 cell survival are two significant consequences of these cytokines. Furthermore, these cytokines have various direct impacts on the skin and gradually grow from non-lesional to chronic diseases. These include more TSLP generation by keratinocytes, suppression of antimicrobial peptide synthesis and impeded epidermal differentiation. The ensuing disruption of the skin barrier raises the risk of infections linked with

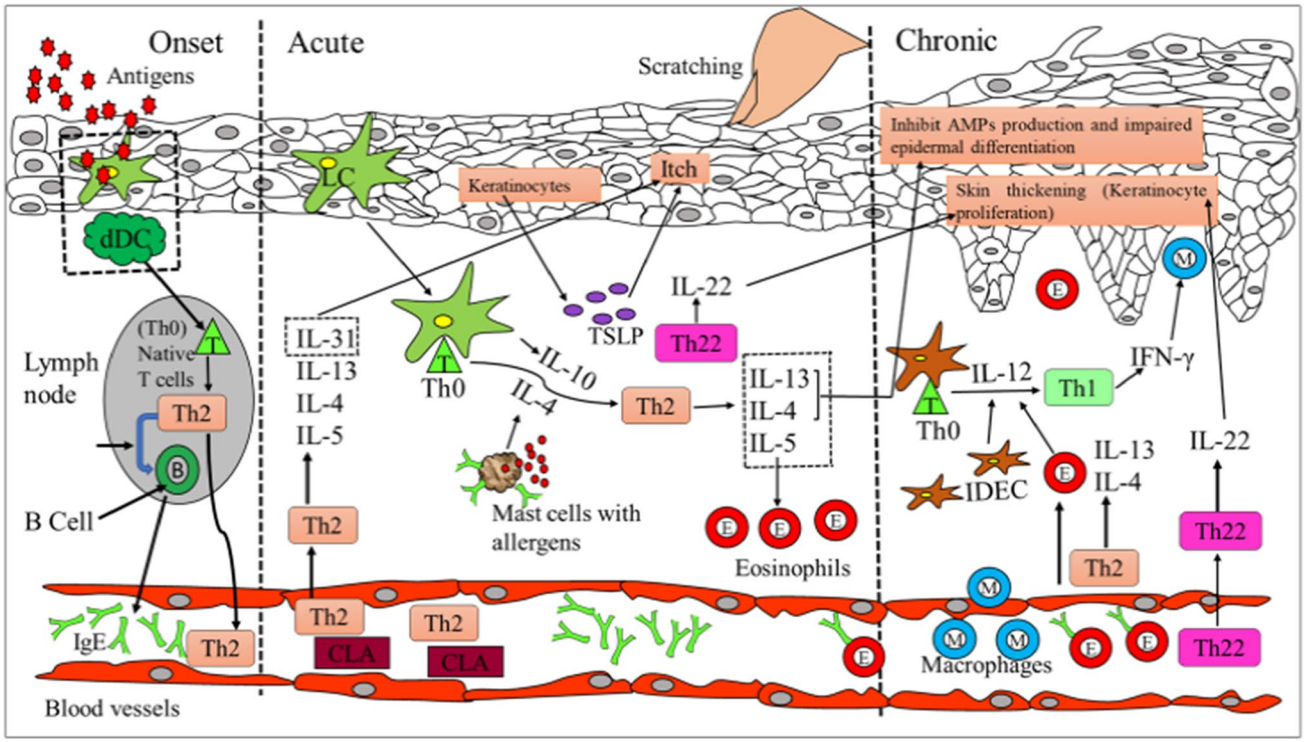

Fig. 1 Pathophysiology of atopic dermatitis. TNF: tumour necrosis factor; TSLP: thymic stromal lymphopoietin; Th: T helper; Th0: naive T cell; IL: interleukin; LC: Langerhen cells; dDC: dermal dendritic cells; AMP: antimicrobial peptide; CLA: cutaneous lymphocyte-associated antigen; IDEC: inflammatory dendritic epidermal cells; IgE: Immunoglobulin E

AD. Th2 T cells and DCs also stimulate peripheral eosinophils and mast cells with their inflammatory mediators. An increase in Th22 cells in AD skin is also significant; this subgroup generates IL-22, which is greatly higher in chronic AD skin. IL-22 prevents terminal differentiation and causes epidermal hyperplasia, a common characteristic of a chronic condition. As a result, the barrier abnormality in atopic dermatitis is most commonly caused by a combination of Th2 and Th22 cytokines. Dendritic cells and Langerhans cells, like T cells, show a progressive rise from non-lesional to chronic AD. When compared to psoriasis, the involvement of Th17 T cells and their cytokine, IL-17, in the development of AD is less important, and more MODEST elevations in this cytokine were seen in acute and chronic AD. This could explain why Individuals having AD produce less antimicrobial peptides (AMPs) than psoriasis patients, as a result of both Th2 cytokine suppression and lesser concentrations of IL-17 (Wang and Xu 2015; Leung et al. 2004; Kim and Kim 2019; Sugita and Akdis 2020; Zallmann et al. 2017; Guttman et al. 2013).

Triggering factors for atopic dermatitis

The skin serves as a barrier between the human body and its surroundings. As a result, it is vulnerable to a variety of assaults that serve as inflammation stimulants. These variables cause scratching, which initiates and maintains the inflammatory cascade started by proinflammatory cytokines released by atopic keratinocytes (Leung et al. 2004).

Food allergy

Food allergies are a major cause of AD, especially in children. Most people equate true diet allergies with non-allergic diet reactions like food intolerance, giving the world the impression that actual IgE-mediated food allergy is more common than it is. There are over 170 items that were linked to IgE-mediated reactions, although cow's

milk, egg, nuts, fish and shellfish are the most prevalent allergens. Food allergies usually occur in the manner in which a person is exposed to a particular food. As a result, early childhood allergies to cow's milk and egg develop (Sugita and Akdis 2020; Mastrorilli et al. 2017; Panel NS, 2010) food allergies to wheat and fresh fruit occur in older children, while the most prevalent food allergies in adults are to nuts and shellfish, and also food allergies caused by pollen cross-reactivity. Around 10–15% of children and adults have self-reported signs that are indicative of an allergy to certain foods. But only around 3–5% have a diagnosed food allergy. Anaphylaxis caused by food is a life-threatening reaction that affects less than 0.1% of the population. Many children having food allergies will finally be able to accept cow's milk, egg, soya and wheat, while only a small percentage will be able to eat tree nuts and peanuts. Food allergy remission in children takes different amounts of time depending on the food and can happen as late as adolescence. For example, two-third of children with an egg allergy will be tolerant by the time they reach school age, and the majority of children with a cow's milk allergy will tolerate cow's milk by the time they reach adolescence. An elevated initial concentration of egg serum IgE, the occurrence of additional atopic conditions and the existence of an allergy to some other foods are all possible causes for egg allergy recurrence. Approximately 15–20% of children will stay allergic on an avoidance diet, and the intensity of the responses may worsen over time. In these extreme situations of egg allergy, sticking to the avoidance diet becomes much more challenging, resulting in a considerable decrease in the patients' quality of life (Giannetti et al. 2019; Devdas et al. 2018). A decline in IgE serum concentrations over time in children is usually a sign of the beginning of food tolerance. In other cases, however, food allergies can develop in adult years, and the food allergy may continue even after a decrease in IgE rates over time. An increased initial amount of serum IgE against food is linked to a slower rate of clinical allergy remission over time. Food allergies that occur in adult years have a far worse prognosis and, in most cases, will last the rest of one's life. Food allergies are significantly linked to the development of other atopic conditions. Atopic dermatitis affects roughly half of all children with food allergies, while asthma affects around 40% and allergic rhinitis affects approximately 30% (Bergmann et al. 2013; Martorell et al. 2013).

Genetic factors

The importance of genetics as a major potential cause for atopic dermatitis was initially discovered in observation research, which described a positive parental history in AD patients, as well as in twin studies demonstrating a greater concordance rate in monozygotic twins in comparison to dizygotic twins (Thomsen et al. 2016, 2007). Then, using genetic linkage analysis and association analyses, numerous genes connected to epidermal function or the immune system were discovered. Recent progress has been done in knowing the importance of genetics in AD, with the identification of the filaggrin (FLG) gene being the most significant thus far (Palmer et al. 2006; O'Regan and Irvine 2010). The FLG gene that codes for filaggrin an essential epidermal structural element was discovered. Filaggrin is an important element of the skin barrier (Cabanillas and Novak 2016; McAleer and Irvine 2013) and an important epidermal protein that is required for the corneocyte development and also for the synthesis of intracellular metabolites that aid in the hydration of the stratum corneum and pH of the skin (Brown et al. 2020; Bussmann et al. 2011). The common loss-of-function (LOF) mutations in the FLG gene have recently been identified as the greatest common genetic risk factor for AD, and the occurrence of two homozygous mutations has been linked to greater chronic disease. Skin barrier impairment has been linked to FLG gene mutations, and the deficiency in the skin barrier significantly increases trans epidermal water loss, or TEWL, that describes the related xerosis or dryness observed in AD individuals, and also allows significantly larger penetration of irritants, allergens and skin colonising organisms that can cause infectious disease (Kezic et al. 2008; Marenholz et al. 2015). Abnormalities in epidermal barrier function may lead to an enhanced Th-2 inflammatory response, as well as the raised formation of pro-inflammatory cytokines like IL-4 and IL-13, prolonging the inflammatory cycle found in atopic dermatitis (Sullivan and Silverberg 2017).

SPINK5/LEKT1 is one among the other skin-related genes that are also linked to AD (Moffatt, 2004), and various tissue-specific DNA methylation patterns have been discovered as the initial indication for the importance of epigenetic changes in AD. Overall, these findings have aroused desire in the significance of skin barrier damage in the onset of atopic dermatitis and allergy sensitisation (Kim and Leung 2018; Cork et al. 2019; Brough et al. 2014).

Family history

The most powerful known triggering cause for AD is a family history of atopic diseases, mainly AD (Dhar and Banerjee 2010). A positive family history of atopic or allergic condition in either parent has been linked to the progression of AD. It is estimated that around 70% of individuals having AD have a positive family history of the disease (Sidbury and Kodama 2018; Eichenfield et al. 2014). A child having one atopic parent has a 25% chance of developing atopy, while a child having two atopic parents has a 50% chance (Thomsen 2015). Children whose mothers had atopic

dermatitis are likely to have a higher risk of getting AD (Lee et al. 2007a, b; Purvis et al. 2005). According to one investigation, having a mother with an FLG mutation was linked to a 1.5-fold greater chance of acquiring the atopic disease, irrespective of the patient's carrier status (Esparza-Gordillo et al. 2015). Individuals with a positive family history of atopic disorders, as well as those with FLG gene mutations in some populations, especially Caucasians of Eastern European descent and Asian populations, are at a greater risk of acquiring AD. There is a considerable indication that the frequency of atopic disease is greater among people who identify as Black or of African ancestry than in Caucasians (Shaw et al. 2011; Wegienka et al. 2012).

Autoallergens

IgE antibodies specific against human proteins were observed in individuals having severe AD. To date, the autoallergens found in AD sera have intracellular proteins that can be recognised in IgE immune complexes. These findings demonstrate that, while environmental allergens induce IgE immune reactions, allergic inflammation in chronic AD can be sustained by the secretion of human proteins generated from injured skin (Leung 2000; Hradetzky et al. 2015).

House dust mites

House dust mite allergy was first connected to atopic dermatitis in 1932, and clinical improvement was shown when patients having the disease were taken out of their houses and resettled in a dust-free environment. House dust mites were detected in 1964, and it was established in 1969 that *Dermatophagoides pteronyssinus* was the most common allergen source in house dust. Mite excrement contains the most common allergen in house dust. House dust mites thrive in rooms with wall-to-wall carpeting, high indoor humidity and temperatures ranging from 17 to 24 °C. Bedding, upholstery furniture and carpeting are the most common sources of mites. Mites feed on the scales of human skin, and researchers discovered that people having AD were subjected to more mites in their mattresses compared to non-AD control participants with identical indoor humidity levels. Inhalation and skin contact are believed to play a role in the exacerbation of AD induced by house dust mites (Miller 2019; Bouton and Ducommun 2009; Kim et al. 2013). Besides from early indications of a dust-free environment alleviating AD, other research results which endorse the significance of the house dust mite in AD involve increased concentrations of IgE and IgG to mite antigen in individuals with and without respiratory atopy, positive patch test reactions to mite antigens in individuals with AD and clinical improvement in individuals with AD using allergen-antibody therapy. Household mite control includes removing or vacuuming carpets and upholstered furniture regularly, applying acaricidal treatments to carpets, using hypoallergenic mattress covers and washing linens in hot water (Fernández et al. 2014; Gavino et al. 2008).

Hormones

Women often report changes in the clinical course of AD as a result of hormonal effects. Exacerbations have been linked to menstruation, pregnancy, parturition and menopause. However, the reverse impact is possible, and the effects can differ even among patients. Regrettably, no treatment measures are known to impact the course of AD aggravated via hormonal factors (Cho et al. 2010; Kiriyama et al. 2003).

Microbes

The majority of AD patients have *Staphylococcus aureus* colonisation and experience relapses of their skin disorder as a result of this organism's overgrowth (Leung 2003). In AD patients with secondary infection, therapy using a combination of anti-staphylococcal medicines and topical corticosteroids improves clinical outcomes more than therapy using topical corticosteroids only, supporting the significance of *S. aureus*. *S. aureus* worsens AD by producing toxins termed superantigens, which increase T cell and macrophage activation. Most AD produces specific IgE antibodies towards staphylococcal superantigens (Ogonowska et al. 2020; Tomczak et al. 2019), and the severity of skin disease is related to these IgE anti-superantigens. Superantigens also cause corticosteroid resistance, implying that superantigens cause AD severity through a variety of mechanisms. Enhanced *S. aureus* skin binding is a result of underlying AD skin inflammation. Studies have revealed that topical corticosteroids or tacrolimus lower *S. aureus* levels in atopic skin, which is clinically supported. Because of IL-4-induced fibronectin production, *S. aureus* binding was considerably higher in skin sites with Th2-mediated skin inflammation in comparison to Th1-mediated skin inflammation in experimental animal models. Antimicrobial peptides required for host defence against bacteria, fungus and viruses have also been discovered to be lacking in AD skin (Ong et al. 2002; Nomura et al. 2003). As a result, once *S. aureus* adheres to AD skin, the bacteria can colonise and grow due to a lack of host resistance. The absence of skin innate immune responses may make these patients more susceptible to infection from fungus and viruses. Patients with AD are more likely to develop disseminated herpes simplex or vaccinia virus infections. As a result, smallpox immunisation is not recommended in people with AD unless they are at immediate risk of contracting smallpox (Ogonowska et al. 2020).

Climate

The progression of AD is influenced by the seasons. Some patients' atopic disease worsens during the winter months, while others have exacerbations in the spring or autumn, while still others have worsening symptoms in the summer. Furthermore, a change in the environment may have an impact on the condition. Stays by the sea or in the mountains, especially over 1500 m, are usually linked to improved skin conditions. Although sun exposure is usually good, some patients may notice a worsening of unprotected skin areas during the summer months. Some people get actinic prurigo or a polymorphous light eruption, while others have a real worsening of their AD. This condition is known as photosensitive AD, and it can lead to chronic actinic dermatitis. Routine photo testing in photosensitive AD normally produces normal findings; however, ultraviolet light B (UVB) can occasionally cause lesions (Patrizi et al., 2009; Napolitano et al. 2020). Seasonal impacts on AD may be influenced by various factors such as antigen exposure, perspiration, UV exposure, low air humidity during the winter months and cold winds that dry the skin. For chronic situations of AD, climatotherapy (in the mountains or at the sea) can provide a significant duration of relief. Holidays in climate-friendly places should be recommended to every individual having AD. It has been suggested that permanently relocating to a different environment is advantageous (Engebretsen et al., 2016; Fieten et al. 2015).

Clinical features and diagnostic

Atopic dermatitis is a chronic disease with a wide range of clinical phenotypes that are influenced by factors such as age, ethnicity and disease severity. AD is defined by eczematous, oozing or weeping pruritic sores on dry skin that flare up. Brownish or red dry, cracked or scaly skin patches with prurigo nodules and lichenification are characteristics of chronic lesions. Itchy skin causes sleep disturbances, weariness and mental health issues, particularly at night. For AD, there are no specific diagnostics tests available. The disease is diagnosed using specific criteria that consider the patient's history and clinical characteristics (Weidingeret al. 2018). A skin biopsy has been revealed to be ineffective and is mainly because all dermatitis clinical occurrences are histologically identical (Williams 2005). Although several diagnostic characteristics for atopic dermatitis were suggested and verified, most of these characteristics are time-consuming to apply and often need intrusive testing. The Diagnostic Criteria of the United Kingdom Working Party, on the other hand, were found to be the most well-validated in a 2008 systematic review. The sensitivity and specificity of a simplified version of these criteria are up to 95 and 97%, respectively

Table 1 Efficient diagnostic criteria for the diagnosis of atopic dermatitis that do not need intrusive testing and have been found to possess excellent sensitivity and specificity

Essential criteria	Important criteria	Associated criteria
1.Intense itch 2.Eczematous lesions (acute, subacute, chronic) 3.Chronic or relapsing disease course 4.Age-related distribution pattern and parts affected •Infants—widespread and more acute skin sores marked by severe erythema, oedema, excoriations and serious discharge presenting as oozing and crusting, typically over the face/cheeks and trunk, with the diaper area spared •Childhood—more localised and persistent, with paler erythema, xerosis and thickened skin from scratching impacting flexor regions •Adolescents and adults—diffuse pattern with localized lesions, hands, eyelids and flexures affected •Adults—chronic, head, hand, upper trunk, shoulders and scalp affected	1.Early onset (typically during the first year of life) 2.Personal and/or family history of atopic diseases 3.Presence of generalized skin dryness	1.Densely aggregated follicular papules 2.Frequent in dark-skinned people 3.Chronic prurigo 4.Erythematous, excoriated papules and indurated nodules (Silvestre et al. 2017; Lyons et al. 2015; Buys 2007)

(Brenninkmeijer et al. 2008; Gu et al. 2001). Itchy skin with at least three of the symptoms, i.e. history of allergic rhinitis or asthma, history of widespread dry skin, history of flexural involvement, rash beginning before 2 years of age and evident flexural dermatitis, is among the simplified criteria. Patients should be asked how many days per week they have symptoms like pruritus, bleeding, leaking clear fluid or dry, flaky skin (Table 1).

Prevention

There is a compelling urgency to enhance disease prophylaxis, considering the load on healthcare resources, the effect on the standard of life of patients and their caregivers and the growing evidence that AD can proceed to additional allergy phenotypes (Flohr and Mann 2014). This goal is helped by our expanding understanding of the pathoetiology of AD and environmental risk factors (Flohr 2011). Because the disease is more common in children, preventative efforts are concentrated in the perinatal phase. Prevention should begin as early as possible, focusing on the skin barrier, immune/allergy systems and environmental factors (Nutten 2015). Primary prophylactic measures, such as breastfeeding, dietary supplementation, hypoallergenic milk with hydrolysed formulae, prebiotics and probiotics, have yielded mixed outcomes and, to date, have been unable to prove a considerable influence on reducing the possibility of getting atopic dermatitis.

Breastfeeding

Breastfeeding has been shown to be beneficial to children's health, despite the fact that there is minimal information that prolonged breastfeeding after the age of 3 months is beneficial (Flohr C, et al., 2011). Although food avoidance was once suggested, current observational investigations have indicated that halting the intake of solids is a risk factor for AD; therefore, tolerance induction strategies are now adopted (Roduit et al. 2012; Filipiak et al. 2007; Sariachvili et al. 2010). Infant formulae have been produced for children who cannot be breastfed. Formulas that are partially hydrolysed or completely hydrolysed are recommended for infants who are at risk of developing an allergy to cow's milk as well as newborns who currently have symptoms of an allergy to cow's milk. In comparison to cow's milk formula, protracted feeding with a partially hydrolysed whey formula has been demonstrated to result in a 45% reduction in infantile AD in at-risk infants in intervention studies (Alexander and Cabana 2010; Szajewska and Horvath 2010). The German Infant Nutritional Intervention research found that infants who were given a partially hydrolysed whey formula or a completely hydrolysed casein formula had a significantly lower incidence of AD up to the age of 10 years. One possible explanation for this finding is that a minimal level of protein or peptides (like hydrolysed proteins) could teach the immune system to acquire tolerance (Von et al. 2003, 2013; Von et al., 2008).

Dietary supplementation

Supplementing the diet with vitamins, selenium, zinc, oils and other nutrients has been also analysed prenatally and postnatally. Vitamin D has been researched in the perspective of preventing AD because of its immune-modulatory impact; nevertheless, the findings are still contradictory. Several studies have also found that eating a lot of fish when pregnant lowers the chances of the baby acquiring AD. When fish was eaten in late infancy, similar outcomes were seen (Kim et al. 2016; Vaughn et al. 2019).

Preventing a skin barrier breakdown

Protecting the epidermis barrier, which plays a crucial role in the onset of AD, could be a potent approach to prevent the disease, particularly in children with skin barrier gene abnormalities and who exhibit initial signs and symptoms of skin barrier damage. Furthermore, the skin barrier could be the main target for preventing eczema from progressing to allergic airway disorders. The use of emollients in combination with the avoidance of soap has yielded encouraging results (Williams and Chalmers 2020; Kamińska 2008).

Gut flora modulation

Pre- and probiotics were also utilised throughout the prenatal and/or postnatal time with an aim to change the gut microbiota to greater diversity and a 'healthier' composition. Various probiotics (especially Lactobacilli and Bifidobacteria), utilised either alone or in combination and administered at various times (prenatally and/or postnatally), have been employed in clinical studies. A current meta-analysis linked probiotic use throughout pregnancy and early childhood with a 21% decrease in the incidence of AD. Promising outcomes have also been achieved with prebiotics (substrates inducing growth and activity of probiotics) (Sestito et al. 2020; Peluchi et al. 2012; Osborn and Sinn 2013).

Disease management and therapeutic approaches

Individual clinical variability of atopic disease must be taken into account when managing the disease; therefore, highly uniform treatment guidelines are not suggested (Wollenberg et al. 2018). The goal of treatment is to minimise pruritus and achieve long-term control of the disease so that patients can function normally at home, at work and in school.

As a result, a multistep treatment is required, involving interventions focused on preventing relevant triggers, strengthening the skin barrier, restoring skin dysbiosis and lowering inflammation (Tsakok et al. 2019). The intensity of the condition generally determines the choice of therapy, with changes made dependent on the patient's age, the existence of atopy-related and unrelated comorbidities, therapeutic response, compliance concerns and pricing. The goal of therapy in AD is to restore the epidermal barrier, which comprises moisturising and healing the skin, controlling itching and reducing inflammation as needed. As a result, effective therapy of AD necessitates a multifaceted strategy which includes patient and caregiver education, appropriate skincare habits, anti-inflammatory therapy with topical calcineurin inhibitors (TCIs) and/or topical corticosteroids (first-line), and skin infection treatment (Krakowski et al. 2008; Akdis et al. 2006). Microbial colonisation and superinfection can exacerbate the condition and necessitate further therapy. In some circumstances, allergen-specific immunotherapy using aeroallergens is an option. Stress-related exacerbations should be treated with psychosomatic counselling (Abuabara et al. 2018). Most suggested medications that target inflammation and skin barrier breakdown are effective in treating pruritus; however, some patients may require additional treatment (opioid receptor antagonists, cannabinoid receptor agonist, memolizumab) (Pereira et al. 2019). Identification of specific trigger variables is critical in the treatment of AD, and avoiding them allows for prolonged periods of remission or complete symptom clearing. Mechanical irritants (e.g. irritant fibres and fabrics and wool), chemicals (bleaches, acids, fabrics, solvents and surfactants in hygiene and cosmetic products), air pollutants (volatile organic compounds, tobacco smoke and traffic exhaust) and biological (microbes, allergens) are all known to irritate AD skin and cause eczema flare-ups. In addition, proper skincare and hygiene routines in cleansing, bathing and clothing are important in the treatment of AD (Boguniewicz et al. 2017; Brar et al. 2019).

Emollients

Atopic dermatitis is associated with xerosis (skin dryness), and most patients report that controlling their xerosis parallels controlling their dermatitis. As a result, whether or not active symptoms are evident, people having atopic dermatitis should use emollients generously all over their bodies (Hanifin et al. 2004). The basis of therapy for people having mild-to-moderate AD is moisturising and lubricating topical treatment, as well as sufficient bathing/cleansing, practices, which are primarily aimed at restoring disrupted barrier function. Patients must use moderate, unscented soaps or soap-free cleansers and bathe in warm (not hot) water. After showering, sufficient doses of a lubricant or emollient cream must be applied to the skin. Emollients must be used once or twice a day to keep skin from drying out and becoming irritated. Moisturisers contribute to the retention and replenishment of skin moisture. Emollients containing a greater lipid content and a minimal water content are preferred in general. Thick creams (e.g. Eucerin, Cetaphil) or ointments (e.g. petroleum jelly, Aquaphor) with a minimal water content are recommended. Emollients are commonly utilised as they help to improve the appearance and symptoms of dry skin caused by AD. When administered in conjunction with corticosteroid therapy, they are regarded as the backbone of AD maintenance therapy (Ng et al. 2015; Nygaard et al. 2017).

Topical corticosteroids

The first-line therapy for atopic dermatitis is topical corticosteroids. Antiproliferative, anti-inflammatory and immunosuppressive properties of these drugs efficiently reduce atopic flare-ups. The potencies range from the maximum effective—group I (e.g. clobetasol)—to the minimum effective—group VII (e.g. hydrocortisone 1%). In general, the potency should be adjusted according to the seriousness of the condition. Higher-potency corticosteroids for extended durations of time are generally required for people with lichenified plaques that are associated with chronic eczema (e.g. lichen simplex chronicus), and occlusive therapy can be beneficial. For the neck, face, groin, axillae and flexor surfaces, mild-potency corticosteroids are suggested to avoid atrophy. It is allowed to use moderate potencies in these regions for brief durations of time (e.g. 2 weeks or less) if the individual is having a major flare-up (Thomas et al. 2002; Hanifin et al. 2002; Atherton 2003). Topical corticosteroids are used to treat itchy, red or inflammatory regions of the epidermis before applying emollients. Some individuals have mistakenly changed the order, reducing the topical corticosteroid's effectiveness dramatically. Ointment formulations are usually recommended over creams because they give more consistent application and penetration. Topical corticosteroids are highly efficacious and safe when administered properly. Striae (stretch marks), petechiae (tiny purple/red spots), telangiectasia (narrow, dilated blood vessels on the skin surface), atrophy, skin thinning and acne are all potential local adverse effects of long-term topical corticosteroid use; moreover, these effects are unusual with low or moderate potency drug formulations. Systemic adverse effects from topical corticosteroids are unusual and are mainly related to the administration of higher-potency formulations on a large surface area of the body (Schmitt et al. 2011). The anti-inflammatory effects of corticosteroids are mediated via a cytoplasmic glucocorticoid receptor (GCR) in target cells. The corticosteroid/GCR complex translocates into the nucleus after ligand attachment, where

it exerts anti-inflammatory actions through two mechanisms. The GCR complex can initially activate gene transcription via attaching GCR dimers to glucocorticoid response factors in the promoter regions of target genes (a process is termed as transactivation). The undesired adverse effects of glucocorticoids are mostly caused by transactivation. Transrepression, which is independent of GCR DNA interaction, is the main mechanism by which GCR exerts its anti-inflammatory actions. Topical corticosteroids have not been recommended for maintenance treatment in AD, mainly on nonlesional skin, because of concerns regarding possible adverse effects related with long use. Normal-appearing skin in AD, on the other hand, is linked to subclinical inflammation, indicating that anti-inflammatory medication on a long-term basis may be considered necessary to avoid recurrence (Berth-Jones et al. 2003).

Topical calcineurin inhibitors

Topical calcineurin inhibitors are immunosuppressive drugs that have been found to be effective and safe in the therapy of AD as well as the prevention of flare-ups (Broeders et al. 2016; Siegfried et al. 2016). Pimecrolimus and tacrolimus are second-line immunosuppressive drugs that decrease T-lymphocyte activation and prevent the transcription of genes that code for a variety of inflammatory cytokines (Hanifin et al. 2004). Pimecrolimus and tacrolimus both block calcineurin activation, a calcium-dependent phosphatase implicated in T lymphocyte signalling. Tacrolimus and pimecrolimus prevent T cells and mast cells from becoming activated, which is a crucial effector cell in AD. They are usually used for short-term or intermittent long-term treatment in people having moderate to severe atopic dermatitis, particularly when there is a risk of side effects like atrophy from long-term usage of topical corticosteroids (Fonacier et al. 2005; Berger et al. 2006). These medicines are especially beneficial for regions of thinner skin such as the neck, face and skin folds as they do not produce skin atrophy. Another advantage is that, even after lengthy treatment, they do not exhibit tachyphylaxis (a reduction in reaction to a medicine when it is administered frequently) (Werfel 2009). Tacrolimus and pimecrolimus have side effects as well; however, they are not as severe as those caused by topical corticosteroids. Skin burning and itching are the most typical local side effects. People who are taking topical calcineurin inhibitors should be advised on proper sun protection, which includes the use of sunscreen (Segal et al. 2013). Tacrolimus was found to be somewhat better effective than pimecrolimus in investigations evaluating their efficacy in the therapy of mild to severe atopic dermatitis. Pimecrolimus is an inferior corticosteroid than moderate or strong corticosteroids; however, there were not any research comparing it to mild corticosteroids. In adults, tacrolimus 0.1% has been proven to be as effective as a strong corticosteroid, and in children, it has been found to be better effective (at 0.1% or 0.03%) than a weak corticosteroid (Ashcroft et al. 2005, 2007).

Antibiotics

Staphylococcus aureus colonisation is prevalent in atopic dermatitis individuals; however, methicillin-resistant *S. aureus* colonisation is unusual. When a secondary bacterial infection occurs, topical and/or oral antibiotic therapy is advised for a short period of time. For extensive secondary infection, proper systemic antibiotics are necessary, and first- or second-generation cephalosporins or anti-staphylococcal penicillins for 7–10 days are usually successful in controlling the disease. Macrolides are less-effective alternatives since erythromycin-resistant organisms are widespread in patients with AD. Frequent viral infections are common in patients having AD. Eczema herpeticum (a severe disseminated herpes infection that usually appears at places of skin injury; also known as Kaposi's varicelliform eruption) is a considerable danger in individuals with extensive AD and is sometimes misinterpreted as a bacterial superinfection. Systemic antiviral therapy with acyclovir or other antiviral medications are required for patients with this disorder (Suh et al. 2008; Akdis et al. 2006; Błażewicz et al. 2017; Belloni and Neri 2015). In patients with severely colonised skin, diluted bleach showers are also advised to help minimise the amount of *S. aureus* skin infections and the necessity for systemic antibiotics. Diluted bleach showers include showering the patient for about 10 min in a tub filled with lukewarm water and one-quarter to one-half cup (60–120 mL) of chlorine bleach (concentration similar to that found in a pool). To avoid dehydration and dryness, the patient is properly cleansed with fresh water and a moisturiser or emollient is applied immediately. Some authors suggest taking diluted bleach baths twice a week for 3 months (Barnes and Greive 2013; Huang et al. 2009).

Antihistamines

Although first-generation antihistamines (e.g. diphenhydramine, hydroxyzine, chlorpheniramine) do not effectively decrease the itching related to AD, their sedative actions have been proven to assist individuals with the disease sleep better. However, these drugs have been shown to diminish REM sleep, impede learning and decrease work performance, and thus are not regularly suggested for individuals with AD. They could be used as a short-term adjunctive therapy for people who are having severe AD flare-ups and are having problems in sleeping or scratching during sleeping. Because of their sedative characteristics, long-term and/

or daytime usage of first-generation antihistamines must be avoided (Church et al. 2010; He et al. 2018).

Systemic immunosuppressive agents

Short-term treatment using systemic immunosuppressive drugs like azathioprine, cyclosporine and methotrexate has been found to be beneficial in people who have failed to respond to topical therapy; hence, these drugs are frequently prescribed for severe, resistant AD. Moreover, it is essential to remember that stopping cyclosporine can result in a rapid return of the condition. People using these immunosuppressive drugs should be observed for side effects like cyclosporine-induced kidney or liver dysfunction and azathioprine-induced myelosuppression. As a result, this type of therapy should be provided by specialist clinics or, ideally, hospital dermatology departments (Lee et al. 2016; Denby and Beck 2012; Arkwright et al. 2013).

Wet wrap therapy

Wet wrap therapy, which was first documented over two decades ago, involves applying dilute topical corticosteroids and emollients following a soaking bath, then by a layer of moist dressing or cloths, and finally dry garments. People having moderate to severe dermatitis who do not respond well to conventional skin treatment can benefit from wet wraps. Wet wraps moisturise the skin, keep it hydrated, decrease itching and enhance topical corticosteroid absorption. In clinical trials, wet wraps containing dilute topical corticosteroids proved successful at preventing flares and preserving control lasting many weeks. Wet wraps are reported to be effective in remission of AD in people having severe AD when used in conjunction with a regular skin care regimen over a 1-year period. Wet wraps can cause skin maceration, folliculitis and increased topical corticosteroid absorption; hence, they must be applied under medical supervision. Appropriate skin care is essential, during wet wrap therapies, especially with the liberal application of emollients (Nicol and Boguniewicz 2017; Devillers and Oranje 2006; Lee et al. 2007a, b; Schnopp et al. 2002; González-LG et al., 2017).

Phototherapy

The use of UV light to treat severe dermatitis is beneficial. Narrowband UVB light is especially effective for treating refractory dermatitis in adults. Severe refractory dermatitis can be treated with UVA light or a mixture of UVA light and the photosensitising medication psoralene. Phototherapy 3 to 5 times a week, particularly paired with topical corticosteroids, generally helps to clear challenging-to-treat atopic dermatitis in 1–2 months. Phototherapy is typically employed as a secondary- or tertiary-line therapy. However, phototherapy should be used with care because it promotes early ageing of the skin and enhances the chance of skin cancer in the long term (Gambichler et al. 2005; Kemény et al. 2019; Rodenbeck et al. 2016).

New therapies for atopic dermatitis

Emollients for dry skin, topical steroids and tacrolimus for skin inflammation, and oral antihistamines for pruritus are among the first-line therapies for AD, which are supplemented by second-line adjunct treatments like short-term oral steroids, systemic cyclosporine and UV radiation. Despite the fact that several studies confirm the effectiveness of traditional treatments, patient satisfaction and compliance to therapy are often poor in AD patients. Given significant advances in our knowledge of the pathomechanisms of Alzheimer's disease, there is room for innovative techniques and medicines in the treatment of the disease (Saeki et al 2016; Murota et al. 2015).

Dupilumab

For people having moderate atopic dermatitis, dupilumab is a potential therapeutic approach. It is the first biologic that has been licenced to treat atopic dermatitis. Dupilumab is a human monoclonal antibody that suppresses IL-4 and IL-13 signalling by binding with the receptor subunits IL-4R-alpha and IL-13R-alpha-1. As a result, it suppresses receptor signalling downstream of the JAK-STAT pathway by inhibiting signalling. It is an effective and safe therapeutic approach for people having moderate to severe atopic dermatitis who have failed to respond to topical treatments. A dupilumab effectively improves sleep disturbances and overall quality of life after 16 weeks of therapy. According to these results, dupilumab is a potential novel anti-inflammatory and antipruritic medication for AD (Seegräber et al. 2018; Simpson et al. 2016; Hendricks et al. 2021).

Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 (PDE4) inhibitors are a novel class of nonsteroidal anti-inflammatory drugs that are being studied for the therapy of Atopic dermatitis and psoriasis. Phosphodiesterase 4 is a major factor of inflammatory cytokine generation that changes cyclic adenosine monophosphate into 50–adenosine monophosphate, which stimulates proinflammatory reactions. PDE activity is elevated in people having AD, and inflammatory cytokines like interleukin (IL)-4, IL-13 and IL-31 are highly expressed. To enhance intracellular levels of cyclic adenosine monophosphate and inhibit the production of inflammatory mediators, cytokines, PDE is a potential target in AD. In experimental animals,

phosphodiesterase 4 inhibitors have immunosuppressive action by increasing the intracellular level of cyclic AMP and inhibiting IL-4 and tumour necrosis factor-alpha. Various topical PED-4 inhibitors, such as OPA-15406, E6005 and crisaborole, have shown efficacy in clinical studies to reduce inflammation and pruritus in AD. Although apremilast, an oral PDE-4 inhibitor, is efficacious in the prevention of AD and psoriasis, a greater dosage may be required in AD relative to psoriasis (Ahluwalia et al. 2017; Yang et al. 2019; Papier and Strowd 2018).

Janus kinase inhibitor

The JAK-STAT system is a key signalling pathway for numerous growth factors and cytokines; it is not astonishing that it plays a role in immunological development and inflammatory illness. JAK 1, JAK 2, JAK 3 and tyrosine kinase 2 are members of the JAK family, and their stimulation causes one or more members of the STAT family to become activated, which then causes cellular gene expression. JAK 1 and JAK 3 are required for cytokine signalling like IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21; however, JAK 2 and tyrosine kinase 2 are required for IL-12 and IL-23 signalling. The Th2 immune response is important in the development of atopic dermatitis, and IL-4 signalling is a crucial cytokine in Th2 differentiation. JAK 1, JAK 3 and STAT 6 mediate 3333333IL-4 signalling and hence could be used as therapeutic targets in AD (Levy et al. 2015). Oclacitinib, a JAK-1 inhibitor, blocks JAK1 of the JAK signal transducer and activator of transcription (JAK-STAT) system, which is involved in pro-inflammatory cytokine signalling in both dogs and people having AD. Ruxolitinib and tofacitinib are JAK inhibitors that have been licenced by the FDA for the therapy of myelofibrosis and rheumatoid and psoriatic arthritis, respectively. Tofacitinib is a JAK1 and JAK3 inhibitor that has been found to be effective in the therapy of atopic dermatitis when used topically and orally (Haugh et al. 2018).

Topical tropomyosin receptor kinase A inhibitor

Tropomyosin receptor kinase A (TrkA) is an NGF receptor with a great affinity. Nerve fibres positive for TrkA have been found in the epidermis, dermis and dorsal root ganglia of humans. A recent study by Takano et al. demonstrates that the repeated administrations of AG879 or K252a reduced nerve fibres in the epidermis while improving established dermatitis and itching behaviour (Takano et al. 2007).

Anti-IL-31 A receptor antibody (CIM331)

Another possible treatment for the atopic itch is an anti-IL-31 receptor A antibody. IL-31 is mostly formed by Th2 cells in humans and animals, and its cutaneous administration produces pruritus. According to recent clinical research, a single injection of an anti-IL-31 receptor A antibody (CIM331) dramatically reduces pruritus in individuals with moderate to severe AD for up to 4 weeks following delivery, with no dangerous side effects. CIM331 improves sleep quality and reduces the need for topical hydrocortisone butyrate. IL-31 receptor A, for example, is classified as a downstream molecule of FcεRI activation (Cevikbas et al. 2014; Nemoto et al. 2006; Yamaoka et al. 2009; Feld et al. 2016).

Conventional therapeutic approaches for atopic dermatitis.

Nanoparticles (NPs) are materials having a diameter of fewer than 100 nm that have been recommended for topical drug delivery in the treatment of skin disorders (Khan et al. 2019). Because of the site-specific distribution, NPs may help to decrease the side effects of traditional medications (e.g. topical corticosteroids), as the former has a better safety profile. NPs have also been recommended as a preferred way to improve skin bioavailability by addressing poor medication solubility and inadequate skin permeability. Different nanoparticles have been proposed for topical delivery of a variety of medications that are effective in atopic dermatitis, such as antibiotics and corticosteroids (Campos et al. 2021). NPs have the potential to improve medication penetration across the stratum corneum, improve drug retention time and create superior drug release profiles to achieve therapeutic aims. As a result, NP-based preparations may be a better option than traditional medication preparations. One of the most important benefits of NPs is the considerable decrease of serious side effects associated with poor patient compliance and, as a result, decreased therapeutic outcomes. Because of their compatibility with the lipid skin makeup, NPs made of lipid materials have exhibited significant benefits among the various NPs (Ramos Campos et al., 2020; Souto et al. 2019) (Table 2).

Patents and clinical status of therapeutic modalities of atopic dermatitis

Patent and related data were searched using analytics on the World Intellectual Property Organization's official website to assess and organise current work in the field of atopic dermatitis treatment from 2020 to 2021 (Table 3). Numerous innovative treatment approaches for atopic dermatitis are in different stages of clinical trials, with the primary goal of either treating the condition or investigating the development of immunity in people who are susceptible to it and a few of them are listed in Table 4 (https://clinicaltrials.gov).

Table 2 Conventional therapeutic approaches for atopic dermatitis

Drug (technique)	Excipients	Dosage form	Outcome and significance	Reference
Hydrocortisone (solvent displacement method)	Poloxamer 188, SLS, polydimethylsiloxane, disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dehydrate, poly(ε-caprolactone)	Drug PCL-nanoparticles [ointment]	Faster disease control and minimise the adverse effects associated to the long-term application	(Rosado et al. 2013)
Mizolastine (emulsification solvent evaporation method)	Poly(dl-lactide-co-glycolide)-methoxy-poly (ethyleneglycol) (PLGA-mPEG), polyvinyl alcohol, dichloromethane	Microparticles [injection]	Suppresses both the plasma level of immunoglobulin E and inflammatory cell infiltration into the ears	(Feng et al. 2015)
Phosphatidylserine (emulsification solvent evaporation method)	L-α Phosphatidylcholine, polyvinyl alcohol, poly(D,L-lactide)	Microparticle [injection]	Decrease in production of inflammatory cytokine	(Kumar et al. 2015)
Hydrocortisone and hydroxytyrosol (ionic cross-linking of CS with TPP using an ionic gelation method)	(TPP)-Pentasodium tripolyphosphate, (CS)-chitosan	Chitosan nanoparticles (CSNPs) [cream]	Bioavailability and accumulation of drug at the site of action improved and also a reduction in toxicity	(Siddique et al. 2016)
Hydroxytyrosol and hydrocortisone (ionic cross-linking of CS with TPP)	TPP, CS	CSNPs [cream]	HC–HT-NPs extensively accumulated both drugs in the dermal layers and successfully reduced erythema intensity, dermatitis index and TEWL as well as have the potential to reduce dermatosis signs and symptoms	(Hussain et al. 2013)
Tacrolimus (ionic gelation method)	Nicotinamide (NIC), chitosan, 1–chloro–2, 4–dinitrobenzene	NIC–CS–NPs [ointment]	Greatly improved permeation through and into the layers of skin and reduced dose for treatment as well as plays an adjuvant role in anti-AD	(Yu et al. 2018)
Hydrocortisone (ionic cross-linking of CS with TPP)	2,4-Dinitrofluorobenzene, CS	HC-loaded CS-NPs [cream]	Reduction in dermatitis index, inhibited fibroblast infiltration, inhibition of several immunopathological processes, like IgE synthesis and secretion, PGE2, histamine, VEGF, as well as other AD-related inflammatory mediators	(Hussain et al. 2014)
Levocetirizine (thin-film hydration method and ionic gelation method)	Carbopol 934, Span 20, dinitrochlorobenzene, Tween 40, cholesterol, Arabic gum, chitosan	Niosome and chitosan nanoparticles [gel]	Optimised niosomes gel had superior skin retention (30.24 ± 02.5%) compared to optimised chitosan nanoparticle gel (18.24 ± 3.2%) and traditional LCZD gel preparation (10 ± 2.8%). Significant decline in erythema index shown by optimised niosomes gel preparation compared to other two	(Pal et al. 2021)
Tacrolimus (hot high-pressure homogenisation method)	Glyceryl trimyristate, sorbitan monooleate, Carbopol 980, Tween 80	Lipid nanoparticles [gel]	Significantly improved penetration to the deeper layers of skin as well as higher drug accumulation	(Pople and Singh 2010)

Table 2 (continued)

Drug (technique)	Excipients	Dosage form	Outcome and significance	Reference
Tacrolimus (high-pressure homogenisation–evaporation method)	Hyaluronic acid, polyvinyl alcohol, chitosan	Polymeric nanoparticles [ointment]	In comparison to TCS-CS-NPs, HA-TCS-CS-NPs follow a sustained release pattern and exhibit excellent dermal targeting and therapeutic efficacy	(Zhuo et al. 2018)
Mometasone furoate (solvent injection method)	GMS, cetyl palmitate, Compritol 888, Syncrowax-HRC, Apifil, stearic acid, Tefose-63, Syncrowax-HGL, Tween-80, Phospholipon-80 H, Emulcire, soya lecithin, Carbopol 974p, methyl-paraben, propylparaben	SLNs [gel]	In comparison to marketed cream, skin permeability and skin deposition of SLN-loaded gel was found to be 15.21 times and 2.67 times greater respectively	(Madan et al. 2014)
Prednicarbate and prednisolone (high-pressure homogenisation either hot homogenisation technique or cold homogenisation technique)	Betamethasone, Precirol® phosphatidylcholine, Poloxamer 188, Compritol® 888 ATO, Witepsol®, sodium cholate, Dynasan ® 114	SLNs [cream]	Epidermal targeting produced by lipid nanoparticles potentially enhances the topical therapy's benefit-to-risk ratio	(Santos Maia et al., 2002)
Tretinoin (emulsification-solvent diffusion method)	GMS, Compritol 888, Dynasan 116, Carbopol® Ultrez 10, mono- and di-basic sodium phosphate, Carbopol® 940, xanthan gum, Carbopol® ETD 2020, Tween 80, Epikuron 200, Cutina CBS, Tween 20	SLNs [gel]	Compared to marketed preparations, SLN-based TRE gel showed improved topical delivery of TRE and also significantly less irritating to the skin	(Shah et al. 2007)
Isotretinoin (hot homogenisation method)	Soybean lecithin, Tween 80, Precirol ATO 5, Compritol 888, GMS	SLNs [cream]	As compared to control tincture, IT-SLN preparations avoid the systemic uptake in the skin and significantly improve the skin targeting effect	(Liu et al. 2007)
Betamethasone-17-valerate (hot high-pressure homogenisation)	Cetyl palmitate, Precirol® ATO 5, Polysorbate 80, Soluene® 350, 1-^{14}C tripalmitate, Hionic-Fluor	SLNs [ointment]	In comparison to the ointment, greater levels of drug molecule are retained in the skin, intact as well as barrier impaired, when SLN used as a vehicle and forms a depot of drug molecule in the stratum corneum	(Jensen et al. 2011)
Tacrolimus (modified emulsification and low temperature solidification.)	Cocoglyceride, Poloxamer 188, Brij® 93, Brij® 58, soybean lecithin	Thermosensitive SLNs [ointment]	Compared to the reference product, it penetrates deeper into the epidermal layers and delivers more drugs into deeper layers of skin	(Kang et al. 2019)
Halobetasol propionate (solvent injection method)	GMS, Tween 80, IPA, methyl and propylparaben	SLNs [gel]	Non-irritating to the skin, improved occlusivity, prolonged drug release, enhanced drug stability and encapsulation in comparison to a typical gel and a commercially available product	(Bikkad et al. 2014)

Table 2 (continued)

Drug (technique)	Excipients	Dosage form	Outcome and significance	Reference
Betamethasone valerate (high-pressure homogenisation–evaporation method)	Chitosan, hyaluronic acid, polyvinyl alcohol, mannitol	CS-NPs [ointment]	HA-BMV-CS-NPs showed a better-sustained release pattern, as well as greater drug retention capacity than uncoated BMV-CS-NPs, but the efficiency of drug permeation of BMV was greater in the case of BMV-CS-NPs than HA-BMV-CS-NPs	(Pandey et al. 2019)
Oat-ceramides (emulsification solvent evaporation method)	Soybean GlcCER, Euxyl® PE 9010, Miglyol® 812, Carbopol®980, 1,2-Pentanediol, Phosal®75 SA, silica gel 60, Pluronic® F-127	Lecithin-based microemulsions (MEs) and starch-based nanoparticles (NPs) [gel]	ME gel increases the permeation of oat CERs in comparison to NP gel into the deeper layer of the skin	(Tessema et al. 2018)
Hydrocortisone (modified solvent displacement method)	Poloxamer 188, Polysorbate 80, methylparaben, PCL, cetyl alcohol, SLS, propylparaben, PDMS, stearic acid	Poly(ε-caprolactone) NPs [ointment]	Controlled release of the drug, after encapsulation no drug toxicity effects and significant variations in the permeation of encapsulated and free hydrocortisone	(Rosado et al. 2013)
Cyclosporin A (hot homogenisation method)	l-α-Phosphatidylcholine, Tween 80, DSPE-PEG, Ticaprin	Drug-loaded SLNs [cream]	CsA-loaded SLN on topical application penetrates effectively into both the SC and viable skin region in comparison to CsA-oil mixture	(Kim et al. 2009)
Cobalamin (thin-film hydration method via a pH gradient method)	Cholesterol, Carbopol® 940, disodium EDTA, DNCB, TEA, L-α-phosphatidylcholine, hydroxyethylcellulose	AdCbl-loaded liposomes [gel]	Better therapeutic efficacy against murine AD	(Jung et al. 2011)
Advanced adipose stem cell–derived protein extract (evaporation on 'matrix' method)	Soy phosphatidyl choline, Poloxamer 407, sorbitol, bovine serum albumin	Proliposomes [powder]	On topical application of AAPE proliposome. Significant decrease in IgE concentrations and potential for the treatment of AD	(Jahn et al. 2014)
Cetirizine dihydrochloride (thin-film hydration method with slight modification)	Phospholipon 90G, Span 80, Tween 80, stearylamine, cetyl alcohol, Carbopol 980, cetyl alcohol, TEA, GMS, isopropyl myristate	Elastic vesicles [gel]	Greatly effective in lowering the itch index, non-toxic, and safe for skin	(Goindi et al. 2013)
Silver (high-pressure hot melt homogenisation.)	Cetyl palmitate, inulin lauryl carbamate, hemp seed oil, Tego Care 450®	NLCs [cream]	Reduce/mitigate atopic dermatitis symptoms as well as restoration of skin condition	(Keck and Schwabe, 2009)
Tacrolimus (titration method)	Capmul MCM C8, Transcutol P, Tween 80	Microemulsion [cream]	Improved drug penetration, decrease in inflammatory cytokine expression, greater drug retention in the skin in comparison to conventional preparations	(Lalan et al. 2012)

Table 3 Published patent literature about atopic dermatitis therapies

Patent name	Patent number	Applicant	Publication date	Reference
Palatable formulations	NZ779157	Zoetis Services LLC	27.08.2021	Cunningham et al. 2021
Formulations of human anti-TSLP antibodies and methods of treating inflammatory disease	WO2021163504	Amgen Inc. [US]/[US]	19.08.2021	Lueras et al. 2021
Topical composition comprising tofacitinib and fingolimod	WO2021138525	Vyne Pharmaceuticals Ltd. [IL]/[IL]; Elliott, Russell [US]/[US]; Hazot, Yohan [IL]/[IL]; WINCKLE, Gareth [GB]/[FR]; Margulis, Ariel [IL]/[IL]	08.07.2021	Elliott et al. 2021
Topical formulations comprising montelukast and combinations with mussel adhesive proteins	US20210145819	Jiangyin Mucocare Pharmaceutical Co., Ltd	20.05.2021	and Ming, 2021
Peptide immunogens of IL-31 and formulations thereof for the treatment and/or prevention of atopic dermatitis	US20210079054	UBI US Holdings, LLC	18.03.2021	Chang Yi Wang 2021
Cerdulatinib-containing topical skin pharmaceutical compositions and uses thereof	US20200390689	Dermavant Sciences GmbH	17.12.2020	Charles et al. 2020a, b, c, d, e
Cerdulatinib-containing topical skin pharmaceutical compositions and uses thereof	EP3737354	Dermavant Sciences GMBH	18.11.2020	Charles et al. 2020a, b, c, d, e
Cerdulatinib-containing topical skin pharmaceutical compositions and uses thereof	CN111818910	Dermavant Sciences GMBH	23.10.2020	Charles et al. 2020a, b, c, d, e
Peptide immunogens of IL-31 and formulations thereof for the treatment and/or prevention of atopic dermatitis	EP3724218	UBI IP Holdings	21.10.2020	Chang Yi Wang 2020
Peptide immunogens of IL-31 and formulations thereof for the treatment and/or prevention of atopic dermatitis	IN202017024485	UBI IP Holdings, UBI US Holdings, LLC	02.10.2020	Wang, Chang Yi., 2020a
Fenoldopam topical formulations for treating skin disorders	IN201927011937	Taro Pharmaceutical Industries Ltd.; Yissum Research Development Company of the Hebrew University of Jerusalem Ltd	02.10.2020	Khan et al. 2020
Cerdulatinib-containing topical skin pharmaceutical compositions and uses thereof	IN202017032069	Dermavant Sciences GMBH	18.09.2020	Charles et al. 2020a, b, c, d, e
Nanocrystals based formulations for improved topical delivery of Apremilast	IN201911003539	National Institute of Pharmaceutical Education and Research (NIPER)	28.08.2020	Arvind Kumar Bansal and Prashant kumar Khodabhai Parma 2020
Palatable formulations	WO2020172232	Zoetis Services LLC [US]/[US]	27.08.2020	Singh et al., 2020
Combined multistage microbial preparations and method of their application	US20200254030	BiomCare S.R.O	13.08.2020	Karel et al. 2020
Combined multistage microbial preparations and method of their application	EP3692980	BiomCare S.R.O	12.08.2020	Karel et al. 2020
Cerdulatinib-containing topical skin pharmaceutical compositions and uses thereof	NZ765501	Dermavant Sciences GMBH	31.07.2020	Charles et al. 2020a, b, c, d, e
Peptide immunogens of IL-31 and formulations thereof for the treatment and/or prevention of atopic dermatitis	SG11202005526W	UBI IP Holdings	29.07.2020	Wang and Chang Yi 2020
Cerdulatinib-containing topical skin pharmaceutical compositions and uses thereof	SG11202005781W	Dermavant Sciences GMBH	29.07.2020	Charles et al. 2020a, b, c, d, e
Peptide immunogens of IL-31 and formulations thereof for the treatment and/or prevention of atopic dermatitis	CN111448208	UBI US Holdings LLC.; UBI IP Holdings	24.07.2020	Wang, Chang Yi., 2020a
New formulations containing leukotriene receptor antagonists	WO2020143744	Jiangyin Mucocare Pharmaceutical Co., Ltd. [CN]/[CN]	16.07.2020	Samuelsson, 2020
Pharmaceutical cream compositions and methods of use	US20200188517	Epi Health, LLC	18.06.2020	Shanler et al., 2020
Topical formulations comprising montelukast and combinations with mussel adhesive proteins	EP3648767	Jiangyin Mucocare Pharmaceutical Co Ltd	13.05.2020	Samuelsson, 2020
Composition for preventing or alleviating atopic dermatitis and method for manufacturing same	KR1020200029981	Sim, Je Duk	19.03.2020	Sim, 2020
Formulations, methods, kits and dosage forms for treating atopic dermatitis and for improved stability of an active pharmaceutical ingredient	EP3615032	Asana Biosciences LLC	04.03.2020	Railkar et al., 2020
Formulations, methods, kits and dosage forms for treating atopic dermatitis and for improved stability of an active pharmaceutical ingredient	CN110809471	Asana Biosciences LLC	18.02.2020	Railkar et al., 2020
Topical formulations comprising montelukast and combinations with mussel adhesive proteins	SG11201911841P	Jiangyin Mucocare Pharmaceutical Co Ltd	30.01.2020	Samuelsson, 2020

Table 4 Clinical status of in-progress treatment strategies for atopic dermatitis

Study title	Sponsor	NCT no	Phase
Efficacy, Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Study of the Topical Formulation SB011 Applied to Lesional Skin in Patients with Atopic Eczema	Sterna Biologicals GmbH & Co. KG	NCT02079688	Phase 2
Bioequivalence of Two Tacrolimus 0.1% Topical Ointment Formulations in Patients with Atopic Dermatitis	Taro Pharmaceuticals USA	NCT00833079	Phase 1
The Effectiveness of a Topical Palmitoylethanolamide (PEA) Formulation (Levagen+) for Reducing Symptoms of Eczema	RDC Clinical Pty Ltd	NCT05003453	Phase 2 Phase 3
Efficacy and Tolerability of New Topical Formulations in Subjects with Atopic Dermatitis	Procter & Gamble Beauty	NCT02732314	Phase 4
Safety, Efficacy and Pharmacokinetic Study of Allegra in Pediatric Patients with Atopic Dermatitis (AD)	Sanofi	NCT01244230	Phase 2 Phase 3
VANOS Cream and Skin Barrier Function	Oregon Health and Science University	NCT00819507	Phase 4
Single Dose and Multiple Dose Study to Assess Safety and Tolerability of LOU064	Novartis Pharmaceuticals	NCT03918980	Phase 1
A Phase I Study to Assess the Safety and Tolerability of Topical CRx-197 Formulations in Healthy Volunteers	Zalicus	NCT00721331	Phase 1
A Study to Test the Effect of 2 Different Doses of Topical GW870086X on Atopic Dermatitis Also Including a Postive Control and a Placebo	GlaxoSmithKline	NCT01299610	Phase 2
A Trial of a Botanical Drug Containing East Indian Sandalwood Oil (EISO) For Treatment of Atopic Dermatitis	Santalis Pharmaceuticals, Inc	NCT02871479	Phase 2
Topical GW842470X In Adults Patients with Moderate Atopic Dermatitis	GlaxoSmithKline	NCT00354510	Phase 2
A Phase 1 Trial of OPA-15406 Ointment in Healthy Adult Male Subjects	Otsuka Pharmaceutical Co., Ltd	NCT02334787	Phase 1
Safety and Efficacy of DNK333 in Atopic Dermatitis Patients	Novartis Pharmaceuticals	NCT01033097	Phase 2
Evaluate Efficacy, PK, and Safety of FB825 in Adults with Atopic Dermatitis	Oneness Biotech Co., Ltd	NCT04413942	Phase 2
Topical Steroid Formulation and Wet Wraps	Seton Healthcare Family	NCT02680301	Phase 4
Assessment of the Effects on Barrier Impairment, Clinical Features and Bacterial Colonization of Topical Formulations in Patients with Atopic Eczema; a Phase IIa, Single-center, Randomized, Observer-blind Study	Moberg Pharma AB	NCT00863005	Phase 1 Phase 2
Study to Investigate Skin Conditions and Patient Assessment of LAS 41,002 in the Treatment of Atopic Eczema	Almirall, S.A	NCT01119313	Phase 2
Safety, Tolerability, Pharmacokinetics and Efficacy of WOL071-007 in Atopic Dermatitis Patients	Dr. August Wolff GmbH & Co. KG Arzneimittel	NCT02576093	Phase 1
Dose Ranging Study to Assess Efficacy, Safety, Tolerability and Pharmacokinetics of PF-06700841 Topical Cream in Participants with Mild or Moderate Atopic Dermatitis	Pfizer	NCT03903822	Phase 2
A Phase 2 Study of PH-10 for the Treatment of Atopic Dermatitis	Provectus Pharmaceuticals	NCT00690807	Phase 2
Study of the Safety, Tolerability and Efficacy of BTX 1204 in Patients with Moderate Atopic Dermatitis	Botanix Pharmaceuticals	NCT03824405	Phase 2
Skin Tolerance Study of Betamethasone Creams in Atopic Eczema and the Preventative Properties of a Moisturiser	ACO Hud Nordic AB	NCT00576238	Phase 3
A Study to Evaluate the Safety and Tolerability of MOR106 Administered Concomitantly with Topical Corticosteroids, in Adult Participants with Moderate to Severe Atopic Dermatitis (GECKO)	Galapagos NV	NCT03864627	Phase 2
A Phase II Study of Bermekimab (MABp1) in Patients with Moderate to Severe Atopic Dermatitis	Janssen Research & Development, LLC	NCT03496974	Phase 2
To Assess the Safety and Activity of GBR 830, Compared to Placebo, in Adults with Moderate-to-severe Atopic Dermatitis	Ichnos Sciences SA	NCT02683928	Phase 2
Effect of Dupilumab (Anti-IL4Rα) on the Host-Microbe Interface in Atopic Dermatitis	National Institute of Allergy and Infectious Diseases (NIAID)	NCT03389893	Phase 4

Table 4 (continued)

Study title	Sponsor	NCT no	Phase
Tralokinumab in Combination with Topical Corticosteroids for Moderate to Severe Atopic Dermatitis—ECZTRA 3	LEO Pharma	NCT03363854	Phase 3
Tralokinumab in Combination with Topical Corticosteroids in Subjects with Severe Atopic Dermatitis Who Are Not Adequately Controlled With or Have Contraindications to Oral Cyclosporine A (ECZTRA 7)	LEO Pharma	NCT03761537	Phase 3
Tralokinumab Monotherapy for Moderate to Severe Atopic Dermatitis—ECZTRA 2 (ECZema TRAlokinumab Trial no. 2) (ECZTRA 2)	LEO Pharma	NCT03160885	Phase 3
Tralokinumab Monotherapy for Moderate to Severe Atopic Dermatitis—ECZTRA 1 (ECZema TRAlokinumab Trial no. 1) (ECZTRA 1)	LEO Pharma	NCT03131648	Phase 3
Topical NanoDox® for Atopic Dermatitis	University of Florida	NCT02910011	Phase 2
Tralokinumab in Combination with Topical Corticosteroids in Japanese Subjects with Moderate-to-severe Atopic Dermatitis (ECZTRA 8)	LEO Pharma	NCT04587453	Phase 3
Vaccine Responses in Tralokinumab-Treated Atopic Dermatitis—ECZTRA 5 (ECZema TRAlokinumab Trial No. 5) (ECZTRA 5)	LEO Pharma	NCT03562377	Phase 2
A Study Evaluating Relative Bioavailability of an Oral Suspension of Abrocitinib and Effect of an Acid Reducing Agent on the Bioavailability of Abrocitinib and Assessing the Taste of Abrocitinib Oral Formulations	Pfizer	NCT04903093	Phase 1
A Single Dose Phase I Exploratory Study in Healthy Volunteers with GSK2894512 Cream	Stiefel, a GSK Company	NCT02411162	Phase 1
Drug-drug Interaction Trial with Tralokinumab in Moderate to Severe Atopic Dermatitis—ECZTRA 4	LEO Pharma	NCT03556592	Phase 1
Study of Commercial and Phase 3 of PF-04965842 Formulations, Estimation of Effect of Food on Commercial Formulation	Pfizer	NCT04065633	Phase 1
A Study Assessing GW870086's Potential to Cause Skin Thinning	GlaxoSmithKline	NCT01381445	Phase 1

Conclusion

Atopic dermatitis is a prevalent chronic skin disorder that begins in early childhood and has a negative influence on patients' and caretakers' quality of life. The cornerstones of treatment for the condition are optimal skincare techniques and topical corticosteroids. In patients who are susceptible to common flare-ups, TCIs have been demonstrated to be an effective second-line alternative to topical corticosteroids. In extreme cases where adequate skincare and topical medications have failed to control the condition, systemic immunosuppressive drugs may be used. Allergy testing to foods and aeroallergens may be recommended depending on the patient's medical history and/or if the patient showing a poor response to proper skincare and pharmaceutical treatment. A variety of biologics, including dupilumab, are being studied in atopic dermatitis and could be potential future alternatives for treating this terrible skin disorder.

Future perspectives

The development of better and safer medications for the treatment of AD would be our future challenge. Because of the complexity of the immunological mechanisms that contribute to atopic disease, it is possible that the more targeted anti-inflammatory or immunomodulatory drugs will be ineffective. As a result, it is essential to better describe the major immunological mechanisms that contribute to the various phenotypes of AD, as drugs for treating various kinds of AD may differ in their efficacy. It is crucial to figure out whether the immunological pathways that contribute to intrinsic (or pure) vs. extrinsic (IgE-mediated) AD are significantly different. The role of IgE in allergy illness is still a point of discussion. IgE-knockout mice can develop allergy models in the lab. At relatively low allergen levels in the environment, this molecule may mainly function to promote allergen processing for Th2 cell activation and quick response. Immune reactions to allergens may exist in the absence of IgE in intrinsic AD, although in

the absence of an immediate reaction, larger allergen concentrations are required for T cell activation. Atopy patch tests can be positive in a subset of Atopic patients who do not have IgE reactions to the allergen. Further research is needed to determine the relative roles of microorganisms and autoantigens in the onset and development of AD. Better definitions for the various clinical phenotypes of AD are likely to be required in the future, including the identification of susceptibility genes that contribute to the various kinds of AD and the delineation of the relative role of immunoregulatory abnormalities and structural epidermal barrier defects underlying AD skin. Immunosuppressive macrolides, ultraviolet therapy and corticosteroids are all helpful and beneficial in regulating complicated inflammatory processes of chronic AD. Future research should focus on measures to prevent the progression of atopic dermatitis. Considering the significance of TH2 cytokines and chemokines in the progression of allergic skin inflammation, efforts aimed at lowering TH2 responses and inhibiting chemokine action with the chemokine receptor CCR3 and CCR4 antagonists will therefore be essential. Additional research is required to determine how IL-12, IL-18 and IFN-γ contribute to restoring the shift towards a more balanced TH0 response involving equal secretion of TH1 and TH2 cytokines. Novel therapeutic approaches are required to prevent AD from progressing to more severe types of this skin condition and to prevent the so-called atopic march, which leads to asthma development. The elements that influence the disease's chronicity, skin remodelling and natural history are still unknown. The advancement of pharmacogenetics and the targeting of efficacious medicines to several phenotypes of AD will be linked to an identification of the genes essential for individual variance in response to medication.

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