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MINIREVIEWS

Atopic eczema treatment now and in the future: Targeting the skin barrier and key immune mechanisms in human skin

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Abstract

The skin facilitates a number of key roles but its functioning can be impaired by disease. Atopic eczema is a chronic inflammatory disease where the skin barrier has become leaky, and inflammation occurs. It affects up to 20% of children and 3% of adults worldwide, manifesting as red itchy patches of skin with varying severity. This review aims to investigate the leaky skin barrier and immune mechanisms from the perspective of potential novel treatments. The complexity of atopic eczema as a disease is what makes it difficult to treat. Genome-wide association studies have highlighted possible genetic variations associated with atopic eczema, however in some cases, individuals develop the disease without these genetic risk factors. Loss of function mutations in the filaggrin gene are one of these associations and this is plausible due to its key role in barrier function. The Th2 immune response is the link with regards to the immune mechanisms as atopic inflammation often occurs through increased levels of interleukin (IL)-4 and IL-13. Eczematous inflammation also creates susceptibility to colonisation and damage by bacteria such as Staphylococcus aureus. Potential novel treatments are becoming ever more specific, offering the hope of fewer side effects and better disease control. The best new treatments highlighted in this review target the immune response with human beta defensin 2, phosphodiesterase-4 inhibitors and monoclonal antibodies all showing promise.

Key words: Atopic eczema; Novel treatment; Filaggrin; Skin barrier; Immune dysfunction

Core tip: Atopic eczema (atopic dermatitis) is an itchy inflammatory skin disease with complex aetiology, including impairment in barrier function and concomitant inflammation. Increased understanding of the molecular

mechanisms in eczema pathogenesis has opened up opportunities for new therapeutic targets. This review summaries current understanding and highlights some novel treatments in development.

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INTRODUCTION

Atopic eczema is a prevalent disease with substantial morbidity

Atopic eczema (also called atopic dermatitis) is a skin disease that has shown a rise in prevalence in Africa, Eastern Asia and Western Europe[1]. It is a chronic inflammatory disease that manifests as red patches of itchy skin and in severe cases excoriated or infected lesions[2]. Inflammation is believed to occur when the skin barrier becomes leaky and an immune response is stimulated; *vice versa*, the inflammatory response can itself impair the skin barrier function[3].

There are two forms of eczema: Atopic, when an increased IgE response occurs, and non-atopic when this response is not observed. Eighty percent of cases are atopic[4] and the feature of atopy (raised IgE) is what relates the disease to other allergic responses such as food allergies, allergic rhinitis and asthma which can all show an IgE response. The so-called "atopic march" describes the progressive acquisition of atopic diseases in a step-wise manner throughout childhood[5]. Therefore children affected by one atopic disease will often show phenotypes of the others too[5]. Atopic eczema is predominantly a childhood disease that affects up to 20% of children[6] and this is one of the reasons why it is among the most common skin diseases worldwide[2]. In the 2010 WHO article into the global burden skin diseases, atopic eczema was ranked first by causing the most number of days that people were not at full health[7]. The effects of atopic eczema are not limited to skin. Children with more extreme atopic eczema suffer from reduced sleep and increased psychological problems[8]. Atopic eczema not only has a large effect on the health of the sufferer but it also has a substantial economic effect. In the United States, the direct cost for the treatment of atopic eczema may be as high as $3.8 billion per year[9], studies in the United Kingdom are not recent enough to compare as one of the most recent was in 1996[10,11]. This shows from an economic stance that research into a more cost effective treatment is of great importance.

Atopic eczema is a complex trait and current treatment options are sub-optimal

The development of specific treatment modalities in atopic eczema is difficult due to the complexity of this disease. For example, there are a number of strong genetic risk factors associated with the disease and variations in these genes are often seen in atopic eczema; however in a subset of cases, a mutation is present but there is no disease[12]. Another feature involved with atopic eczema is environmental allergens such as dust or animal hair which can precipitate the disease or elicit a flare up. Therefore the disease is now believed to be caused by a combination of both genetic and environmental factors[13]; this complexity is why treatments are only partially effective and why there is currently no cure[14].

Atopic eczema arises due to interactions between a leaky skin barrier and the immune response that occurs both in the skin and the systemic circulation; therefore current treatments aim to reduce the inflammation and repair the skin barrier at sites of inflamed or dry skin. Due to the complexity and range of severity of the disease, there are a number of different treatments[15]. These have been summarised in Figure 1. The most commonly used treatment is the application of emollients; these act by increasing the lipid content in the stratum corneum (outermost layer of the skin) to repair the barrier, thereby improving hydration[15]. However, in all but the mildest cases emollients are insufficiently effective so a combination therapy is used with another agent targeting the inflammatory response. Topical corticosteroids act through the corticosteroid-receptor complex to downregulate synthesis of the proteins involved in inflammation[16]. Topical corticosteroids come in different forms from sprays to creams and ointments but more potent steroids must be used sparingly as they have been found to reduce dermal thickness[17]. Topical calcineurin inhibitors also target the immune mechanisms and act by binding to intracellular protein macrophilin-12, thereby decreasing the production of inflammatory cytokines interleukin (IL)-4 and IL-13; this treatment does not decrease dermal thickness[18,19].

Other treatments include wet-wraps[15,20], oral antihistamines[13] and phototherapy[21] where ultraviolet light is administered to the skin for its immunosuppressive effect. Atopic eczema sufferers frequently have to undergo two or more treatments (Figure 1), one for the disease itself and the other for co-existent bacterial or viral infection[22].

Staphylococcus aureus (*S. aureus*) is a bacterium that may be carried in the nose and flexural skin of some individuals and on the apparently healthy skin of atopic individuals. In individuals with atopic eczema it can cause infections within actively inflamed lesions and lead to increased skin barrier damage[22]. There is a more permissive environment for the growth of *S. aureus* because atopic skin shows a reduction in the expression of antimicrobial peptides[23]. Topical corticosteroids have been found to reduce the colonisation by *S. aureus*[24], but the most effective treatment involves combining these topical corticosteroids with an antimicrobial preparation[25]. However, this combination therapy only shows

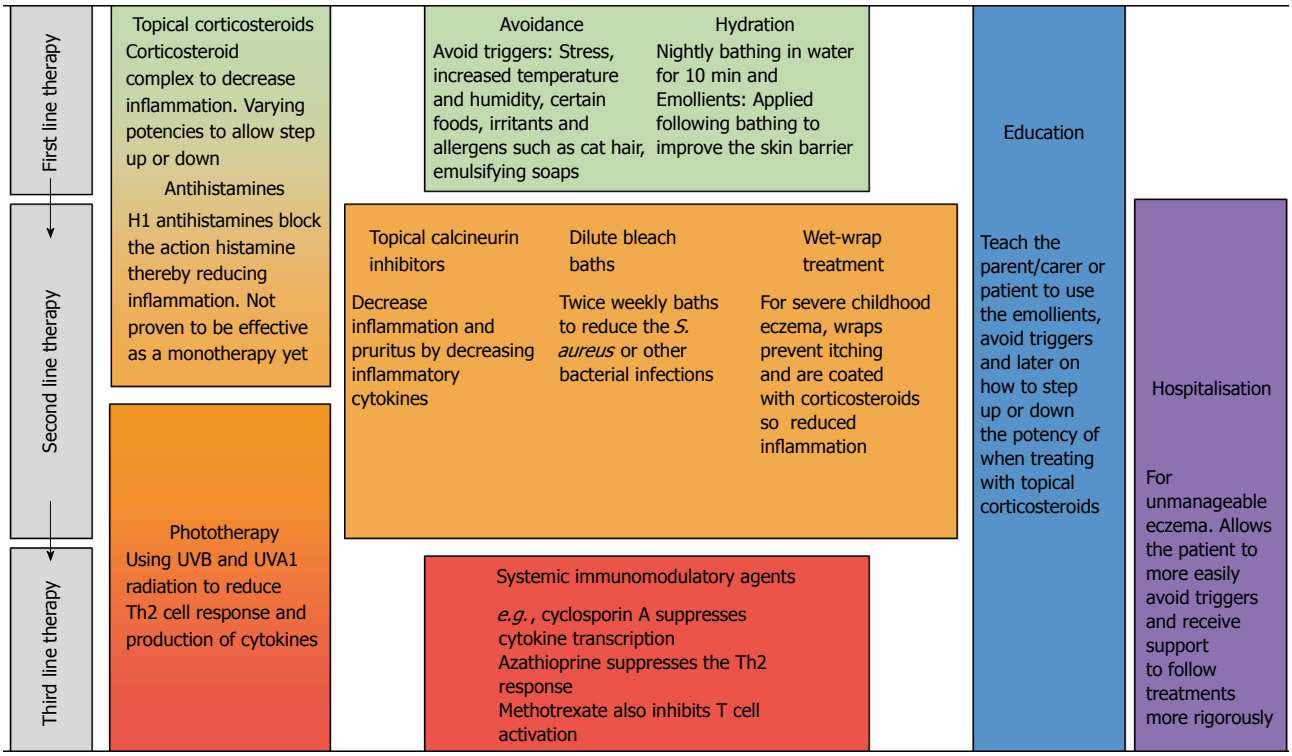

Figure 1 Current treatment options for atopic eczema. A summary of current treatment for atopic eczema, showing stepwise progression for more severe or treatment-resistant disease[13,15-18,20,21].

efficacy in the short-term as over a long period there is no significant benefit in comparison to corticosteroids alone. Therefore a more effective treatment is required to prevent *S. aureus* re-infection.

The stepwise approach to treating atopic eczema, shown in Figure 1, highlights the varying severity in this disease. It also illustrates the range of treatments in use, because of the variation in individual response to each therapy. The currently available treatments target atopic eczema in a rather non-specific way; it is hoped that novel treatments, such as monoclonal antibodies, will be able to target the specific problem(s) in each individual's atopic eczema.

WHAT IS KNOWN ABOUT BARRIER FUNCTION AND IMMUNE MECHANISMS IN ATOPIC SKIN?

This review will focus on the skin barrier and the immune mechanisms of the skin and how irregular function of both lead to atopic eczema, as well as the novel and theoretical treatments designed for targeting each component of the disease.

The skin barrier plays an essential role in protecting the body against the entry of allergens and loss of water

The skin is the largest organ in the body[26] and it plays a number of key roles in survival. A central function is to act as a physical barrier to prevent the entry of allergens and irritants while also vitally retaining water within the body[4]. The skin is composed of three main layers: epidermis, dermis and hypodermis[27]. The outermost layer of the epidermis is called the stratum corneum (Figure 2); this contributes to the control of trans-epidermal water loss (TEWL)[28], *i.e.,* water lost through evaporation. The stratum corneum includes 18-20 layers constructed from dead cells containing keratin called corneocytes; this is surrounded by a matrix of lipids mainly consisting of ceramides and cholesterol[29]. The epidermis provides the physical skin barrier function through the matrix of lipids but also through corneodesmosomes and tight junctions with the stratum granulosum layer below[29].

An essential component of the barrier function of the skin is filaggrin (filament-aggregating protein), an intracellular protein[30] important for formation of the stratum corneum[31]. Filaggrin is formed from the dephosphorylation and proteolysis of profilaggrin when the keratinocytes in the stratum granulosum are undergoing differentiation to the corneocytes of the stratum corneum[32]. Filaggrin monomers bind to keratin molecules to strengthen the filament network and contribute to the changes in shape of keratinocytes as they mature into corneocytes. Filaggrin also plays a key role in control of TEWL. Filaggrin undergoes proteolysis to release hygroscopic amino acids at the surface of the stratum corneum, when the outer skin starts to become dehydrated. These amino acids contribute to natural moisturising factor (NMF) for the skin, maintaining hydration of the stratum corneum and controlling TEWL[33]. Another key role played by filaggrin

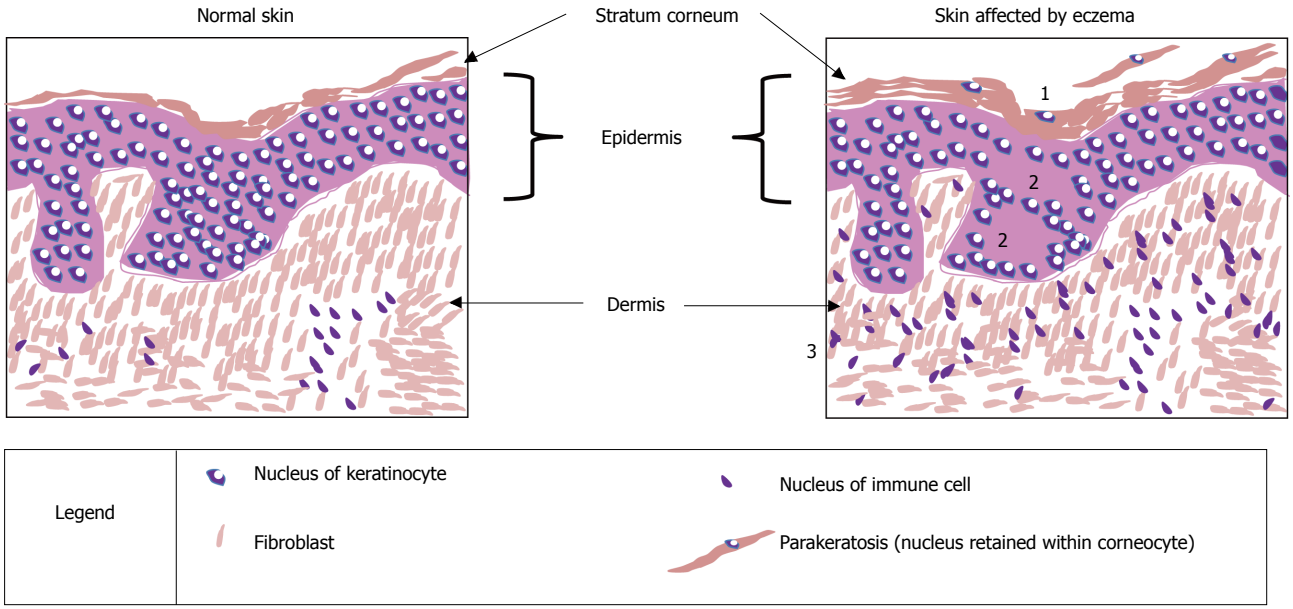

Figure 2 Histological features of atopic eczema. This figure represents sections of skin biopsies, stained with haematoxylin and eosin, to highlight the changes that can be observed under a light microscope, comparing skin affected by atopic eczema and a control sample. Three characteristic features of atopic eczema are illustrated: Increased thickness of the stratum corneum (hyperkeratosis and parakeratosis) is caused by a disruption to the cornification process; spongiosis occurs when there is a reduction or damage of the proteins involved in tight junctions, thereby leading to uncontrolled movement of fluids in the paracellular space; infiltration of the dermis by immune cells is a sign of the immune response as a primary feature of atopic eczema itself or in response to the entry of allergens through a leaky skin barrier. The effects of eczema: 1: Increased thickness of stratum corneum; 2: Spongiosis - oedema (water retained between cells); 3: Increased number of immune cells.

and its degradation products is in the control of skin pH. The acidic pH of skin acts as an antimicrobial defensive mechanism to limit bacterial colonisation[34]. If the pH of the skin is increased, filaggrin proteolysis can contribute acidic amino acids to return it to the optimal slightly acidic pH[34].

Tight junctions hold the keratinocytes together, control the flow of fluids paracellularly and are key as they act as another barrier; the stratum corenum acts as the first physical barrier to allergens and irritants while tight junctions form the second[35]. This barrier is particularly important if the stratum corneum becomes diseased, since the tight junctions provide a second line of defence against allergens, to prevent their entry into the skin and the resultant immune response.

Atopic eczema has profound effects on the skin barrier of an affected individual

The difficulty in describing the causes of atopic eczema are that the mutations or genetic variants being proposed as the culprits of the skin barrier dysfunction only occur in a proportion of affected individuals. There have been a number of genetic studies aiming to highlight potential risk factors for atopic eczema; they have discovered links between certain mutations or genetic variants that are associated with increased risk for the disease[36-40]. The majority of candidate gene association studies point to null mutations in the filaggrin gene, *FLG*, and genes involved with the type 2 T helper lymphocytes (Th2 cell) function[41,42]. Loss of function mutations in *FLG* were first identified in 2006 and this remains the strongest genetic risk factor for atopic eczema identified to date[43].

The section above highlighted the importance of the protein filaggrin in a number of key roles involved with producing the skin barrier; therefore it is understandable that a loss of function mutation in *FLG* may increase the risk of atopic eczema. Other related diseases such as ichthyosis vulgaris, atopic asthma, allergic rhinitis and food allergies are also often associated with mutations in filaggrin[44]. Filaggrin is key in cross-linking keratins to flatten the shape of cells, in the stratum corneum; consequently null mutations will lead to malformed corneocytes and allergens may be able to enter through this leaky skin barrier and incite an inflammatory response[26]. In atopic eczema there is an increased rate of TEWL and again it is possible that filaggrin may play a role, as null mutations mean filaggrin cannot be degraded to form NMF, hence skin hydration is reduced[26]. Another often vital part of the disease is the colonisation by bacteria and this is more likely to occur in the alkaline conditions of the skin when filaggrin is absent or reduced in amount[45]. This is one of possibly several factors that allows binding of bacteria such as *S. aureus*, and it can contribute to the development of atopic eczema or worsen its severity[46]. The main mechanism by which *S. aureus* damages the skin barrier is through secretion of SspA/V8 protease. This protease acts to degrade the proteins in the corneodesmosomes in the stratum corneum but also proteins in the tight junctions of the stratum granulosum, thereby compromising both elements of the skin barrier and allowing entry of allergens and irritants[47,48].

In some cases of atopic eczema it has been shown that key proteins involved with tight junction function, claudin-1 and claudin-23, are reduced[35]. It was believed that mutations in the filaggrin gene may also affect tight junction functionality, however mouse models demonstrated that filaggrin insufficiency did not have a direct effect[49]. Other mouse models have demonstrated the importance of claudin-1 in maintaining normal levels of TEWL: When mice lack this protein, they die within a day[50]. On closer inspection, it was observed that claudin-deficient mice died of dehydration as a result of increased TEWL and this was due to non-functioning tight junctions[50]. Therefore, the reduction in claudin-1 seen in atopic eczema patients may contribute to their increased TEWL and dry skin. Tight junctions are vital for paracellular control of fluids, as well acting as a physical barrier, and what is often observed with atopic eczema is spongiosis, where oedema is occurring between the keratinocytes in the epidermis (Figure 2).

Another characteristic of atopic eczema which can be seen as scaliness (white flaky skin) when directly observing the skin, or by light microscopy of a histological section of diseased skin, is an increased thickness of the stratum corneum[51]. Normally epidermal cells undergo transformation from keratinocytes of the stratum basale, in the lower epidermis, to corneocytes of the stratum corneum, in the upper epidermis, and begin to shed off the skin; however in atopic eczema this cornification process is disrupted[52]. In atopic eczema the keratinocytes retain their nucleus and remain attached instead of shedding, contributing to the thickened stratum corneum. This feature can also be seen in Figure 2.

Immune dysfunction plays a key role in eczema pathogenesis

The balance of immune mechanisms in the skin is a closely regulated process, which involves a number of different immune and non-immune cells interacting to protect the body from pathogens[53]. However, this balance is susceptible to a number of diseases. Above, we have mostly described how skin barrier dysfunction leads to an increased immune response thereby causing atopic eczema; nevertheless the disease may also be caused by immune dysfunction leading to skin barrier damage. It has been demonstrated that IL-4 and IL-13, the two cytokines that are greatly increased in atopic eczema, are able to significantly decrease the expression of filaggrin[54]. When IL-4 and IL-13 were incubated with keratinocytes for 24 h they decrease the expression of filaggrin[54]. Hence these two interleukins can cause damage to the barrier *via* their effects on keratinocyte differentiation[54]. This study also highlighted that environmental allergens such as soap and detergents would cause the same damaging effects through increased levels of IL-4 and IL-13[54]. A different study demonstrated that histamine may also contribute to immune dysfunction causing a leaky skin barrier and atopic eczema[55]. This study again observed keratinocyte differentiation as a measure of barrier damage but also investigated the important barrier proteins keratin 1 and keratin 10, loricrin and filaggrin[55]. The study showed that expression of these proteins was reduced by as much as 80%-95% in the presence of histamine thereby affecting keratinocyte differentiation and the skin barrier[55]. The final part of this study demonstrated that histamine also caused down-regulation of the claudins involved in tight junction formation and therefore this may also contribute to the leaky skin barrier in atopic eczema[55].

The adaptive and innate immune responses have both been highlighted as possibly playing a role in atopic eczema[56]. The candidate gene and genome-wide association studies mentioned earlier have illustrated that variation in genes involved with the adaptive response of the Th2 cells is associated with risk of atopic eczema. In a number of cases of atopic eczema there will be increased levels of the Th2 cell and its cytokines IL-4 and IL-13; these are important for instigating inflammation[56]. IL-4 is key for production of eosinophils and importantly IgE, which then acts through Fc-εRI receptors to cause mast cells degranulation, stimulating inflammation[57]. IL-13 has not been as extensively studied in skin, however its mechanism of inflammation appears to occur through interacting with the IL-4Rα receptor[58]. Another mechanism by which atopic eczema may occur is when someone begins to scratch, causing mechanical damage. The traumatised keratinocytes release thymic stromal lymphopoietin (TSLP), another cytokine. Studies have demonstrated that TSLP levels are increased in skin affected by atopic eczema compared to normal skin[59]. TSLP acts on dendritic cells which activate Th2 cells producing IL-4 and IL-13 resulting in a cycle of increased inflammation and atopic eczema[59,60].

The innate immune system may also play a role in causing an individual's atopic eczema. One of the first lines of response to pathogens is by antimicrobial peptides which are secreted and activated once toll-like receptors (TLR) identify pathogens[61]. Defects in these TLRs have been implicated in potentially allowing the colonisation of bacteria and therefore instigating atopic eczema[62]. A study using a mouse model found that mice with defective TLR4 or TIR-domain-containing adapter-inducing interferon-β (TRIF) had increased levels of TEWL, resulting in atopic eczema[62]. The peptides themselves are found to be reduced in eczema-affected skin and therefore fail to prevent colonisation and damage by pathogens such as *S. aureus* or infection with herpes simplex resulting in eczema herpeticum[63]. Cathelicidin and human beta defensin 2 (hβD-2) have been shown to be reduced in atopic eczema, lowering the threshold for this damage to occur[64,65]. *S. aureus* releases alpha and delta toxins which activate the adaptive immune response resulting

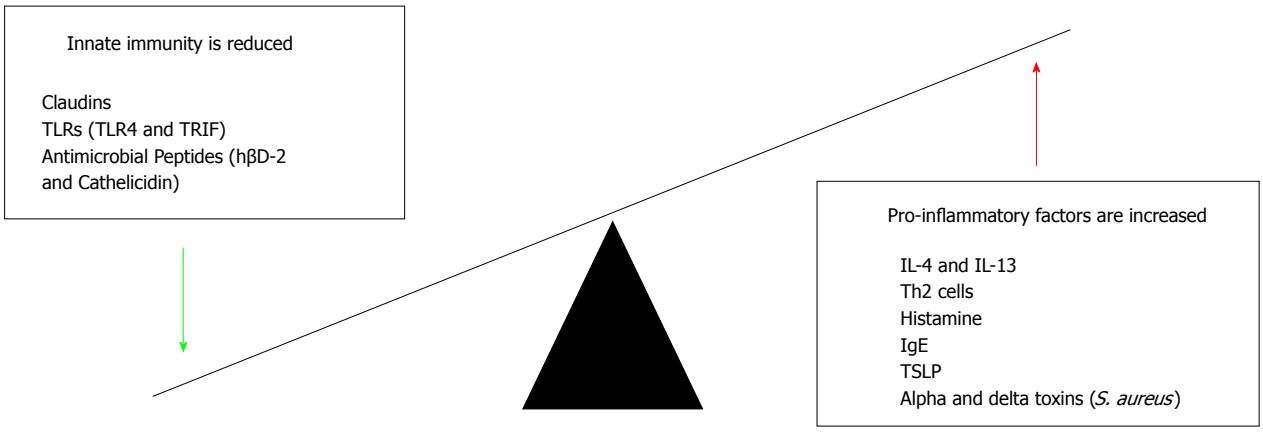

Figure 3 Immune dysfunction in atopic eczema. This figure summaries the number of immune factors discussed in the review. Increased and decreased levels of different factors contribute to the pathogenesis atopic eczema. TLR: Toll-like receptors; hβD-2: Human beta defensin 2; *S. aureus*: *Staphylococcus aureus*; IL: Interleukin; TSLP: Thymic stromal lymphopoietin.

in increased Th2 cell activity[53,66] and driving further inflammation (Figure 3).

HOW CAN THIS KNOWLEDGE BE APPLIED?

Novel treatments target the leaky skin barrier and immune mechanisms in eczema

This knowledge of the molecular mechanisms in skin barrier function and immune response is creating opportunities for novel treatment approaches for atopic eczema, summarised in Figure 4 and Table 1.

One potential therapeutic avenue may involve using vitamin D to decrease the severity of atopic eczema; studies have shown that it is important in both barrier repair and modulation of the immune mechanism[67,68]. A study in mice demonstrated that those treated by phototherapy had greatly increased levels of filaggrin which also lead to decreased time for barrier repair to occur[69]. This was believed to be due to the action of vitamin D on keratinocytes to increase levels of calcitriol, thereby normalizing the faulty keratinocyte differentiation seen in atopic eczema, to improve barrier function[69,70]. Oral supplementation of vitamin D has not shown a therapeutic effect, so alternative methods of administration are required.

The knowledge of a central role for dry skin in atopic eczema has stimulated interest in the development of bespoke emollients as treatment for xerosis[71]. In one study a standard emollient (the control) was compared to an emollient cream containing 5% urea, a skin ceramide N-stearoyl phytosphingosine (NP) and lactate[71]. When skin that had previously been treated with the cream containing ceramide NP was changed to the control there was an increase in TEWL from 11.58 to 11.94 g/m^2 per hour; this suggested that skin barrier function was improved more by using investigated cream than the control[71]. However this improvement between the creams may be due to the sodium lauryl sulfate in the control having an emulsifying effect and increasing barrier damage[71]. When hydration was also considered, the application of the ceramide NP cream showed greater hydration compared to the control, suggesting improvement of the stratum corneum barrier[71]. There is the possibility of damage if the ceramide NP cream is used with atopic eczema as it increases pH slightly and further work is needed to define the optimal emollient treatment for atopic eczema.

Another potential treatment aimed at the leaky skin barrier involves using a synthetic elastic "second skin"[72]. This skin is made of a cross-linked polymer (XPL) and has been used initially as anti-ageing solution where it can be applied to remove signs such as wrinkled skin; it has demonstrated dramatic results, especially around the eyes[72]. It has been subsequently proposed as a potential treatment for atopic eczema as the XPL will act as an extra skin barrier, for up to 24 h, preventing entry of allergens or irritants to affected areas of skin[72]. However this very interesting application remains speculative, as no research has yet been conducted.

It has recently been highlighted that increasing levels of the antimicrobial peptide hβD-2 can be used to reduce damage caused to the skin barrier by *S. aureus*[48]. In atopic eczema there are reduced levels of hβD-2 so its IL-1β defensive mechanism cannot prevent damage by the SSpA/V8 protease[48]. It was demonstrated that purified recombinant or synthesised hβD-2 could decrease skin barrier damage by 15% and 10% respectively[48]; this may be a useful avenue for future topical treatments.

Phosphodiesterase-4 (PDE-4) inhibitors can be taken orally to prevent cyclic-AMP degradation in cells involved in immune mechanisms of atopic eczema; however, this often leads to side effects such as nausea and diarrhoea[73]. An ointment based PDE-4 inhibitor has therefore been developed called crisaborole; it is one of the few non-steroidal based ointments developed recently[73]. It has just finished phase 3 clinical trials and has demonstrated improvements as high as 41%

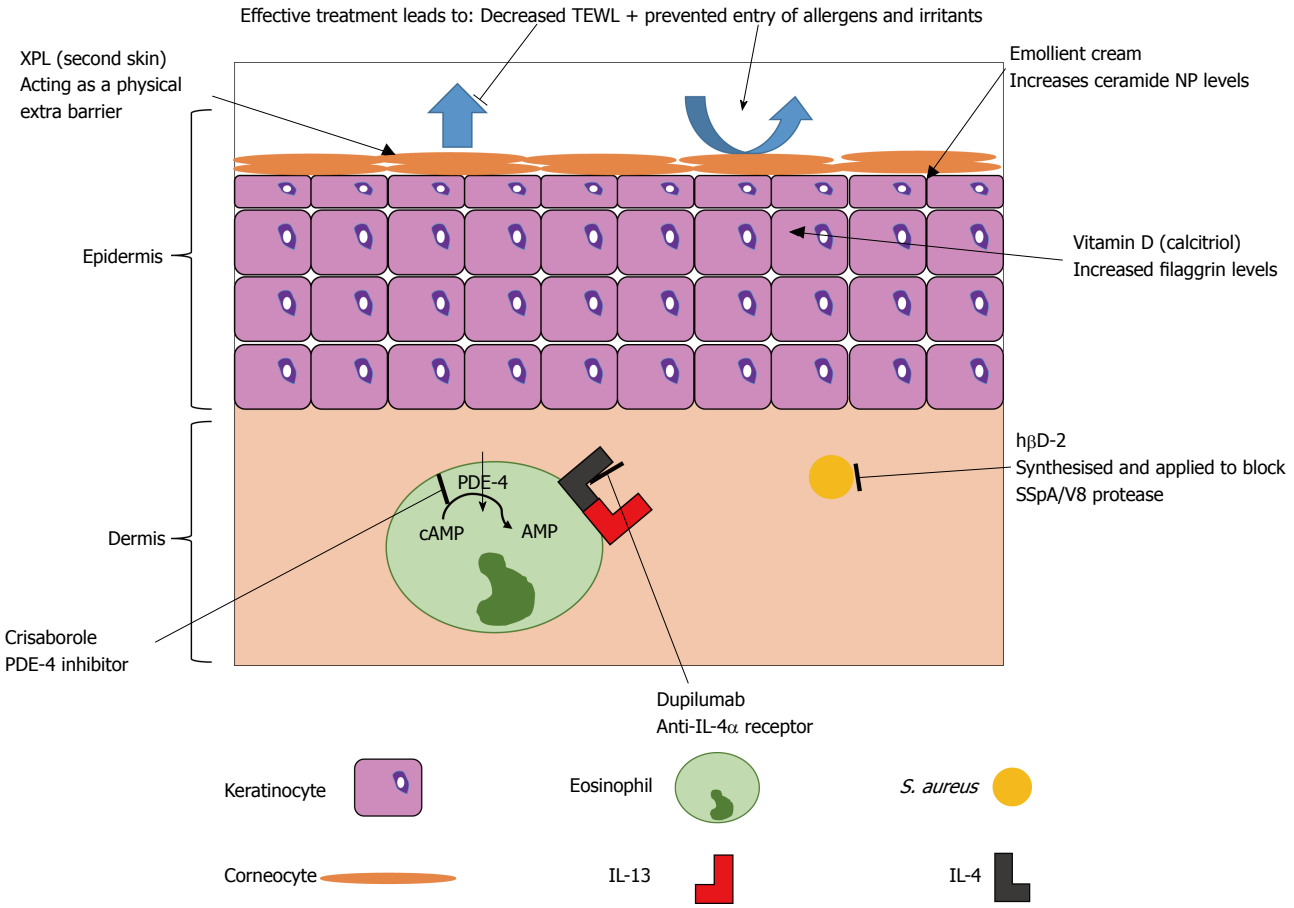

Figure 4 Novel treatment targets in atopic eczema. This figure highlights the keys roles of treatment: to decrease TEWL, prevent entry of irritants and allergens into the skin and to decrease the action of the immune response. TEWL: Trans-epidermal water loss; IL: Interleukin.

Table 1 Novel therapeutic strategies targeting atopic eczema

Repairing the damaged skin barrier	Reducing atopic inflammation
XPL (second skin)	Crisaborole
Emollients with increased ceramide NP levels	Dupilumab
Vitamin D (calcitriol)	hβD-2

Novel therapeutic strategies and mechanisms of action in atopic eczema. XPL: Cross-linked polymer; hβD-2: Human beta defensin 2.

compared to a placebo moisturiser, in terms of atopic eczema severity scores[73]. This drug may soon be approved by the FDA for treatment of atopic eczema.

A novel treatment that presents the greatest opportunity to powerfully target atopic eczema inflammation involves using monoclonal antibodies which are currently being developed to treat several different atopic diseases[74]. Currently one of the only commercially available monoclonal antibody treatments for atopic disease is omalizumab which is licenced for the treatment of asthma[74]. It targets the IgE Cε3 domain which leads to decreased severity in asthma and has the potential to be used in atopic eczema[74].

However a more promising monoclonal antibody treatment is dupilumab, which is an anti-IL-4α receptor, so stops the action of IL-4, thereby preventing the inflammation by both IL-4 and IL-13[74]. It is currently showing promising results in phase 2 trials (up to 85% of patients showing a 50% reduction in eczema severity score)[75] and phase 3 trials (in which up to 38% of patients were clear or almost clear after 16 wk of treatment)[76]. Drawbacks of this treatment are that it involves an injection which is more invasive than the other treatments and that the long-term safety is currently unknown[74].

CONCLUSION

Atopic eczema is a complex and chronic inflammatory disease of the skin that affects a large proportion of people. The pathomechanisms include a leaky skin barrier and an immune response: Both are able to occur first thereby causing the other. The problems associated with atopic eczema extend far beyond skin disease, affecting a whole family and not just the individual or child affected, causing mental health problems as well as economic impact. Mutations in the gene encoding filaggrin (*FLG*) have been highlighted as an important part of the disease; filaggrin plays a number of roles in maintaining the skin barrier so this is plausible. However, not every case of atopic eczema

has these null mutations in *FLG* and the same can be seen with the immune mechanisms of the disease. The Th2 cell response often occurs in atopic eczema and is central to causing the atopic inflammation. Bacterial infection contributes to atopic eczema pathogenesis and this is potentiated *via* reduced antimicrobial peptides or mutations in filaggrin leading to a reduction in the acidic pH of skin.

The multitude of causes is what has brought about the variety of treatments for atopic eczema. Different treatments are effective or ineffective in different individuals. The ideal treatment for atopic eczema would be able to target and repair the leaky skin barrier but also normalise the increased immune response of atopic skin. In milder atopic eczema, the best treatments often involve educating patients and children to avoid their own triggers and more education may improve overall treatment. Novel treatments have become more specific in targeting molecular mechanisms in atopic eczema, which, it is hoped, will make them more effective and with fewer side effects. However a considerable amount of research is still required to develop the most effective treatment to target both key mechanisms - the skin barrier dysfunction and immune response - to fully control this complex disease.

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