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Review Article

TREATMENT CHALLENGES IN ATOPIC DERMATITIS WITH NOVEL TOPICAL THERAPIES

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ABSTRACT

Atopic dermatitis (AD), a chronic inflammatory skin disease affecting children and adults, presents as mild to-moderate disease in the majority of patients. Pruritus, one of the key diagnostic criteria for AD, is associated with reduced quality of life and disease aggravation. Current treatments include emollients and topical pharmaceutical agents. Topical corticosteroids (TCSs) are commonly used, but are associated with safety concerns with cutaneous and systemic side effects. Topical calcineurin inhibitors (TCIs) inhibit T-lymphocyte activation, but their use is limited because of application-site infections and a boxed warning for potential malignancy risk. Despite recent reports indicating there is no malignancy risk, long-term treatment with TCIs is still considered with hesitancy. In addition, while both TCSs and TCIs provide some relief of pruritus, it often takes over a week for improvement to occur. The development of a more specific anti-inflammatory treatment which is easy to use and targets pruritus could provide clinically meaningful improvements for patients with AD. The majority of emerging therapies for AD are focused on inhibiting phosphodiesterase 4 (PDE4), an enzyme which is increased in inflammatory disorders such as AD. This review will update readers on the recent advances in topical therapies for the treatment of AD.

Keywords: Atopic dermatitis, Prutitus, Topical treatment, Corticosteroids, Phosphodiesterase-4 inhibitors, JAK inhibitors.

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, recurrent, inflammatory skin disease characterized by pruritic lesions for which presentation varies according to patient age and disease severity [1-3]. AD occurs more frequently in younger individuals; in industrialized countries, prevalence ranges from 15% to 30% in children and 2% to 10% in adults [1, 4, 5]. Approximately 50% of children with AD develop symptoms within the first 6 months of life, and 85% of affected individuals develop symptoms before reaching 5 years of age [1] [1, 4]. Results of the 2007–2008 National Survey of Children's Health conducted in the United States indicated that 93% of children with AD exhibit mild-to-moderate disease, and severity increases with age [6]. In individuals with AD, intense pruritus is the predominant symptom, affecting all patients and representing a significant therapeutic challenge for physicians and dermatologists [7-9]. Often described as ''the itch that rashes,'' pruritus also tends to be the first symptom to become apparent [7, 8]. Pruritus promotes scratching, which can cause further inflammation, excoriation, aggravation of the underlying disease, and increased risk of infection [7, 8, 10]. Pruritic symptoms are often worse at night, which can cause unwitting scratching and disrupted sleep [7, 8, 10]. The combination of pruritus and the visible nature of symptoms associated with AD have broad impact on quality of life for affected individuals and their parents and families, and can range from impairment of physical and emotional health to inhibited social functioning (Figure 1) [11]. Pruritus can cause anger, a feeling of helplessness, and frustration [9], and the relentless itch can significantly disrupt sleep and concentration [12]. Daily functioning can also be affected in AD, with patients reporting difficulties undertaking general tasks (such as walking and dressing), reduced participation in leisure activities and sports, and impairment in work ability. For patients with extensive hand involvement, even simple tasks such as gardening, child care, and food preparation can become difficult [13]. Individuals with AD are at risk for psychosocial difficulties and psychological comorbidity, including anxiety, depression, and suicidal ideation [14]. AD is also associated with financial burdens on the individual, caregivers, and the health care system [13]. Several large population-based studies have shown an increased incidence of other atopic manifestations, including asthma, hay fever, allergic rhinitis, allergic conjunctivitis, and food allergies [5, 15]. Atopic dermatitis is also associated with an increased incidence of other non-atopic comorbid conditions such as headaches [16], injuries requiring medical assistance [17], and obesity [18]. As the largest organ of the human body, skin provides many vital functions, including protection against physical and chemical injury, prevention of body water loss, temperature regulation, immunological function, and sensation [19]. Atopic dermatitis (AD) is a common disorder of the skin with a complex pathophysiology, developing in individuals with a genetic predisposition and exogenous provocation factors [20]. More specifically, the cause of AD is thought to be related to epidermal barrier defects and immune dysregulation of the innate and adaptive immune system. Barrier abnormalities are caused by many factors, such as chemical exposure, microorganisms, low temperature, and low humidity [21, 22] The filaggrin gene (FLG) also plays a significant role in skin barrier formation. FLG regulates terminal epidermal differentiation, creates a template for assembly of the cornified envelope, and

provides a substrate for natural moisturising factor. Consequently, mutations in FLG can cause AD in a particular subset of patients [23]. The AD phenotype begins with pruritus, erythema, and dermatitic plaques that may weep, crust, or scale, depending on the duration of the lesions [24]. In infants and young children, AD tends to present on the face, neck, and extensor surfaces. In older children and adults, lesions are typically lichenified and found on flexural surfaces of the extremities [2].

Current topical AD treatment landscape:

The goals of treatment for AD include improving the skin's barrier function, suppressing inflammation, and relieving pruritus [4, 8]. Topical therapies are central to the management of AD because they may treat these symptoms with a lower risk for adverse events (AEs) than systemic therapies [8]. The most commonly used topical treatments include emollients, corticosteroids, and calcineurin inhibitors (Table 1) [8, 25-29].

Emollients and Moisturisers:

One of the fundamental principles behind the effective longterm treatment of atopic dermatitis is the maintenance of the patient's skin barrier. This may be achieved in a variety of ways, such as the use of emollients and moisturisers and more appropriate bathing habits—namely, using tepid versus hot water and mild versus strong soaps [24]. Emollients are a very effective treatment modality in the range of mild to severe disease [30], so much so that regular use of emollients can drastically reduce the amount of topical steroid usage in more severe patients [31]. In fact, regular application of emollients in neonates at high risk for developing AD can help prevent its development. One study demonstrated that application of full-body emollient therapy at least once per day, initiated within 3 weeks of birth, had a statistically significant protective effect on the incidence of AD in the infants at 6 months compared to those who did not use emollients. Importantly, there were no adverse events related to emollient application [32]. Another neonatal study also demonstrated significantly decreased incidence of AD with regular emollient application in the first 32 weeks of life compared to controls. This study also investigated allergic sensitisation in both the intervention and control groups, and it was found that the proportion of infants sensitised by egg white allergen was similar in both [33]. It is important to note the distinction between the terms *emollient* and *moisturiser*. Colloquially, they are often used synonymously; however, moisturisers often include humectants, such as urea and alpha hydroxyl acids, which hydrate the stratum corneum, whereas an emollient refers to a material designed to soften the skin [20]. However, for simplicity, they will be considered synonymous in this review. Despite the proven efficacy of these substances, there are barriers to patient compliance regarding their use. For example, petroleum, a highly effective occlusive, is greasy and can be messy, which may negatively affect patient adherence [34]. Ideally, emollients should be applied once or twice daily, within 3 minutes of bathing for optimal occlusion of a hydrated stratum corneum [24]. There have been many

emollient preparations with varied effectiveness at improving skin barrier function in patients with atopic dermatitis [24]. For instance, 1 trial found a barrier improving cream (with 5% urea) to be superior to a reference cream [35]. Another trial found that a ceramide-dominant, barrier repair emollient decreased transepidermal water loss (TEWL) compared to nonceramide-dominant moisturizers [36]. In addition to urea and ceramides, compounds such as glycerin, lactic acid, hyaluronic acid, and nicotinamide are other additives commonly found in moisturizers [24]. Simpson and Dutronc34 reported a series of trials showing the effects of a moisturiser designed for patients with AD containing a ceramide precursor, FLG breakdown products, humectants, emollients, and occlusives. Skin hydration was assessed to be superior to 2 reference moisturisers after a single application. The ceramide product was also superior at restoring the skin barrier after disruption with a 24-hour patch of sodium dodecyl sulfate compared to the reference products.34 Furthermore, the ceramide product was also tested in a splitbody design on 127 patients with AD who used topical steroids on all lesional areas but also used the ceramide product on only half of the body. The ceramide + topical steroidtreated side had superior hydration and more rapid and significant improvement in EASI score at days 7, 14, and 21 compared to the side using only topical steroid, although effect sizes were small due to milder disease ($P < .05$) [37]. In addition, it has been found that severe AD is associated with a lower degree of bacterial biodiversity, specifically an underrepresentation of Actinobacter, Proteobacteria, and Cyanobacteria [38]. An increased proportion of *Staphylococcus* is known to play a role in atopic dermatitis severity [39]. Therefore, it is not surprising that untreated AD flares have reduced microbiome diversity and high *Staphylococcus* proportions compared to baseline, postflare, and intermittenttreatment flares [38]. In many patients with AD, recurrent *Staphylococcus aureus* skin infections are a problem. In such patients, dilute bleach baths twice weekly have been shown to reduce the severity of AD, thus helping prevent reinfection.

Topical corticosteroids:

Topical corticosteroids (TCSs) have been the mainstay treatment for moderate to severe AD since the early 1950s, except on sensitive or thin-skinned areas of the body [27]. They are recommended by the American Academy of Dermatology (AAD) for proactive and reactive treatment of AD (Table 2) [2, 40]. TCSs decrease the

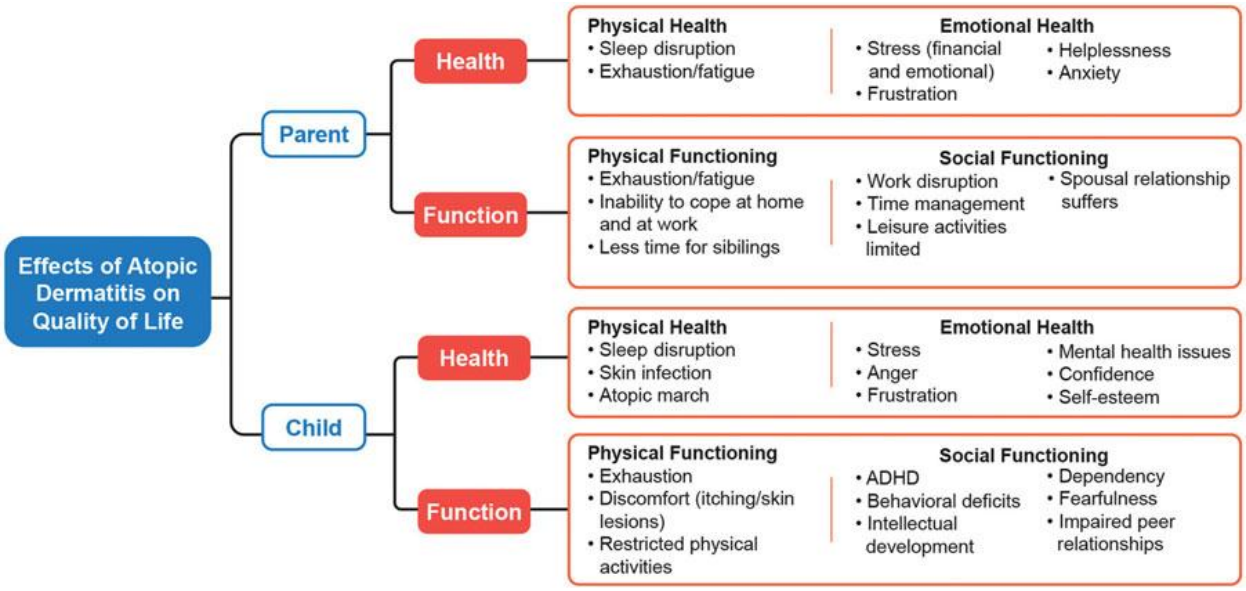

Figure 1: Effects of atopic dermatitis on patients and their caregivers. Effects have been categorized into eight health- and function-related domains. Figure adapted with permission from Chamlin et al. [11].

Treatment	Usage	Mechanism of action	Adverse effects
Moisturizers and emollients	All patients	Increase the hydration of the epidermis, primarily by acting as an occlusive layer preventing transepidermal evaporation	Greasy texture Can cause folliculitis and sweat retention Preservatives and fragrances may cause contact dermatitis

Topical corticosteroids (TCSs)	Low potency is recommended to treat AD of the face, groin, and axillae Only low-potency agents should be used to treat infants Once control is attained, TCSs should only be used intermittently	Activate nuclear glucocorticoid receptors to alter cytokine expression	Local: cutaneous atrophy, striae distensae, stellate pseudoscars telangiectasia, purpura milia, erythema, perioral dermatitis, rosacea, hyperpigmentation, hypopigmentation, tachyphylaxis, hypertrichosis, etc Systemic: HPA axis suppression, Cushing disease, glaucoma, decreased growth rate, hypertension, hypercalcemia, hyperglycemia, cataracts, femoral headosteonecrosis
Topical calcineurin inhibitors (TCIs)	Indicated for children <2 years of age Patients with facial or eyelid dermatitis Patients with extensive AD not controlled with mild TCSs	Calcineurin inhibition blocks early T-cell activation and the release of cytokines	Transient burning, pruritus, and erythema Boxed warning regarding carcinogenesis with long-term use Allergic contact dermatitis

Table 1: Summary of topical treatment for AD [8, 25-29].

AD: atopic dermatitis; HPA: hypothalamic–pituitary–adrenal.

severity of AD and reduce pruritus through their broad-ranging anti-inflammatory effects [29]. Their use can be tailored to the individual through the prescription of varying potencies, which range from mild to very strong based on their vasoconstrictive abilities, and the use of different vehicles, such as ointments, creams,

gels, or oils [8, 25]. Because of the chronic and recurrent nature of AD, patients often require long-term treatment to relieve symptoms and prevent exacerbations. This need for therapy can last for decades: results of one study indicated that the majority of children with AD require treatment well into their 20s [41]. However, the extended or inappropriate use of high-potency TCSs can result in cutaneous and systemic AEs [42]. These AEs are particularly relevant in children, who have a greater surface area to body weight ratio and potential for more substantial TCS exposure [40]. Of primary concern is the potential for cutaneous AEs such as skin atrophy (resulting in bruising, skin fragility, and dyspigmentation), irreversible striae, telangiectasia, and rebound reactions [27], and local effects such as the development of posterior subcapsular cataracts [29]. Systemic effects occur more rarely, but include serious conditions such as suppression of the hypothalamic–pituitary axis, femoral head osteonecrosis, glaucoma, hyperglycemia, and hypertension [27, 29]. The risk for AEs has led to the restriction of the use of high-potency TCSs in certain parts of the body, particularly in thin-skinned areas such as the eyelids, face, axillae, and genitals [40]. An additional concern with prolonged or inappropriate use of TCSs is a condition known as TCS withdrawal [43, 44]. Alternatively known as topical corticosteroid-induced rosacea-like dermatitis, topical steroid-dependent face, or red skin syndrome, TCS withdrawal is a condition that involves the exacerbation of AD symptoms after discontinuation of TCS treatment [27, 44, 45]. In mild cases, this can involve erythema with or without exudative edema [44]. In more severe cases, the rebound eruption can be diverse and extensive and may include papules, pustules, or erosions [44]. The severity of the exacerbation seems to be correlated with duration of TCS use, with a treatment duration of <1 year resulting in milder withdrawal symptoms than a treatment duration of >1 year [45]. Furthermore, treatment adherence can be negatively affected by the fear of TCS withdrawal, the potential for AEs, and previous experience with those AEs [26, 44, 45].

Topical calcineurin inhibitors:

The topical calcineurin inhibitors (TCIs) tacrolimus ointment and pimecrolimus cream have been used to treat AD since they gained approval in 2000–2001, and they are also recommended by the AAD for proactive and reactive treatment of AD (Table 2) [25, 28]. TCIs limit inflammation by inhibiting the activation of T lymphocytes, resulting in reduced expression of proinflammatory cytokines [28, 29]. Apart from complementary and alternative remedies for which there is little evidence of efficacy, TCIs represent the only non-steroidal topical AD treatment with efficacy comparable with TCSs. TCIs exhibit benefits over TCSs by avoiding many of the AEs associated with TCS use [28, 29]. Current recommendations suggest that TCIs should be used for long-term treatment of young children with AD or for patients requiring treatment on delicate areas such as the face or intertriginous areas [2, 40]. Tacrolimus 0.03% and pimecrolimus 1.0% are as effective as low potency steroids and tacrolimus 0.1% is as effective as Mid potency steroids [40]. The AEs most commonly associated with TCI use are transient burning sensation, pruritus, and erythema [8].

	AAAAI/ACAAI	**AAD**
Moisturizers and emollients	Moisturizers should be recommended as first-line therapy	Moisturizers should be an integral part of treatment
Topical corticosteroids (TCSs)	TCSs should be recommended if AD is not controlled with moisturizers alone Low-potency TCSs TCSs are recommended for maintenance therapy Intermediate and high-potency TCSs are recommended for short-term exacerbation Potent corticosteroids should not be prescribed for use on the face, eyelids, genitalia, and intertriginous areas or in young infants The risk for systemic adverse events should be considered	TCSs are recommended for AD-affected individuals who have failed to respond to good skin care and regular emollient use Patient age, areas of the body affected, degree of xerosis, patient preference, and cost of medication should be considered Twice-daily application of TCSs is recommended, although once daily may be sufficient Proactive, intermittent use of TCSs is recommended on areas that commonly flare The potential for side effects should be considered Monitoring for cutaneous side effects during long-term, potent TCS use is recommended

Topical calcineurin inhibitors (TCIs)	TCIs can be considered for the management of AD TCIs should be considered for delicate areas that are unresponsive to low-potency TCSs because, unlike TCSs, TCIs do not cause skin atrophy Patients should be counseled regarding the potential for localized burning and itching during the first week of TCI use	TCIs are recommended for short-term, long-term, and maintenance treatment of AD in adults and children TCIs are preferable in situations that include recalcitrance to steroids, sensitive areas, steroid-induced atrophy, and long-term uninterrupted topical steroid use TCIs are recommended for use as steroid-sparing agents For patients <2 years of age with mild-to-severe disease, off-label use of TCIs can be recommended Side effects, including skin burning and pruritus, should be considered and patients should be informed Proactive intermittent use with TCIs is recommended on areas that commonly flare Clinicians should be aware of the boxed warning on the use of TCIs
Concomitant use of TCSs and TCIs	No recommendations	TCSs and TCIs can be used sequentially and concomitantly

Table 2: Joint AAAAI and ACAAI, and AAD guidelines for the use of topical treatments for AD [2, 40].

AAAAI: American Academy of Allergy, Asthma & Immunology; AAD: American Academy of Dermatology;
ACAAI: American College of Allergy, Asthma and Immunology;
AD: atopic dermatitis.

The incidence of burning sensation observed in clinical trials ranged from 20% to 58% with tacrolimus and 8% to 26% with pimecrolimus. There is also some concern regarding the potential prevalence of viral infection with TCIs because of several case reports attributing eczema herpeticum to TCI use; thus,

TCI use on infected lesions is not recommended [2, 40]. Although TCIs are generally considered safe for the management of AD [40], the addition of a boxed warning for them by the US Food and Drug Administration (FDA) in 2006 regarding a potential risk for malignancy has resulted in hesitancy to prescribe them [29, 46]. Despite recent reports that question the validity of this claim, the FDA has retained the warning, citing that there may still be a possible association between TCIs and an increased risk for lymphoma [28, 46]. The lower range of efficacy and the boxed warning make long-term treatment with TCIs somewhat challenging.

TCI and TCS Combination:

TCIs and TCSs may be combined for the treatment of AD. Traditionally, an acute flare may have started treatment with a 4- to 7-day course of medium- to high-potency TCS, followed by application of emollients twice daily to prevent or delay the onset of the next flare.7 Now, however, there is increasing evidence showing that TCSs should first be used to control the flare, followed by TCIs while in remission, to spare TCS use and to prevent relapse [40]. Some clinical trials have explored the combination of TCIs and TCSs concomitantly and sequentially with encouraging results. One randomized controlled trial evaluated the concomitant use of tacrolimus ointment and clocortolone pivalate 0.1%, a mild TCS, against either drug alone for the treatment of AD. Statistically significant improvements in various efficacy parameters were observed with combination therapy compared to either drug alone [47]. Concerning the sequential use of TCSs followed by TCIs, 1 trial compared patients applying 0.05% betamethasone butyrate propionate ointment bid for 4 days followed by the application of 0.1% tacrolimus ointment bid or white Vaseline emollient bid for the following 3 days. After 4 weeks, it was found that the TCS/TCI sequential therapy improved lichenification and chronic papules in patients with AD more efficiently than the TCS/emollientsequential therapy [48].

Ease of use:

Although topical therapies are the cornerstone of treatment for AD, several factors must be considered with their use. Of primary importance with TCSs and TCIs are the quality and type of vehicle used. Not only does this alter the absorption and effectiveness of the drug, but it can also significantly affect patient adherence to treatment [42]. Ointments are often preferred by physicians for the treatment of chronic AD because they provide more lubrication and occlusion than other preparations; however, they can appear oily, shiny, and thick [49]. Creams and lotions have the advantage of vanishing into the skin but are frequently less potent than ointments, can worsen dry skin, and can contain preservatives that may cause further irritation or hypersensitivity reactions [27, 49]. Patient education is one of the most important factors in the success of topical treatment. Treatment considerations include which medication to use and where, how often to apply a medication, how much of the agent should be applied, how long the medication should be used, and the potential side effects that might result from treatment [27]. These factors can impact the effectiveness of and patient adherence to treatment. Physicians might also be hesitant to prescribe sufficient quantities of medications or high-potency agents because of concerns about toxicity and cost, which can result in

undertreatment [26].

Emerging Topical Treatments in AD:

Targeting Janus Kinase/Signal Transducer and

Activator of Transcription Pathways

The Janus kinase/signal transducer and activator oftranscription (JAK/STAT) pathway is utilized by numerous cytokines and growth factors for signal transduction in AD, involving augmentation of Th2 cell response, activation of eosinophils, and suppression of regulatory T cells [50]. Moreover, it downregulates the expression of structural skin proteins, and weakens the epidermal barrier function [51-55]. Additionally, downstream signaling in this pathway has been shown to prevent the induction of genes encoding innate immune response proteins, including β-defensins and cathelicidin in keratinocytes [56], thus raising the vulnerability of patients to both viral and bacterial skin infections. Inhibitors of the JAK/STAT signalling axis are categorized as small molecules blocking intracellular targets in comparison with anticytokine/antireceptor agents. The relevance in targeting this family of kinases is that they constitute the main signalling pathway for several cytokines, thus providing an opportunity to prevent the downstream signalling of numerous AD-typical Th2 cytokines. Several pharmaceutical agents targeting this group of tyrosine kinases (comprising TYK2, JAK1, JAK2, and JAK3) are being evaluated in patients with AD both as systemic and topical therapies. The small size of the JAK inhibitors makes them suitable for topical use, and this is in part substantiated by a recent study demonstrating great antipruritic and anti-inflammatory effects from topically administered tofacitinib and oclacitinib in a mouse model of allergic dermatitis [57].

Tofacitinib:

Tofacitinib (NCT02001181) is approved for rheumatoid arthritis and has previously been investigated in a range of dermatological conditions like psoriasis, alopecia areata, and systemic lupus erythematosus. It inhibits JAK1 and JAK3 and in theory interferes to a larger extent with lymphocyte activation and Th2 skewing than the inhibitors also targeting JAK2, which are more involved in Th1 signalling [58]. Moreover, tofacitinib has been shown to directly inhibit cytokines, most importantly IL-4, thereby rapidly attenuating JAK-STAT signalling in keratinocytes [59, 60]. While the results in psoriasis trials have shown quite varying results [60, 61], the single published trial on topically administered tofacitinib in adults with mild to moderate AD revealed significantly better efficacy. Most importantly, for the primary analysis at week 4, the mean percentage change from baseline in the Eczema Area and Severity Index (EASI) total score was significantly greater ($p < 0.001$) for patients treated with tofacitinib (81.7%) versus patients treated with vehicle (29.9%). Topical tofacitinib also displayed an early onset of effect, a comparable safety profile, and local tolerability to vehicle, with the most common adverse events being mild self-limiting infections (e.g., nasopharyngitis) and application site pain and pruritus [62]. In conclusion, it seems that JAK1/JAK3 inhibition, through topical delivery, is possibly a capable treatment target for AD, though due to the nature of

the trial, additional studiesare warranted to address the use for long-term control.

Ruxolitinib:

Ruxolitinib (INCB018424), a JAK1/JAK2 inhibitor, is approved for the treatment of adult patients with polycythemia vera and for the treatment of disease-related splenomegaly or symptoms in patients with myelofibrosis. Moreover, use of ruxolitinib in the field of dermatology is emerging, as it has already been trialled in a number of diseases e.g., psoriasis (only topical), alopecia areata (topical and oral), vitiligo (only topical), and graft-versus-host disease [63].A phase II placebo-controlled study to evaluate the safety and efficacy in adult AD patients is planned (NCT03011892). The participants are to be randomized between the ruxolitinib cream once or twice daily compared with vehicle cream twice daily. With an estimated enrolment of 300 participants, the study would provide well-powered data on the possible benefits of topical ruxolitinib in AD.

Inhibiting the Enzyme Phosphodiesterase-4:

The potential therapeutic use of phosphodiesterase-4 (PDE4) inhibitors in AD is based on the recognized intracellular role of PDE4 in keratinocytes [64]. Circulating leukocytes in AD patients have PDE4 activity, which has been associated with higher production of proinflammatory mediators and lower production of the anti-inflammatory mediator IL-10, in part due to hydrolization of cyclic adenosine monophosphate (cAMP) [65-67]. This consequently diminishes levels of cAMP, which leads to increased transcription of numerous cytokines, accelerating a number of intracellular functions involved in acute and chronic inflammation [65]. Thus, targeting PDE4 has been shown to directly attenuate inflammation due to inhibition of the breakdown of cAMP, consequently reducing the levels of tumour necrosis factor-α, IL-12, IL-23, and other signaling effectors [68, 69]. Of note is that a number of topical PDE4 inhibitors have been investigated previously, but despite completion of these trials several years ago no results have been presented and the drugs are no longer in clinical trial, e.g., DRM02 (NCT0199342, completed in 2014) and LEO 29102 (NCT01037881, NCT00958516, NCT01005823, NCT01447758, NCT00891709, and NCT01423656, the last one completed in 2011). To lessen systemic exposure, a topical PDE4 inhibitor with little transdermal bioavailability might be clinically advantageous, as systemic treatment with agents from this drug class have so far been compromised by a significant rate of mechanism-associated adverse reactions, most prominently gastrointestinal discomfort and headache. Thus, it is promising that the low molecular weight of PDE4 inhibitors ensures excellent skin penetration, and safety studies have shown minimal systemic uptake. Currently, there are several trials investigating 5 different topically administered PDE4 inhibitors.

Crisaborole:

The boron-based benzoxaborole named crisaborole (AN2728) is a small molecule specifically inhibiting PDE4 activity (NCT02118792) and the first in its class to be approved by the FDA. Seven studies have been conducted on the topical formulation of the compound to date, and two of them have reached phase III (NCT02118792 and NCT02118766). Data on the previous phase I and II studies showed positive results across a accumulated cohort of 189 subjects with AD as young as 2 years of age [68, 70-72]. The first study conducted assessed the safety profile and pharmacokinetics in both children and adolescents under conditions with a supposed maximal use of topical crisaborole. The drug showed swift absorption and minimal systemic exposure. However, circulating levels increased in parallel with the extent of the skin area treated, yet displayed no correlation with the incidence of adverse events. Crisaborole had an acceptable safety profile, but a high percentage of participants experienced local self-limiting and mild application site adverse events. Both the pruritus score (after 5 days) and signs and symptoms (after 4 weeks) significantly improved with treatment. However, as application site adverse events were present in the majority of patients in the treatment group across all trials, varying drop-out rates directly linked to this have been reported. In two of the phase II studies both pruritus and individual scores of signs and symptoms were positively affected by crisaborole treatment in comparison with placebo vehicle, though all studies were underpowered and did not report data on the most common disease severity scores e.g., EASI and Scoring Atopic Dermatitis (SCORAD). Therefore, these conclusions on efficacy should be cautiously interpreted. In contrast, the two phase III trials completed in 2015 were published in late 2016 and evaluated in parallel [73]. The two identically designed, vehicle-controlled, double-blind studies enrolled and randomly assigned (2: 1, crisaborole:vehicle) patients aged 2 years or older with an Investigator's Static Global Assessment (ISGA) score of mild or moderate for twice-daily application for 28 days. The primary end point of the ISGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline was achieved in a greater percentage of crisaborole-treated patients than placebo-treated subjects. Time to success in the ISGA score was significantly shorter in the crisaborole- treated group than in those treated with vehicle. Lastly, the individual score tool (signs of AD scale) revealed a significant reduction in the severity of AD signs, and the twice-daily pruritus severity scoring showed a swift (significant after 8 days) and sustainable improvement in pruritus [73]. However, to summarize the bulk of data on topically administered crisaborole, the difference of approximately 10% in both the ISGA success rate and the improvement score of pruritus between crisaboroleand placebo-treated subjects is modest, and the minimal clinically important difference (MCID) was not defined for the reported outcome measure. Therefore, it is difficult to thoroughly assess the impact of treatment on the key domain "signs of disease" as communal severity scores were not included.

E6005:

E6005 (RVT-501) is a selective PDE4 inhibitor and has shown antipruritic abilities in mouse models

mimicking AD [74-76]. E6005 is able to suppress C-fibre depolarization and activation of the dorsal root ganglion through elevation of cAMP levels, thereby exerting an antipruritic effect [75]. An early phase I/II study evaluating safety, tolerability, and pharmacokinetics showed no application site adverse event related to treatment and systemic absorption was below the detection limit [77]. The following phase II trial of 78 adults with eczema on 5–30% of the skin showed a reasonable safety profile, with a slight increase in incidence of AD exacerbation in the E6005- treated group compared with placebo (13.5 vs. 7.7%). At the end of week 4, EASI, objective SCORAD, visual analogue scales for pruritus and sleep loss, and the severity of the targeted eczematous lesions in the topical E6005 group showed insignificant but trending improvement compared with those in the vehicle group [78]. The trial last to be completed, E6005 (NCT02094235), included a fairly low number of adult Japanese males with mild to moderate AD (n = 40) randomized 1: 1:1: 1:1 to either 1 of 4 doses of twice-daily E6005 or placebo vehicle [79]. The study, possibly due to being severely underpowered, was not able to produce many significant end point measures of efficacy between the E6005- and vehicle-treated subjects. Of note, however, were a few significant changes on days 5 and 11 in the SCORAD and EASI scores that lay above the defined MCID threshold for these severity measures. In summary, the highest potency formulation of E6005 seemed to have the best efficacy, though results should be interpreted with caution, as the total enrolment numbers across studies are still low. An active phase II study with an expected number of 150 participants is in the pipeline (NCT02950922), but enrolment has yet to commence.

OPA-15406:

OPA-15406, another specific PDE4 inhibitor, has solely been investigated as topical treatment of AD (NCT02068352). With two phase I and one phase II trials already completed and three ongoing phase II trials (two recruiting and one active but not yet recruiting) there is extensive activity related to the drug. Published data comprise a single paper communicating the results from the completed randomized, double-blind, vehicle-controlled, phase II study of 121 patients aged 10–70 years with mild to moderate AD who received either 1 or 0.3% doses of topical OPA-15406 or vehicle twice daily for 8 weeks (randomized 1: 1:1) [78]. The primary end point, a score of 0 or 1 in the Investigator's Global Assessment (IGA) scale with a greater than or equal to 2-step reduction, was seen at week 4 in the OPA-15406 1% group (p = 0.0165 vs. vehicle). Secondly, the study showed a significant mean improvement from baseline EASI score for OPA- 15406 1% in week 1 (31.4 vs. 6.0% for vehicle; p = 0.0005), which was even greater in week 2, persisting for the duration of the study. The pruritus scores improved significantly within the first week in the OPA-15406 1% group (p = 0.0011), though they declined during the study and were no longer significant at week 6. Circulating OPA-15406 levels were insignificant, and the safety profile was good as the rate of adverse events was low, with most events considered mild and transient. In conclusion, the PDE4 inhibitor show somewhat promising results; however, the study size is a considerable limitation and larger studies are needed.

Roflumilast:

Roflumilast is a selective, long-acting inhibitor of PDE4. It has previously been used as systemic therapy but in the context of AD solely as topical treatment. The primary proof-of-concept trial, designed to assess the safety and efficacy of 0.5% dermal roflumilast cream, was withdrawn prior to enrolment. A subsequent phase II study evaluating the effect of topical roflumilast on the reduction of AD lesions in 40 adults with moderate AD randomized 1: 1 to either topical roflumilast 0.5% cream twice daily or a parallel regimen with vehicle has been completed, with results available at clinicaltrials.gov. The primary outcome measures were change from baseline to day 15 in modified local SCORAD, transepidermal water loss, and participants' assessment of pruritus. The study showed significant results only in the mean difference between day 15 pruritus score in the roflumilast-treated group compared with vehicle (difference,1.56, p = 0.013). However, this difference between roflumilast and placebo did not meet the proposed MCID for pruritus reduction measured on a visual analogue scale [80]. In summary, roflumilast showed little to no potential as topical PDE4 selective therapy in AD. However, to settle the matter completely, larger trials are to be conducted.

DRM02:

DRM02 is a new PDE4 inhibitor that was investigated in three single studies for psoriasis, rosacea, and AD (NCT01993420). The double-blind, randomized, withinsubject control, phase II study enrolling 21 adult subjects with stable moderate AD was designed to assess the safety, tolerability, and preliminary efficacy of DRM02. Despite all three trials being completed in 2014, no results have been communicated.

Other Emerging Treatments of Interest:

Benvitimod:

Benvitimod (2-isopropyl-5-[(E)-2-phenylethenyl]- benzene-1,3-diol) (GSK-2894512, WBI-1001) is a nonsteroidal, anti-inflammatory small molecule that was originally derived from the metabolites of nematodes. Benvitimod holds properties enabling a reduced expression of several proinflammatory cytokines (e.g., IFN-γ, IL-2, and TNF-α) and the inhibition of T-cell viability and infiltration, ultimately diminishing skin inflammation [81-84]. Two phase II trials have been completed and published on the safety and efficacy of topical benvitimod treatment. The first trial (NCT00837551) of 37 men and women with a baseline EASI <12 was designed with randomized (1: 1:1) application twice daily of benvitimod 0.5%, benvitimod 1.0%, or vehicle for 4 weeks. Results showed that both of the benvitimod concentrations were well tolerated [84]. Both 0.5 and 1.0% benvitimod were superior to vehicle in improving AD at week 4 determined by a statistically significant reduction in the EASI, SCORAD, IGA, and body surface area (BSA) scores. The second trial (NCT01098734) was set to further test the safety and efficacy of benvitimod as a topical treatment studied over a 12-week period in 148 patients with mild to severe AD (randomized 1: 1:1 to

placebo, benvitimod 0.5%, or benvitimod 1.0% applied twice daily for 6 weeks). At the end of this phase, patients receiving benvitimod continued the same treatment for an additional 6 weeks. Patients receiving placebo entered into a 6-week double-blind phase with re randomization (1: 1) to benvitimod (0.5 or 1.0%). The study showed that there was a decrease of 1.3 ($p < 0.001$) and 1.8 ($p < 0.001$) in IGA at day 42 in the benvitimod 0.5 and 1.0% groups, respectively, compared with a decrease of 0.5 in the placebo group [82]. The EASI, SCORAD, BSA, and pruritus scores were significantly improved with each active treatment compared with placebo on day 42, demonstrating a swift elimination of these differences (on days 56 and 84) when the subjects initially treated with placebo switched to either 0.5 or 1.0% benvitimod treatment. Adverse events encompassed limited cases of folliculitis, contact dermatitis, and headache. A completed but not published trial (NCT02564055) that enrolled 247 AD patients could confirm the existing data and perhaps endorse benvitimod as a novel topical treatment in AD.

Less-Investigated Therapies:

DGLA (dihomo-γ-linolenic acid) is a 20-carbon ω – 6 fatty acid that has been investigated in mice models of AD and as both oral (NCT02211417) and topical treatment (NCT02925793) of AD for a decade or more [85-87]. Somewhat positive results have been observed in both of the administered formulations of the drug as communicated in press releases. However, no crude data or scientific papers have emerged. There are ongoing studies of topical and systemic DGLA treatment with DS107 , both enrolling approximately 300 AD patients.

The transient receptor potential vanilloid type 1 (TRPV1) is a cation channel activated by various stimuli like pH changes or heat. Several studies have shown that TRPV1 could be deeply associated with skin permeability barrier function, and is a likely mediator of chronic pruritus, as TRPV1 antagonists have shown positive effects in animal models of AD [88-93]. Results from previous phase I and II studies have not yet been published, and ongoing phase II and III studies (NCT02748993 + NCT02965118) of the topical TRPV1 antagonist PAC- 14028 are expected to shed better light on the efficacy and safety of this therapy.

The isoprenylcysteine analogue DMT210 is a topical therapy designed to mimic the amino acid tail found at the C-terminus of G proteins, and is thus supposed to downregulate the inflammatory response via the G-protein- coupled receptor [94]. It is being trialled in various dermatological conditions, including AD (NCT02949960), but further research is needed to illuminate the properties of the drug.

Another investigational topically applied agent, SB011, contains the DNAzyme hgd40 that targets GATA-3, a key regulatory factor of Th2-driven immune responses. Hgd40 was initially designed for the treatment of allergic bronchial asthma [95]by cleaving GATA-3 mRNA capable of mitigating cytokine production, consequently reducing key features of atopic inflammation [96]. The now completed primary proof-of-concept study addresses the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of the topical formulation of SB011 (containing 2% hgd40) twice daily in 25 AD patients with mild to moderate disease (NCT02079688). Results are pending.

VTP-38543 is a liver X receptor (LXR) agonist. The LXR agonists have been study for years in the context of various cancers, neurodegenerative diseases, and liver disorders, as they are imperative regulators of cholesterol, fatty acids, and glucose homeostasis [97-99] . LXR agonists may intervene with AD typical skin inflammation [100, 101]. A completed, but not yet published, phase I/II proof-of-concept study in a total of 104 adult patients with mild to moderate AD might give preliminary insights into this possible treatment modality (NCT02655679). Importantly, a press release deemed the treatment a "flop" as it failed to show a positive signal in the study, and it is therefore unlikely that the results will ever be issued.

Cytosolic phospholipase A2 (cPLA2) is the rate-limiting enzyme responsible for the release of arachidonic acid and the succeeding production of a range of inflammatory lipid mediators (e.g., leukotrienes, prostaglandins, and thromboxanes). ZPL-5212372 is a selective cPLA2 inhibitor that apparently exhibited long-term action and good efficacy in small and large animal models of airway and skin inflammation [102]. A dermal formulation of ZPL-5212372 has been developed to support an ongoing phase I/IIa study in moderate to severe AD patients (NCT02795832).

MRX-6, a somewhat similar drug to the aforementioned, is another non-steroidal anti-inflammatory cream working through the inhibition of secreted soluble PLA2 and via enriching cell surface glycosaminoglycans. The supposed mechanism of effect is similar to other PLA2 inhibitors [103] . The first study of the drug for allergic contact dermatitis (NCT00867607) was completed in 2015 and results were communicated as positive. However, the sole phase II study in AD patients (NCT02031445) was terminated as interim analysis showed lack of efficacy, hence the likelihood of further investigations is low.

IL-31 is a key mediator of acute and chronic itch in AD patients, and mitigating this cytokine might be beneficial in AD [90, 104-106]. The 5-lipoxygenase inhibitor zileuton has been shown to attenuate the action of IL-31 in mice [107] as IL-31, in addition to direct action on primary sensory neurones, also induces leukotriene B4 production in keratinocytes, the synthesis of which is controlled by the enzyme 5-lipoxygenase. Topical zileuton has shown positive results as an anti-acne agent [108]. However, we are still to see whether the results of the recently completed phase II study assessing 8 weeks of twice daily Q301 (zileuton) cream versus vehicle in adult subjects with moderate to severe AD show positive effects (NCT02426359).

The literature suggests that serotonin, i.e., 5-hydroxytryptamine (5-HT), and the 5-HT 2 receptor family could contribute to dermal inflammation and pruritus both in general and in AD specifically [109-111]. The aminoguanidine derivative and 5-HT 2B receptor antagonist AM1030 significantly diminished the T-cell-dependent and the T-cell-independent inflammatory responses in in vivo mouse and rat models and in an in vitro setting with staphylococcal enterotoxin A-stimulated leukocytes [112]. AM1030 is similar to a previously investigated agent demonstrating anti-inflammatory properties [113], and has been evaluated in a phase I/II study of 36 adults with mild to severe AD (NCT02379910). The study was completed in June 2015, though results have still to be revealed.

SP14019 is a formulation of cyclosporine A (CsA) compatible with cutaneous spray administration. It

has been shown that the formulation delivers CsA to the target layers in the skin, with efficacy in preclinical models of AD as presented as a poster at the 25th European Academy of Dermatology and Venereology (EADV) conference. SP14019 possibly bypasses the severe adverse events commonly seen from systemic CsA treatment [114, 115]. Moreover, topical CsA has been extensively used in the field of ophthalmology [116]. An ongoing phase IIa trial of 36 patients with AD (3 age groups) is expected to be complete in late 2017 (NCT02865356). However, it is underpowered, and should be considered no more than a proof-of-concept study to perchance substantiate future studies.

We have, as stated in the introduction, omitted a range of therapies. However, we would like to notify the readers that many other ongoing trials are investigating new topical treatments for AD. These studies assess new TCS molecules and novel formulations of well-known corticosteroids. Moreover, several new formulations of both pimecrolimus and tacrolimus ointments and creams are being explored. Lastly, a range of humectants, emollients, probiotics, eubiotics, antibacterials, and molecules with undisclosed mechanism of action are items for investigation.

CONCLUSION

Although topical therapies are central to the treatment of AD, options are limited. While TCSs and TCIs are somewhat effective, a number of concerns are associated with their use, particularly for the long-term treatment of AD. These safety concerns often lead to hesitancy in prescribing TCSs and TCIs as well as reduced adherence to treatment. Consequently, there is a significant need for novel topical treatment options that can rapidly improve the signs and symptoms associated with the disease, including pruritus. Preliminary evidence suggests that PDE4 inhibitors are promising anti-inflammatory alternatives for the effective management of AD.

Conflict of interest:

None.

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