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Emerging Treatment Options in Atopic Dermatitis: Topical Therapies

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Abstract
Atopic dermatitis is a chronic inflammatory skin disorder affecting children and adults, with the majority presenting mild to moderate disease severity. The use of topical corticosteroids (TCSs) in combination with emollients has been the mainstay for treating mild to moderate atopic dermatitis since the 1950s, and as a supplement to systemic treatment in severe disease. However, while very effective, TCSs are often accompanied by poor adherence due to corticophobia (fear of using corticosteroids in patients or doctors), unwanted side effects, and in some cases insufficient clinical response. Topical calcineurin inhibitors (TCIs) are able to inhibit the activation of T-lymphocytes and thereby diminish inflammation. In some patients the use of TCIs has been limited due to a localized burning sensation on the first days of treatment, and also due to fear of other adverse effects. Consequently, there has been a need for the development of new topical products for atopic dermatitis. Novel topical therapies are in the pipeline and comprise both new doses and formulations of well-known pharmaceutical molecules and novel approaches targeting unique inflammatory pathways and mechanisms of disease, with a promise of higher efficacy and less harmful side effects. We review topical drugs in the pipeline for atopic dermatitis, and focus on those available in the clinicaltrials.gov database with a first received date from January 1, 2014 to May 31, 2017.

Introduction

Atopic dermatitis (AD) is chronic inflammatory dermatological disease, with characteristics including pruritus, dry skin, and chronic or chronically relapsing dermatitis. It is the most common inflammatory skin disease with 10–25% of children and 2–10% of adults in affluent nations being affected. The socioeconomic impact on the patient, the family, and the society as a whole is substantial [1–3]. Within the AD population, severity scoring suggests that more than 70% of patients have mild disease that is dealt with in primary care. Approximately 20% have moderate and 5–10% severe AD, commonly requiring referral to a dermatologist [4]. The complexity of AD is demonstrated by a complex pathogenesis comprising a dysregulated immune system, a compromised skin barrier, and a range of trigger factors [5]. There are new risk modifiers and associated comorbidities constantly being identified for this disease, which gives rise to a need for early intervention and new disease modifying strategies [6–13].

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Established Therapies

Various treatment approaches exist for alleviating the disease, including hydration and restoration of the skin barrier with the use of emollients, avoidance of typical AD triggers, specific behavioural approaches to reduce scratching, antibacterial measures, and topical and/or systemic anti-inflammatory drugs [14, 15]. During a 10-year period in the USA, 7.4 million visits of children younger than 18 years were registered at physicians' offices for the diagnosis of AD. Topical corticosteroids (TCSs) were prescribed in 25–34% and calcineurin inhibitors in 23% of visits [16]. In mild disease the regular use of emollients and either TCSs or calcineurin inhibitors are recommended [15, 17]. These agents are in most situations individually or in combination able to bring relief to the patient; they are, however, rarely sufficient in more recalcitrant cases. The therapeutic approach to AD is highly dependent on several factors, e.g., patient insight into their disease, adherence, trigger factors, and psychosocial disturbances, but perhaps the most important factors when choosing a specific drug and way of administration are disease severity and any registered efficacy of previous treatments [18]. Thus, for the purpose of this review of emerging topical treatments, we focus on AD patients commonly alleviated by established topical therapies and emollients [14, 15, 17].

Topical Therapies

The treatment goal is to diminish pruritus, supress inflammation, and restore skin barrier function. In mild to moderate AD the use of topical therapies is advantageous in comparison with systemic treatments as they generally perform well with a minimum risk of adverse events. The most commonly used topical therapies are emollients, TCSs, and topical calcineurin inhibitors (TCIs).

Emollients or moisturisers are widely recommended, as they are effective and safe. They reduce transepidermal water loss by acting as an occlusive layer on the skin [18, 19]. Moreover, advanced moisturisers are able to bind or attract water in the stratum corneum, actively hydrating the epidermal barrier [20, 21], and can reduce the severity of disease and prolong the interval between flares [21]. The addition of moisturisers to topical anti-inflammatory treatment has been shown to be more effective than anti-inflammatory treatment alone and has reduced the amount of TCSs used [20, 21].

For more than half a century the use of TCSs has been the backbone of AD treatment, and they are recommended by European, American, and Japanese Academies of Dermatology [17, 22, 23]. TCSs have anti-inflammatory effects and reduce skin inflammation and pruritus. In most cases, TCSs used correctly bring swift relief to the patient. Due to the chronic and chronically relapsing nature of AD there can be a lifelong need for treatment, with a significant risk of adverse events. These include skin atrophy, and to a lesser extent striae and telangiectasias, while the risk of a rebound phenomenon when tapering TCSs is exaggerated if used appropriately [24, 25]. The risk of systemic side effects is low and correlated to the potency of the TCS, the extent and degree of skin inflammation, and the age of the patient. Infants and children have a higher degree of systemic absorption due to a less mature skin barrier [24]. The biggest challenge faced when prescribing TCSs is patient fear of TCS-related adverse events (corticophobia). In conclusion, TCSs are recommended if AD is not sufficiently controlled by emollient therapy alone; it is the mainstay anti-inflammatory treatment, and proactive use is recommended in skin areas that commonly flare [17, 22].

The use of TCIs was introduced in 2000 as an alternative to TCS. The selective inhibition of T-cell activation decreases the activity of a range of transcriptional factors that control cell division and reduces the expression of pro-inflammatory cytokines which ultimately diminish inflammation. Pimecrolimus cream and a high and low concentration formulation of tacrolimus ointment are currently approved for AD in both children over 2 years of age and adults. Their widespread use is facilitated by their inability to produce skin atrophy, and despite a black box warning from the FDA in 2005 concerning increased risk of malignancy, no solid evidence has been published demonstrating such a causal relationship. TCIs are primarily used for delicate skin areas unresponsive to low-potency TCSs, in AD cases recalcitrant to steroids, and in patients with a need for continuous long-term topical anti-inflammatory therapy [17, 22]. TCIs can also be used as intermittent prophylactic therapy equivalent to TCSs [26].

A systematic review and meta-analysis of TCSs versus TCIs concluded that calcineurin inhibitors and corticosteroids have comparable efficacy. However, TCIs were associated with higher costs and have more adverse events, such as skin burning and pruritus. The results provided a level-1a support for the use of corticosteroids as the first anti-inflammatory therapy of choice for AD [27].

Immunopathology of AD

The pathophysiology of AD involves genetic predispositions, skin barrier dysfunction, increased activity, and Th2/Th22 skewing of the immune system and the impli-

Table 1. Details of the studies included in the review

Name	ID[1]	Status	Phase	*n*	Type/target	Primary end point
PD4 inhibitors						
Crisaborole	NCT02118792	Completed	III	764	PDE4	ISGA day 29
DRM02	NCT01993420	Completed	II	21	PDE4	Physicians' lesion assessment week 6
E6005	NCT02094235	Completed	II	62	PDE4	Pharmacokinetics, safety
OPA-15406	NCT02068352	Completed	II	94	PDE4	Safety, IGA week 4
Roflumilast	NCT01856764	Completed	II	40	PDE4	SCORAD day 15
JAK inhibitors						
Ruxolitinib	NCT03011892	Recruiting	II	300	JAK1+2	EASI week 4
Tofacitinib	NCT02001181	Completed	II	69	JAK1+3	EASI week 4
Others						
MRX-6	NCT02031445	Terminated	II	73	Arachidonic acid inhibitors, phospholipase A2 inhibitors	IGA week 4
ZPL-5212372	NCT02795832	Recruiting	II	43	cPLA2 enzyme inhibitor	Safety and tolerance
DS107	NCT02925793	Recruiting	II	300	DGLA	IGA week 10
SB011 (DNAzyme hgd40)	NCT02079688	Completed	II	25	GATA-3 mRNA	SCORAD day 15
DMT210	NCT02949960	Recruiting	II	25	Isoprenylcysteine analogue	IGA day 28
Q301 (zileuton)	NCT02426359	Completed	II	57	Leukotriene inhibitor	IGA week 8
VTP-38543	NCT02655679	Completed	II	104	Liver X receptor agonist	AE day 28
Benvitimod	NCT02564055	Completed	II	247	NSAID and cytokine, phosphotransferase and T-lymphocyte inhibitor	IGA week 12
AM1030	NCT02379910	Completed	II	36	Serotonin 2B receptor antagonists	AE, tolerability
SP14019	NCT02865356	Recruiting	II	36	T lymphocytes	EASI day 7, 14, 21, 28
PAC-14028	NCT02965118	Recruiting	III	240	TRPV1 antagonist	IGA week 8

All studies are interventional randomized controlled trials. EASI, Eczema Severity and Area Index; IGA, Investigators Global Assessment; ISGA, Investigators Static Global Assessment; SCORAD, Scoring Atopic Dermatitis; AE, adverse events; cPLA, cytosolic phospholipase; DGLA, dihomo-γ-linolenic acid; JAK, Janus kinase; PDE, phosphodiesterase; NSAID, non-steroidal anti-inflammatory drug; TRPV1, transient receptor potential vanilloid type 1. [1] ID, unique National Clinical Trial (NCT) identifier at www.clinicaltrial.gov.

cation of environmental trigger factors. One possible hypothesis of the mechanisms underlying the disease is that reduced function of the skin barrier results in increased transepidermal water loss, xerosis, and subsequent penetration of allergens, pathogens, and irritants, altogether activating and modulating the immune system and producing dermatitis (outside-in hypothesis). A second approach is that of innate and adaptive immune imbalances giving rise to an abnormal T-cell response, elevated IgE levels, and increased type 2 cytokine production, consequently leading to reduced skin barrier function, xerosis, and dermatitis (inside-out hypothesis). Whether one or the other is the primary key pathophysiological mechanism, the bottom line is a state of increased immune activity and reduced skin barrier integrity. Thus, by addressing the first, the latter or both is meaningful [11, 28–33]. Targeting key mediators of disease, either via narrow isolated effects or broader downstream actions, are potential means to alleviate the disease.

Selecting Studies for This Paper

Papers on emerging topical therapies comprise the body of this review in AD combined with data on current and completed clinical trials concerning new topical treatment options for AD identified at clinicaltrials.gov. We selected AD-related therapies that have been reported from randomized, controlled trials in phases II, III, and IV with a first received date from January 1, 2014 to May 31, 2017. If one agent was represented in more than one trial in the clinicaltrials.gov database, it is described in the review and tables in only one study (Table 1). We focused on the emerging drugs which are developed based on rea-

sonable evidence of a potential effect in AD. In doing so, more speculative therapeutic approaches and alternative means of disease modification received a lower priority. Lastly, we excluded therapies that could be categorized as traditional Chinese medicine, herbal medicine, probiotics, emollients, TCSs, or TCIs.

Emerging Topical Treatments in AD

Targeting Janus Kinase/Signal Transducer and Activator of Transcription Pathways

The Janus kinase/signal transducer and activator of transcription (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 [34]. Moreover, it downregulates the expression of structural skin proteins, and weakens the epidermal barrier function [35–39]. Additionally, downstream signalling in this pathway has been shown to prevent the induction of genes encoding innate immune response proteins, including β-defensins and cathelicidin in keratinocytes [40], 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 [41].

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 [42]. Moreover, tofacitinib has been shown to directly inhibit cytokines, most importantly IL-4, thereby rapidly attenuating JAK-STAT signalling in keratinocytes [43, 44]. While the results in psoriasis trials have shown quite varying results [45, 46], 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 [47]. 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 studies are 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 [48].

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 [49, 50]. 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) [51–53]. 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 [51]. 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 signalling effectors [54, 55]. 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 [54, 56–59]. 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 [56]. 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 [60]. 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 [60]. 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 crisaborole- and 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 [61–63]. 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 [62]. 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 [64]. 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 [52]. 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 [65]. 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) [66]. 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 [67]. 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, within-subject 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 non-steroidal, 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 [68–71]. 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 [71]. 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 [69]. 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 [72–74]. Somewhat positive results have been observed in both of the administered formulations of the drug as communicated in press releases [75, 76]. 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 [77–82]. 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 [83]. 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 [84] by cleaving GATA-3 mRNA capable of mitigating cytokine production, consequently reducing key features of atopic inflammation [85]. 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 [86–88]. LXR agonists may intervene with AD typical skin inflammation [89, 90]. 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 [91], 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 [92]. 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 [93]. 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 [30, 79, 94, 95]. The 5-lipoxygenase inhibitor zileuton has been shown to attenuate the action of IL-31 in mice [96] 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 [97]. 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 [98–100]. 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 [101]. AM1030 is similar to a previously investigated agent demonstrating anti-inflammatory properties [102], 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 [103]. SP14019 possibly bypasses the severe adverse events commonly seen from systemic CsA treatment [14, 104, 105]. Moreover, topical CsA has been extensively used in the field of ophthalmology [106]. 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

Despite the use of emollients in combination with TCSs or TCIs being effective mainstay topical treatments for AD, the many concerns from clinicians and patients over their use are significant and comprise an everyday challenge in dermatology. Consequently, the need for new topical treatments in AD is important. Fortunately, novel insights into the etiopathogenesis of AD have led to promising new therapies and treatment modalities. The primary areas of interest are currently the mitigation of the JAK-STAT pathway and PDE4 enzyme inhibition, closely followed by an array of other new drugs and pharmaceutical agents where, in several cases, the mechanisms of action need to be identified.

Key Message

There are several new topical therapies in the pipeline for treating mild to moderate atopic dermatitis and as a supplement to systemic treatment in more severe, recalcitrant, and chronic dis-

ease. In this review, we present emerging topical therapies in a systematic fashion by summarizing the major background information followed by an appraisal of the existing data and studies related to the drugs.

Disclosure Statement

M.D. is an investigator, speaker, and/or advisor for AbbVie, Pierre Fabre Dermo-Cosmétique, Meda Pharma, Leo Pharma, Sanofi-Genzyme, and Regeneron. C.V. is an investigator for AbbVie A/S and Pierre Fabre Dermo-Cosmétique. He has served on advisory boards for Astellas Pharma, and has been a speaker for Leo Pharma, Astellas, MSD, AbbVie, Novartis, and Pfizer. U.N. declares no relevant conflicts of interest.

Author Contributions

All authors have participated sufficiently in the work to take public responsibility for its contents as stated at http://www.publicationethics.org.uk.

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