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REVIEW



Investigational drugs for atopic dermatitis

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ABSTRACT

Introduction: Many novel medications and herbal medicines have claimed efficacy on atopic dermatitis (AD).

Areas covered: This review covers evidence on efficacy of topical and oral forms of novel and investigational drugs. Topical agents include emollients, phosphodiesterase E4 (PDE4) inhibitors, and topical herbs. There is little evidence that ceramides or natural moisturizing factors provide relief in AD. PDE4 inhibitors have shown promise as an effective topical treatment for mild-to-moderate AD with minimal adverse events, and dupilumab as an effective subcutaneous agent for the treatment of moderate-to-severe AD in adult patients with little adverse effects. However, only preliminary data are available for dupilumab in children with AD. The long-term effects of dupilumab are also not known. Potential new systemic treatments include a number of herbal concoctions.

Expert opinion: Randomized, double-blind placebo-controlled trials (RCTs) have demonstrated topical PDE4 inhibitors are effective and safe in the treatment of both children and adults with AD but further evaluations are needed. RCTs have also shown that subcutaneous dupilumab is an effective and safe agent for the treatment of AD in adults. Long-term effects of these topical and systemic investigational drugs are currently unavailable. Regarding herbal medications, scientific methods are often flawed and objective evidence is lacking.

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1. Introduction

Atopic dermatitis (AD) or eczema is a chronically relapsing dermatosis characterized by pruritus, erythema, vesiculation, exudation, excoriation, crusting, scaling, and sometimes lichenification [1–8]. The prevalence of AD has increased two- to threefolds over the past three decades in industrialized countries and there is evidence to suggest that this prevalence continues to increase [1,6,9,10]. AD affects 9–20% of children and 1–3% of adults in the United States [1,3,11–15]. The condition is more prevalent in children that belong to upper socioeconomic classes, smaller family sizes, and families with overzealous hygiene [1,3,11–15]. The increase in prevalence may be due to increased access to medical care, improved recognition, better epidemiological reporting, or increased environmental allergens due to industrialization and pollution. On the other hand, the hygiene hypothesis postulates that an unusually clean environment may result in AD and other allergic diseases. The hypothesis states that exposure to bacteria and other immune system modulators are important during early development, and missing out on such exposure increases the risk for allergy [16,17]. There have been recent advancements in the conceptual description of pathogenesis [18]. The key concept is that skin barrier abnormalities play an essential role in initiation of early AD, and antigen penetration through a compromised barrier leads to increased innate immune responses and subsequent

cutaneous inflammation. The brick-and-mortar hypothesis suggests that there is an intrinsic/genetic defect in the barrier function of the epidermis [19]. It has been shown that loss-of-function mutations in the filaggrin (filament-aggregating protein) (*FLG*) gene are associated with an increased risk of atopic sensitization in these individuals [20–24]. Filaggrin is a key component of the epidermal differentiation complex of the stratum corneum in the epidermal layer of human skin [19]. It forms the natural moisturizing factor in the stratum corneum and plays an important role in the barrier function of the skin [25]. The keratohyalin granules in the granular layers of the epidermis are predominantly composed of pro-filaggrin [26]. *FLG* aggregates the keratin cytoskeleton system to form a dense protein–lipid matrix that is cross-linked by transglutaminases to form a cornified cell envelope [25,26]. The latter prevents epidermal water loss and impedes the entry of allergens, infectious agents, and chemicals [25]. It is believed that defective epidermal function is related to the down-regulation of the *FLG* gene [27]. Recent findings have shown that the affected skin of atopic individuals is deficient in filaggrin degradation products [28].

Many patients with moderate and severe AD are complicated with bacterial infection, most commonly *Staphylococcus aureus*, *Staphylococcal epidermidis*, and less commonly, group A β -hemolytic streptococcus (*Streptococcus pyogenes*) [1,29,30]. Children with AD may suffer from lack of sleep, irritability, daytime tiredness, emotional stress, lowered self-

Article highlights

- AD is a chronic relapsing dermatitis associated with allergy/atopy.
- PDE4 inhibitors show promise as an effective topical treatment for mild-to-moderate AD with minimal adverse events.
- Preliminary results have shown that dupilumab given subcutaneously is an effective agent for the treatment of AD in adult patients with little adverse effects.
- Standardization and manufacture of proprietary herbal medicine have become possible.
- There is a need for more well-designed, randomized control trials in herbal medicine research for AD.

Investigational drug discovery for AD should include both topical and systemic medicine. Objective scientific documentation of drug efficacy and adverse effects must be carried out.

This box summarizes key points contained in the article.

esteem, and psychological disturbance [31,32]. Quality of life of patients and their families are often severely impaired [31,33-35].

Successful treatment of AD requires a systematic multi-pronged approach that consists of avoidance of triggering factors, optimal skin care, pharmacotherapy during acute exacerbations, and education of patients/caregivers [1,8]. Topical corticosteroids are the mainstay of pharmacotherapy for AD, with the choice of potency depending on the severity, site, and extent of the outbreak [8]. Corticosteroids mediate their anti-inflammatory effects through binding to a cytoplasmic glucocorticoid receptor in the target cells and forming complexes that enter the nucleus of the cell. The risk of side effects depends on the potency of the corticosteroid, concomitant use of occlusion, the area being covered, skin integrity, and duration of treatment. Compared with adults, children are at higher risk of both local and systemic effects. Local adverse effects particularly on delicate skin areas include skin atrophy, striae, depigmentation, telangiectasia, decreased subcutaneous adipose tissue, rosacea, perioral dermatitis, folliculitis, and steroid acne. Among systemic side effects are Cushing's syndrome, adrenal suppression, cataracts, glaucoma, osteopenia/osteoporosis, and growth retardation. Rebound flares may occur following discontinuation of therapy. Tachyphylaxis may occur with prolonged treatment [36,37]. There is scanty evidence that growth retardation can also occur from inadequate control of severe eczema [38]. A new autosomal recessive entity has also been reported that severe pre- and postnatal growth retardation and developmental delay is associated with eczema [36-39]. Meanwhile, appropriate usage of topical corticosteroids for AD has been demonstrated to be associated with therapeutic efficacy without any adverse effects [40].

Topical immunomodulators (tacrolimus and pimecrolimus) are beneficial and safe for adults and children over 2 years of age and represent a major new alternative to chronic corticosteroid use. Tacrolimus and pimecrolimus inhibit the activity of calcineurin to dephosphorylate the nuclear factor of activated T-cell (NF-AT), a transcription

factor required to activate interleukin (IL)-2 gene transcription. Inhibition of IL-2 production blocks the activation of T helper cells, T regulatory cells, natural killer cells and monocytes. The immune responses that stimulate inflammation are therefore down-regulated. Both medications have favorable efficacy and safety profiles.

AD involves complex interactions among susceptible genes, cellular and humoral immune mediators, skin barrier defects, infections, neuroendocrine factors, and environmental factors [1,21,41,42].

Investigational drugs are being developed targeting the underlying complex pathophysiology. It is hoped that the new drugs are not only effective in the treatment of AD, but have less side effects than the traditional medications currently in use.

2. Methodology

A PubMed search was conducted and publications about new and emerging treatments for AD were retrieved and analyzed. We used PubMed 'Clinical Queries' search engine and key words 'Atopic dermatitis drug treatment.' Under 'Clinical Study categories' and setting Category as 'Therapy' and Scope as 'Narrow,' 719 hits were obtained. Under 'Systematic Reviews,' 202 hits were obtained. These hits were screened for relevance to our theme to identify publications on investigational drugs. In addition, the bibliographies of the retrieved articles were also hand-searched for relevant referenced and highly cited articles. They are described in the following paragraphs under 'Topical investigational drugs' ($n = 20$ citations), 'Systemic investigational drugs' ($n = 24$ citations), and 'Complementary, Alternative and Chinese Medicines' ($n = 26$ citations).

3. Results

3.1. Topical investigational drugs

In recent years, researches focusing on the skin barrier have provided new data on factors important for epidermal barrier function [43,44]. Key players in the skin barrier are proteins and lipids, especially nature moisturizing factors and ceramides [45]. These products are strictly speaking not considered as drugs. The successfully marketed products are usually commercially sold as emollients [46]. There have been very few efficacious topical agents registered in clinical trials in recent years.

A non-steroidal, anti-inflammatory moisturizing cream containing rhamnosoft, ceramides, and L-isoleucine (ILE) (pro-AMP cream) has been developed for the specific treatment of AD involving the face [47]. Rhamnosoft is a rhamnose-rich polysaccharide with high affinity to keratinocyte receptors sharing anti-inflammatory and bacterial adhesion properties. Topical ceramides can restore defective skin barrier in AD. Topical L-isoleucine is able to stimulate production of AMP at the skin level and potentiate chemoattractant activities of β -defensin. Marseglia et al. evaluated the clinical efficacy and tolerability of pro-AMP cream in the treatment of facial AD in children in comparison with an emollient cream in a randomized,

prospective, assessor-blinded, parallel groups (2:1) controlled trial [47]. One-hundred and seven children (72 allocated to pro-AMP cream and 35 allocated to control group) with mild-to-moderate chronic AD of the face were enrolled. The creams were applied twice daily for a 6-week period. Facial Eczema Severity Score (ESS) was evaluated at baseline, week 3, and week 6, by an assessor unaware of the treatment allocation. Investigator's Global Assessment (IGA) score was assessed at week 3 and at week 6. Tolerability was evaluated at week 3 and at week 6 using a 4-point score (from 0: low tolerability to 3: very good tolerability). At baseline ESS, mean (SD) was 6.1 (2.4) in the pro-AMP cream group and 5.3 (3) in the control group. In the pro-AMP group, in comparison with baseline, ESS was significantly reduced to 2.5 (–59%) after 3 weeks and to 1.0 (–84%) at week 6 ($p = 0.0001$). In the control group, ESS was reduced to 3 (–42%) at week 3 and to 2.6 (–50%) at week 6. Both products were well tolerated. The authors concluded that pro-AMP cream is effective in the treatment of mild-to-moderate chronic facial AD and the clinical efficacy is greater than an emollient cream [47].

Hon et al. investigated a proprietary cream (Ezerra®, HOE Pharmaceuticals, Sdn. Bhd., Malaysia) for AD [48]. Thirty-four patients were recruited; 74% reported 'very good' or 'good,' whereas 26% reported 'fair' or 'poor' general acceptability of treatment of the cream. There were no intergroup differences in pre-usage clinical parameters of age, objective SCORing Atopic Dermatitis (SCORAD) index, pruritus, sleep loss, skin hydration, transepidermal water loss, topical corticosteroid usage, oral antihistamine usage, or general acceptability of treatment of the prior emollient. Following use of the cream, mean pruritus score decreased from 6.7 to 6.0 ($p = 0.036$) and mean Children's Dermatology Life Quality Index improved from 10.0 to 8.0 ($p = 0.021$) in the 'very good'/'good' group. There were no statistically significant differences in the acceptability of wash ($p = 0.526$) and emollients ($p = 0.537$) with pre-trial products. When compared with the data of another ceramide-precursor moisturizer in a previous study, there was no statistical difference in efficacy and acceptability between the two products [49]. So, patients who accepted the cream had less pruritus and improved quality of life following its usage than non-accepting patients. The cream containing shea butter extract did not differ in acceptability or efficacy from a ceramide-precursor product. Thus, patient acceptability is an important factor for treatment efficacy. The authors remarked that there is a general lack of published clinical trials to document the efficacy and skin biophysiological effects of many of the proprietary moisturizers [43,50]. A recent Cochrane review on randomized trials concluded that most moisturizers showed some beneficial effects, producing better results when used with active treatment, prolonging time to flare, and reducing the number of flares and amount of topical corticosteroids needed to achieve similar reductions in AD severity. The Cochrane reviewers also concluded that there is no reliable evidence that one moisturizer is better than another [51].

Silver-coated fabrics or engineered silk has been considered as a form of topical treatment. Lopes et al. carried

out a systematic review of three large biomedical databases [52]. Evidence was graded based on an analysis of outcome measures. The overall quality of evidence was presented using the GRADE approach recommended by the Cochrane Handbook for Systemic Reviews of Interventions. Meta-analyses of comparable studies were carried out. Thirteen studies (eight RCTs and five observational studies) met the eligibility criteria. Interventions were limited to silk (six studies), silver-coated cotton (five studies), borage oil, and ethylene vinyl alcohol (EVOH) fiber (one study each). Silver textiles were associated with improvement in SCORAD index (2 of 4), fewer symptoms, a lower need for rescue medication (1 of 2), no difference in quality of life, decreased *S. aureus* colonization (2 of 3), and improvement of transepidermal water loss (1 of 2), with no safety concerns. Silk textile use was associated with improvement in SCORAD index and symptoms, with no differences in quality of life or need for rescue medication. With borage oil use, only skin erythema showed improvement, and with EVOH fiber, an improvement in AD severity was reported. Thus, recommendation for the use of functional textiles in AD treatment is considered weak, supported by low quality of evidence regarding effectiveness in AD symptoms and severity, with no evidence of hazardous consequences with their use. The authors suggested that more studies with better methodology and longer follow-up are needed [52].

Bianchi et al. evaluate the effect of a new emollient balm on clinical parameters (SCORAD, xerosis, pruritus), skin barrier function (transepidermal water loss and loricrin, filaggrin, corneodesmosin, and involucrin expression), skin microflora biodiversity, and *Staphylococcus aureus* and *Staphylococcus epidermidis* balance in children with mild AD [53]. The randomized, controlled study enrolled 54 young children and compared the emollient balm (emollient group, $n = 28$) with a hygiene product only (control group, $n = 26$) twice a day for 28 days. The investigators found improvement in favor of the emollient group in SCORAD ($p < 0.001$), pruritus ($p = 0.06$), and xerosis ($p = 0.06$) after 28 days of application. Moreover, transepidermal water loss decreased in the emollient group by 34% ($p = 0.06$) and involucrin expression by 37% ($p = 0.001$) at day 28 from baseline in association with improvement in barrier function, whereas other barrier-specific proteins did not vary. *S. aureus* increased significantly in the control group only (6.5 times, $p = 0.01$), whereas *S. epidermidis* remained stable in both groups. The Shannon index ($H' = 2.3$) did not vary with treatment in either group. The investigators concluded that twice-daily application of a new emollient balm in children with mild AD protected the skin from *S. aureus* proliferation and preserved microflora biodiversity.

Hon et al. performed an extensive review on emollient treatment for AD, and tabulated 15 selected proprietary moisturizers/emollients and their claimed ingredients [46]. The investigators concluded that most moisturizers showed some beneficial effects, but there was generally no evidence that one moisturizer is superior to another. Choosing an appropriate emollient for AD patients would improve acceptability and adherence for emollient treatment. Physician's recommendation is the primary consideration

for patients when selecting a moisturizer/emollient; therefore, doctors should provide evidence-based information about these emollients.

Crisaborole 2% topical ointment (Anacor Pharmaceuticals, Inc. Palo Alto, CA 94303 USA), EUCRISA™, Pfizer, NY, USA an anti-inflammatory, non-steroidal phosphodiesterase E4 (PDE4) inhibitor has been investigated for its potential role in the treatment of AD [54]. The 2% strength appeared to be the superior dosing regimen [54]. Crisaborole has several key features in its mode of action which distinguish it from existing treatments for AD, notably its activity against the PDE4 pathway, regulating cyclic AMP (cAMP) levels. PDE4 regulates inflammation which is overactive in patients with AD. Crisaborole is less immunosuppressive than other pathways and has no effect on skin thinning. The ointment interrupts within a few days into treatment. Early treatment of mild-to-moderate AD patients might help to control AD better and improve quality of life. In two identically designed, double-blind studies, 1528 children aged ≥ 2 years with an Investigator's Static Global Assessment (ISGA) score of mild (2) or moderate (3) AD were randomized to receive twice-daily application of crisaborole or vehicle in a ratio of 2:1 for 28 days [55]. The primary end point was ISGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline. One-thousand sixteen patients in the crisaborole-treated group and 506 patients in the control group completed the study. The authors found that more crisaborole-treated than vehicle-treated patients achieved ISGA score success, with a greater percentage with clear/almost clear of AD. Also, crisaborole-treated patients achieved improvement in pruritus earlier than vehicle-treated patients. Crisaborole was well tolerated, with similar treatment-emergent adverse events as the vehicle. The efficacy and safety of crisaborole in the treatment of AD have also been demonstrated in other studies [56–60]. Crisaborole is now approved by US Food and Drug Administration (FDA) [61].

E6005 (RVT-501) is another selective phosphodiesterase 4 inhibitor. E6005 was at the phase 2 stage of clinical trials as a transdermal PDE4 inhibitor for adults and pediatric patients with AD, and with its demonstrated effect on reducing inflammation and suppressing itching as well as favorable safety profile. The efficacy of E6005 in patients with AD was evaluated in a randomized, investigator-blinded, vehicle-controlled, multiple ascending dose study included 40 adult male patients with AD, who were randomly assigned to 10 days of treatment with either E6005 ointment or vehicle ointment. Of 81 patients screened, 40 who had typical lesions on their posterior trunk were randomized into the study. The targeted lesion severity scores decreased in a concentration-dependent manner in patients treated with E6005. This drop was significant in the 0.2% E6005 ointment treatment group. The authors conclude E6005 ointment showed anti-inflammatory efficacy in adult patients with AD [62]. There was no objective measurement to document itch reduction and quality of life improvement. AD was improved but not cured.

OPA-15406 is another novel, topical, nonsteroidal, selective PDE4 inhibitor. In a randomized, double-blind, vehicle-controlled, phase 2 trial, 121 patients aged 10–70 years with mild-to-moderate AD were assigned to receive OPA-15406 0.3% ointment ($n = 41$), OPA-15406 1% ointment ($n = 43$), or vehicle ($n = 37$) twice daily [63]. The primary end point, Investigator

Global Assessment of Disease Severity score of 0 or 1 with ≥ 2 -grade reduction, was met at week 4 in the OPA-15406 1% group ($p = 0.0165$ vs vehicle). Mean percentage improvement from baseline Eczema Area and Severity Index score (EASI) for OPA-15406 1% group was notable in week 1 (31.4% vs 6% for vehicle; $p = 0.0005$), even larger in week 2 (39% vs 3%; $p = 0.0001$), and persisted for 8 weeks. Visual analog scale pruritus scores improved from moderate to mild within the first week in the OPA-15406 1% group (36.4% mean change; $p = 0.0011$). Blood levels of OPA-15406 were negligible. The incidence of side effects was low and most side effects were mild.

An emulsion containing 4% sodium cromoglycate emulsion has been developed for the treatment of AD in children [64]. A meta-analysis of three studies ($n = 490$; mean age = 5.3 years) involving the topical use of 4% sodium cromoglycate emulsion showed the efficacy of this product in the treatment of children with AD.

In another novel trial on topical drug, Wu et al. evaluated the efficacy and safety of 15(R/S)-methyl-lipoxin A(4) in topical treatment of infantile eczema [65]. Lipoxins are potential anti-inflammatory mediators and serve as an endogenous 'braking signal' in the inflammatory process. In the two-center, double-blind, placebo-controlled, randomized, parallel-groups comparative study, 60 patients were randomly assigned to receive either the 15(R/S)-methyl-lipoxin A(4) cream, mometasone furoate (Eloson, Schering-Plough, Shanghai, China), or placebo for 10 days. The efficacy was determined using the Severity Scale Score (SSS), EASI and the Infants' Dermatitis Quality of Life Index (IDQOL). Safety was monitored by physical examination, laboratory investigation, and documentation of clinical adverse events. The treatment of eczema with 15(R/S)-methyl-LXA(4) cream significantly relieved the severity, induced a recovery, and improved the quality of life of the patients, as demonstrated by significantly reduced SSS, EASI, and IDQOL, respectively, in a way similar to the efficacy of Eloson, Schering-Plough, Shanghai, China. All safety parameters remained within normal limits. No clinical adverse event was found. 15(R/S)-methyl-LXA(4) was well tolerated, and significantly reduced the severity of eczema. The investigators suggest that 15(R/S)-methyl-LXA(4) warrants further investigation in the treatment of eczema [65].

Topical Janus kinase inhibitors (JAKi) have attracted attention for their role in treating inflammatory disorders. There has been only one randomized, double-blind placebo-controlled trial (RCT) for treatment of AD with topical tofacitinib [66]. This 4-week study included 69 adults randomized 1:1 to receive either 2% tofacitinib or vehicle ointment twice daily. EASI scores were significantly improved at week 4. The proportion of patients with PGA scores of 'clear' or almost clear was 73% for tofacitinib and 22% for vehicle. Improvements in pruritus were observed as early as day 2. Adverse effects occurred in 44% of patients, 89% of which were considered mild. Tofacitinib ointment showed significantly greater efficacy vs. vehicle across end points, with early onset of effect and comparable safety/local tolerability to vehicle.

3.2. Systemic investigational drugs

There have been a number of emerging drugs in recent years [67,68]. Existing therapies rely largely on allergen avoidance, emollients, and topical and systemic immune-suppressants. Some of the existing topical and systemic immune-suppressants have significant toxicity and transient efficacy. So far, no specific targeted therapies are in clinical use today. As our knowledge of the immune and molecular pathways that cause different subsets of AD increases, a variety of experimental and biologic agents that target pathogenic molecules, have been developed for safe, effective and long-term treatment of AD.

Among the biologics, two T cell inhibitors alefacept and efalizumab have been considered for the treatment of moderate-to-severe AD. However, these agents are not suitable for long-term administration due to their toxicity [69]. There have not been good clinical trials to confirm the effectiveness of alefacept and efalizumab [70].

Targeting Th2 cell-mediated atopic immune response, the human monoclonal antibody dupilumab has been found to be effective in reducing the severity of moderate-to-severe AD in adults in a phase 2 trial [71]. Dupilumab is a fully human monoclonal antibody directed against the IL-4 receptor α subunit that is able to block the signaling of the key Th2 cytokines IL-4 and IL-13, [72]. Early-phase trials demonstrated clinical efficacy of subcutaneous dupilumab in the treatment of adults with moderate-to-severe AD [73-76].

In 2016, two randomized, placebo-controlled, worldwide phase 3 trials were conducted, enrolling 671 adult patients suffering from moderate-to-severe AD whose disease was inadequately controlled by topical treatment [71]. Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo. In these studies, dupilumab significantly improved the symptoms and signs of AD as well as scale value of anxiety, depression, and quality of life, as compared with placebo. The overall incidence of adverse events was similar in the dupilumab and the placebo groups, with the exceptions of injection-site reactions and conjunctivitis which were more frequent in patients receiving dupilumab than in those receiving placebo. The preliminary results are promising, but trials of longer duration are needed to assess the long-term effectiveness and safety of dupilumab [71].

Recently, dupilumab was approved by the US FDA for the treatment of severe AD in adults [77]. It was not possible to translate the published results to children until recently. The pharmacokinetics, safety, and efficacy of dupilumab were evaluated with 38 children, aged 6–11 years, and 40 adolescents, aged 12–17 years, with moderate-to-severe AD. All had failed topical corticosteroid therapy. Some of the children (16%) and adolescents (22.5%) had failed at least one systemic therapy. Both age groups were given either a 2 or a 4 mg/kg dose of dupilumab (administered subcutaneously), nothing for 8 weeks, followed by 4 weekly doses of their respective regimens. Mean EASI scores at baseline were 31.7 among the adolescents and 35.9 among the children. At week 12, mean scores in the younger cohort given either 2 or 4 mg/kg had

improved by 76.2% or 63.4%, respectively, from baseline. In the adolescents, EASI scores at week 12 had improved by a mean of 66.4% in the 2-mg/kg group and 69.7% in the 4-mg/kg group. (<https://www.mdedge.com/dermatologynews/article/133798/atopic-dermatitis/dupilumab-improved-eczema-scores-children-open>) [78] This study has not been published on Medline referenced journal to date.

The future use of dupilumab in pediatric patients could potentially provide insights about its impact as early intervention may modify the course of the disease. Dupilumab is ready to inaugurate a long and promising biological target treatment option for Th2 cell-mediated atopic immune response that characterizes AD and asthma. Mepolizumab (anti-IL-5) and omalizumab (anti-IgE), which have been studied in asthma and allergic rhinitis, were not useful in AD [79,80]. This fact may underlie a pivotal role of IL-4 and IL-13 among the Th-2 signal cytokines in AD.

IL-31 is a recently identified cytokine produced by Th2 cells that is involved in the development of AD-induced skin inflammation and pruritus [81]. Ruzicka et al. assessed the efficacy and safety of nemolizumab (CIM331, Chugai Pharmaceutical Co., Ltd. Toyko, Japan), a humanized antibody against IL-31 receptor A (IL-31RA), in the treatment of AD [82]. In this phase 2, randomized, double-blind, placebo-controlled, 12-week trial, the authors assigned adults with moderate-to-severe AD that was inadequately controlled by topical treatments to receive subcutaneous nemolizumab (at a dose of 0.1, 0.5, or 2.0 mg per kg of body weight) or placebo every 4 weeks or an exploratory dose of 2.0 mg of nemolizumab per kg every 8 weeks. The primary end point was the percentage improvement from baseline in the score on the pruritus visual-analogue scale (on which a negative change indicates improvement) at week 12. Secondary end points included changes in the score on the EASI, on which a negative change indicates improvement, and body surface area of AD. Of 264 patients who underwent randomization, 216 (82%) completed the study. At week 12, among the patients who received nemolizumab every 4 weeks, changes on the pruritus visual-analogue scale were –43.7% in the 0.1 mg group, –59.8% in the 0.5 mg group, and –63.1% in the 2.0 mg group, versus –20.9% in the placebo group, $p < 0.01$ for all comparisons. Changes on the EASI were –23.0%, –42.3%, and –40.9%, respectively, in the nemolizumab groups, versus –26.6% in the placebo group. Respective changes in body surface area affected by AD were –7.5%, –20.0%, and –19.4% with nemolizumab, versus –15.7% with placebo. Among the patients receiving nemolizumab every 4 weeks, discontinuation of treatment occurred in 9 of 53 patients (17%) in the 0.1 mg group, in 9 of 54 (17%) patients in the 0.5 mg group, and in 7 of 52 (13%) patients in the 2.0 mg group, versus in 9 of 53 (17%) patients in the placebo group. The authors concluded that nemolizumab at all monthly doses significantly improved pruritus in patients with moderate-to-severe AD, which showed the efficacy of the medication targeting IL-31RA. The limited size and length of the trial preclude conclusions regarding side effects.

In another study, Cry j 2, one of the major allergens of Japanese cedar pollen, was administered to IL-31RA-deficient or wild-type (WT) mice via nasal or intraperitoneal

injection for induction of specific Th2 responses. After nasal administration of Cry j 2, IL-31RA-deficient mice showed lower Cry j 2-specific CD4⁺ T cell proliferation, Th2 cytokine (IL-5 and IL-13) production, and Th2-mediated (IgE, IgG1, and IgG2b) antibody responses than WT mice. In contrast, IL-31RA-deficient mice administered Cry j 2 intraperitoneally showed stronger Th2 immune responses than WT mice. These results indicate that IL-31R signaling positively regulates Th2 responses induced by nasal administration of Cry j 2, but negatively regulates these responses when Cry j 2 is administered intraperitoneally. Collectively, these data indicate that the induction of antigen-specific Th2 immune responses might depend on tissue-specific cell types expressing IL-31RA. IL-31 is a T-cell cytokine acting through a heterodimeric receptor composed of IL-31RA and oncostatin M receptor (OSMR) which is expressed on epithelial cells including keratinocytes. The authors investigated expression, regulation of the IL-31 receptor, as well as functions of IL-31 in Human primary keratinocytes (HPKs). HPKs were stimulated with TLR-2 ligands (Pam3Cys, lipoteichoic acid and peptidoglycan), or Th1- and Th2-associated cytokines (IFN- γ and IL-4), respectively. IL-31R expression and regulation as well as functional effects of IL-31 stimulation were then investigated at both the mRNA and protein level and compared with HPKs from patients with AD. The STAT signaling pathway and TLR-2 expression were investigated using Western blot and Immunohistochemical stainings, respectively. Pam3Cys or IFN- γ significantly up-regulated IL-31RA and OSMR expression. IL-31 activated STAT-3 phosphorylation in HPKs which was augmented after preactivation with Pam3Cys or IFN- γ . IL-31 enhanced the secretion of CCL2 after up-regulation of the receptor with Pam3Cys or IFN- γ . However, this was not observed in keratinocytes from AD patients where an impaired TLR-2 expression was found. The investigators show a functional role of IL-31 in HPKs and provide a new link between TLR-2 ligands and IL-31 which might be dysregulated in AD [83].

Nemolizumab (CIM331) is a humanized monoclonal antibody against IL-31RA [82]. In a phase 2, RCT involving 216 adults with moderate-to-severe AD inadequately controlled with topical treatments, subcutaneous nemolizumab led to a dose-dependent improvement in pruritus. Specifically, patients who received nemolizumab had reductions of 43.7%, 59.8%, and 63.1% (for the 0.1, 0.5, and 2.0 mg/kg doses, respectively) in the pruritus VAS, which were significantly greater than the 20.9% reduction in patients who received placebo [82]. Improvements in EASI, SCORAD, and sleep-disturbance VAS (40.9%, 39.8%, and 62.6%, respectively) were also greater for nemolizumab than for placebo (26.6%, 18.5%, and 31.9%, respectively).

Tofacitinib (Xeljanz[®], Pfizer, USA) is an oral JAKi that inhibits JAK1 and JAK3 [66]. In a case series of six adults with moderate-to-severe AD who had failed standard therapy (topical and systemic corticosteroids), oral tofacitinib (5 mg twice daily for 29 weeks) significantly decreased the average SCORAD index by 54.8% ($p < 0.05$) at 14 weeks, and was maintained at week 29 with a 66.6% reduction [84]. Both pruritus and sleep loss scores were significantly decreased at week 14, and was maintained at week 29 (by 76.3% and 100%, respectively) [84]. Quality of life was not measured. There has not been any randomized trial to date.

JNJ-39758979 or [(R)-4-(3-amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine] is a H4R-antagonist [85]. In a phase 2a, randomized, double-blind, placebo-controlled, parallel-group study involving 87 adults with moderate AD, administration of JNJ-39758979 at 100 and 300 mg PO daily for 6 weeks led to improvements in week 6 median EASI (primary outcome) of 3.70 and 3.00, respectively, but the changes were not significantly different than that seen with placebo (1.30; $p = 0.1672$ and 0.1992 , respectively)[85]. Nevertheless, improvements in Pruritus NRS Daytime Pruritus Severity and Daytime Pruritus Duration were significantly greater in patients who received 300 mg dose (2.28 and 2.26, respectively) than in those who received placebo (0.57 and 0.91, respectively), with $p < 0.05$ versus placebo in both cases. However, outcome did not include quality of life measure. Despite these favorable outcomes, the trial was terminated prematurely due to two cases of serious neutropenia.

An analysis of systematic reviews in 2014 that summarized the evidence base for treatment of AD showed that intake of probiotics prenatally and postnatally may help prevent AD, but there is little evidence to suggest a role in the treatment of AD [86]. The use of immunotherapy to treat AD-associated aeroallergen sensitivity requires further evaluation [87]. There is insufficient evidence for vitamin D supplementation for the treatment of AD [86]. A recent systematic review and meta-analysis, however, showed that serum vitamin D level was lower in the AD patients and that vitamin D supplementation could be a new therapeutic option for the treatment of AD [88]. Another recent systematic review and meta-analysis on four RCTs comparing the efficacy of vitamin D with a placebo on severity of AD showed that vitamin D supplementation may help ameliorate the severity of AD [89]. Further studies are necessary to confirm or refute these controversial findings.

Sleep disturbance is common in children with AD because of associated pruritus and reduced nocturnal melatonin secretion in affected children. Traditionally, oral first-generation antihistamines are used for treating sleep problems in patients with AD. However, tolerance often develops after a few days of treatment, thereby limiting its usefulness. Oral melatonin is a safe and effective way to improve the sleep-onset latency and disease severity in children with AD, owing to its sedative, immunomodulatory, anti-inflammatory, and anti-oxidative effects [90]. In a recent study, Chang et al. randomized 48 children with AD to receive either oral melatonin (3 mg/day) or placebo for 4 weeks, followed by a 2-week washout period and then cross-overed to the alternate treatment for 4 weeks [90]. The authors found that after melatonin treatment, the SCORAD index decreased by 9.1 compared with that after placebo (95% confidence interval: -13.7 to -4.6 ; $p < 0.001$) from a mean (SD) of 49.1 (24.3) to 40.2 (20.9). The sleep-onset latency shortened by 21.4 min after melatonin treatment compared with after placebo (95% confidence interval: -38.6 to -4.2 ; $p = 0.02$).

3.3. Complementary, alternative, and Chinese medicine

Chinese herbal medicines have been employed for the treatment of AD for many years [91-93]. In recent years, herbal medicine has been converted to various concoctions under

the broad category of proprietary Chinese medicine [92-94]. Herbal formulas are based on ancestral concoctions and often considered as investigational food supplements instead of investigational drugs.

The beneficial effects of oral Chinese medicine in children with AD have not been consistently demonstrated [95-98]. A Cochrane systematic review in 2005 on the topic of Chinese herbal medicine for AD included only four clinical trials [98]. Further meta-analyses were performed which showed no conclusive evidence that oral intake of most Chinese herbs or Chinese herbal formulae used in the included studies could improve AD [99]. So far, there is no convincing evidence that topical application of Chinese herbal medicine whether used alone or in conjunction with oral administration of Chinese herbal formula could reduce the severity of AD in children or adults [100]. Even though some of the included studies claimed that there were statistically significant differences in the outcome measures on Chinese herbal medicine treatment groups compared with those in the control groups, these claims could not be taken for granted due to a low strength of evidence and high risks of bias.

In the early 1990s, a decoction (Zemaphyte, Phytopharm Plc, UK) was found to be efficacious for the treatment of AD in both children [101,102] and adults [103] in the UK. Sheehan et al. carried out a randomized placebo-controlled double-blind trial of a specific prescription formulated for widespread non-exudative AD [101]. The authors found that active treatment was more effective than placebo. There was no evidence of hematological, renal, or hepatic toxicity. The authors concluded that the decoction in the trial have a therapeutic potential in treating AD.

These studies were different from many other studies on traditional Chinese medicine (TCM) in that the investigators tried to clinically evaluate the anti-allergic effects using serum IgE and peripheral blood lymphocytes albeit no objective effects were demonstrated.

Despite the efficacy reported in the UK trials, a subsequent randomized, placebo-controlled, cross-over trial of the same decoction failed to demonstrate beneficial effects on Chinese patients with recalcitrant AD in Hong Kong [96].

In a pilot study, Hon et al. evaluated the clinical and biochemical effects of a Chinese medicine capsule (PentaHerbs capsule) given orally in children with AD [104]. The composition of each herb in the formulation was standardized. The formula comprised 2 g of Flos Lonicerae (Jinyinhua), 1 g of Herba Menthae (Bohe), 2 g of Cortex Moutan (Danpi), 2 g of Rhizoma Atractylodis (Cangzhu) and 2 g of Cortex Phellodendri (Huangbai). The dosage calculation was based on the standard Chinese medicine prescription for children [104] and was equivalent to a daily dose of 20 ml of syrup. This dosage was deemed to be adequate for individuals in the pediatric age group. The syrup had been tested for heavy metals, microbial products, residual pesticides, and corticosteroids [105]. Patients were followed up monthly to ensure compliance, and SCORAD scores were obtained at each visit. There was significant improvement in the overall and component SCORAD scores. There were no significant differences between the pre- and post-treatment values of various serum cytokines. No clinical or biochemical evidence of any

adverse drug reaction was found during the study period. The PentaHerbs capsules were well tolerated by the children and apparent reduction of disease severity was noted clinically. In a subsequent double-blinded RCT, the same group of researchers assessed the efficacy and tolerability of the same decoction in children with AD [106]. Following a 2-week run-in period, children with long-standing moderate-to-severe AD were randomized to receive a 12-week treatment with a twice-daily dose of three capsules of either PentaHerbs or placebo. The SCORAD score, The Children's Dermatology Life Quality Index (CDLQI), allergic rhinitis score, and requirement for topical corticosteroid and oral antihistamine were assessed before and at weeks 4, 8, 12, and 16 of treatment. Adverse events, tolerability, and hematological and biochemical parameters were monitored during the study. Over 12 weeks, the mean SCORAD score fell from 58.3 to 49.7 in the PentaHerbs group ($n = 42$; $p = 0.003$) and from 56.9 to 46.9 in the placebo group ($n = 43$; $p = 0.001$). However, there was no significant difference in the scores at the corresponding time points between the two groups. The CDLQI of PentaHerbs-treated group was more significantly improved than that of the placebo group at the end of the 3-month treatment and 4 weeks after stopping therapy ($p = 0.008$ and 0.059 , respectively). The total amount of topical corticosteroid used was also significantly reduced by one-third in the PentaHerbs group ($p = 0.024$). The formulation was palatable and well tolerated. No serious adverse effects were observed between the groups. The investigators concluded that the PentaHerbs decoction is efficacious in improving quality of life and reducing topical corticosteroid use in children with moderate-to-severe AD.

Bai et al. evaluated the effects and safety of Shuangfujin (SFJ) on acute AD [107]. The investigators only described symptomatic improvement and did not objectively evaluate anti-allergic effects of the treatment.

Hochu-ekki-to, a Kampo formula (consisting of 10 herbs, namely Radix Astragali, Panax ginseng, Rhizoma Atractylodis Macrocephalae, Radix Glycyrrhiza Uralensis, Radix Angelicae Sinensis, Citri Reticulatae Pericarpium, Rhizoma Cimicifugae, Radix Bupleuri, Rhizoma Zingiber officinale, Fructus Jujubae), is effective for patients with *Kikyo* (delicate, easily fatigable, or hypersensitive) constitution. Kobayashi et al. evaluated the efficacy and safety of *Hochu-ekki-to* in the long-term management of *Kikyo* patients with AD [108]. In a multicenter, double-blind, randomized, placebo-controlled study, 91 *Kikyo* patients with AD were enrolled. *Kikyo* condition was evaluated by a questionnaire scoring system. All patients continued their ordinary treatments (topical corticosteroids, topical tacrolimus, emollients, or oral antihistamines) before and after their protocol entry. *Hochu-ekki-to* or placebo was orally administered twice daily for 24 weeks. The skin severity scores, total equivalent amount (TEA) of topical agents used for AD treatment, prominent efficacy (cases with skin severity score = 0 at the end of the study) rate and aggravated rate (more than 50% increase of TEA of topical agents from the beginning of the study) were monitored and evaluated. Seventy-seven out of 91 patients completed the 24-week treatment course (treatment: $n = 37$; placebo: $n = 40$). The TEA of topical agents (corticosteroids and/or tacrolimus) was significantly lower in the *Hochu-ekki-to* group than in the placebo group, whereas

the overall skin severity scores were not statistically different. The prominent efficacy rate was 19% (7 of 37) in the *Hochu-ekki-to* group and 5% (2 of 40) in the placebo group ($p = 0.06$). The aggravated rate was significantly lower in the *Hochu-ekki-to* group (3%; 1 of 37) than in the placebo group (18%; 7 of 39). Only mild adverse events such as nausea and diarrhea were noted in both groups without statistical difference. This placebo-controlled study demonstrated that *Hochu-ekki-to* was a useful adjunct to conventional treatments for AD patients with *Kikyo* constitution. Use of *Hochu-ekki-to* significantly reduced the dose of topical corticosteroids and/or tacrolimus used for AD treatment without aggravating AD. The investigators did not objectively evaluate the anti-allergic effects of *Hochu-ekki-to* with any immune tests.

In a subsequent study, the author confirms the efficacy of *Hochu-ekki-to* in a randomized trial, which was published in Japanese [109].

In a prospective RCT, 71 patients with severe intractable AD were given an 8-week treatment with oral Xiao-Feng-San (XFS; 47 patients) or placebo (24 patients) [110]. Total lesion score, erythema score, surface damage score, pruritus score, and sleep score were measured at 4-week intervals. Fifty-six patients completed both the treatment and follow-up periods. The decrease in the total lesion score in the treatment group at 8 weeks was significantly greater than that of the placebo group ($79.7 \pm 5.8\%$ vs. $13.5 \pm 7.64\%$; $p < 0.001$). There was also a statistically significant difference between the treatment and placebo groups with regard to erythema, surface damage, pruritus, and sleep scores. The difference between the two groups was still significant for all outcome measures except the erythema score at the 12-week follow-up, 4 weeks after the 8-week treatment had ended. Patients reported no adverse effects from treatment, although some patients commented on the unpalatability of the medication. The investigators suggest that XFS may be an alternative choice of therapy for severe, refractory, extensive, and non-exudative AD.

Among all these studies, the lack of information on constituents is always an obstacle. Unlike the PentaHerbs studies, there was no evaluation whether corticosteroid is present in the preparation [105]. Serum cortisol levels were not assessed after therapy. Among the oral Chinese medicines, several case series have been described where they are adulterated with western medicine [92,93].

4. Conclusions

This review covers evidence on efficacy of topical and oral forms of novel and investigational drugs. Topical agents include emollients, PDE4 inhibitors, and topical herbs. There is scanty evidence that ceramide or natural moisturizing factors may provide relief to AD. Among the novel topical agents, PDE4 inhibitors have shown promise as an effective topical treatment for mild-to-moderate AD with minimal adverse events. As for the systemic agents, dupilumab has shown promise as an effective subcutaneous agent for the treatment of moderate-to-severe AD in adult patients with little adverse effects. Clinical trials with dupilumab have not been completed in children with AD. Also, the long-term effects of

dupilumab are not known. New systemic treatment includes a number of herbal concoctions. More research is needed to document efficacy and adverse effects with these agents.

5. Expert opinion

The use of biologics has been major advance for the treatment of AD. Among the various biologics, only dupilumab has been subjected to extensive RCTs and found to be efficacious and safe. The preliminary results are encouraging and give physicians new hope to improve future therapeutic modalities. However, no long-term study has been performed to assess potential adverse effects in the long run. Also, the drug has not completed clinical trials in children. One of the disadvantages of using dupilumab for the treatment of AD in children is that the drug has to be injected subcutaneously twice weekly and can be painful for children. In addition, dupilumab is costly. A number of oral and topical traditional Chinese herbal formulae have been used for the treatment of AD [91,111]. However, systematic reviews have not demonstrated consistent clinical efficacy [98]. To date, there was limited evidence that a Chinese herbal formula (PentaHerbs) capsule given orally may provide benefit for children or adults with AD [91]. There was no conclusive evidence that other Chinese herbs or Chinese herbal formulae used orally improved the condition, nor convincing evidence that topical application of Chinese herbal medicine was of benefit to children or adults with AD. The toxicity of Chinese herbal medicine should also be investigated in future research studies. Participants should be matched for sex, age, and severity of AD to minimize heterogeneous outcomes within the study. Stratified randomization is recommended if the study recruits both children and adults. In addition, allocation concealment should be done to ensure that the participants are selected into two groups by chance rather than by error. Numbers of participants being randomized should be balanced in two groups. Methods for randomization must be clearly described. Blinding method should always be used because outcome measures for AD are subjective in the majority of cases. An open-labeled design study could lead to risks of bias for outcome assessment. Quality control and quality assurance of Chinese herbs to be investigated should be vigorously performed prior to the conduct of clinical trials [105]. Assessment of effectiveness of the intervention should rely on data from both objective and subjective outcome measures assessed at baseline and at the end point of the trial [106,112]. Using published and validated scoring system as a primary outcome measure may help to achieve this and continuous data should always be reported or provided upon request. Adverse events should be reported. Liver and renal function tests should be used as one of the safety parameters in a RCT. Toxicity of Chinese herbal medicine should be well addressed. In summary, experts in the Cochrane reviews have suggested that well-designed, adequately powered trials are needed to evaluate the efficacy and safety of Chinese herbal medicine for managing AD [98,113].

Novel topical and systemic agents have been identified and subjected to various phases of clinical trials with efficacy and side-effect profiles documented. Many of the novel

investigational drugs are receptor or target-specific. With better understanding of pathophysiology involving skin barrier, genetic and immunologic profiles of AD, targeted therapy can be offered to patients. Some of these products have undergone randomized clinical trials to establish efficacy. These products may soon be marketed. There is a potential that patients with severe eczema may be controlled with sustained improvement of quality of life. Realistically, the goal may be to ameliorate disease, as for the time being, disease cure is not possible with these novel drugs. As with many atopic diseases, patients and parents are looking for disease cure and not disease control, but curative medicine is still far from fulfilling its potential, and should be subject to further clinical trials.

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Declaration of Interest

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