


# Experimental Drugs with the Potential to Treat Atopic Eczema

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**Introduction:** Eczema or atopic dermatitis (AD) is a chronically relapsing dermatosis characterized by pruritus and a significant impact on the quality of life.

**Methods:** The authors undertook a structured search of peer-reviewed research articles from PubMed and Google Scholar. Recent and up-to-date studies relevant to the topic were included.

**Results:** This report overviews current treatment and experimental drug for AD. Topical agents including topical phosphodiesterase E4 (PDE4) inhibitors such as crisaborole are efficacious in the treatment of AD with few side effects. Monoclonal antibodies such as dupilumab given subcutaneously are efficacious for more severe disease. Systemic treatment can ameliorate symptoms in severe and recalcitrant AD. New systemic treatment includes several traditional herbal formulations that have undergone clinical trials using modern research methodology to determine their efficacy and safety. AD is associated with many complicating psychosocial issues. Often suboptimal efficacy is due to unrealistic expectations and poor compliance making treatment difficult in spite of effective treatment and efforts in drug discovery. Randomized trials have shown that novel topical and subcutaneous medications are safe and efficacious. Regarding herbs, a methodology for the investigation of herbal medications is often flawed and scientific evidence is lacking. Experimental drugs include various biologics, PDE4 and JAK inhibitors in topical, oral, subcutaneous or intravenous forms are in various phases of trials.

**Conclusion:** Many novel medications demonstrate efficacy for AD. Experimental drugs include various biologics, PDE4 and JAK inhibitors are in various phases of trials.

**Keywords:** atopic dermatitis, biologics, crisaborole, dupilumab, eczema, JAK inhibitors

## Introduction

Eczema or atopic dermatitis (AD) is a chronic relapsing allergic/inflammatory dermatitis characterized by pruritus, xerosis, erythema, vesiculation, exudation, excoriation, crusting, and sometimes lichenification. The condition can have a significant impairment of quality of life.<sup>1-4</sup> AD is very common and affects as high as 20% of children and 1-3% of adults.<sup>3-10</sup> According to an international survey, the prevalence of adult AD ranged from 2.1% to 4.9% across countries.<sup>11</sup> The prevalence of AD in US adults is approximately 7%, and one in four adults with AD report adult onset of their disease.<sup>12</sup>

Epidemiologically, AD is prevalent among small and affluent families.<sup>3-10</sup> Reasons for the increase in AD prevalence in the past decades are probably multifactorial.

The pathophysiology of AD is complex.<sup>13-15</sup> Several theories and hypotheses have been proposed. The “brick and mortar” model hypothesizes that the disease is due to an inherited defect in epidermal barrier function.<sup>16-19</sup> Filaggrin (FLG) is a protein in the

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skin epidermal stratum corneum which is metabolized to a number of natural moisturizing factors (NMF) that contribute to the cutaneous barrier integrity.<sup>16–21</sup> The cytoskeleton with filaggrin forms a protein-lipid matrix, which impedes the entry of chemicals, infectious agents and allergens, and prevents transepidermal water loss (TEWL).<sup>20,21</sup> Down-regulation or loss-of-function mutation in the filaggrin gene sensitizes these individuals to develop atopic skin.<sup>17,22–26</sup> The hygiene hypothesis suggests that immune dysregulation during early childhood increases the risk for allergy.<sup>27,28</sup> The hypothesis states that early childhood exposure to several microorganisms in the gut flora protects against atopic diseases.<sup>29,30</sup> A lack of exposure to the normal gut flora is thought to lead to problems in establishing immune tolerance.<sup>29</sup> Dysbiosis is another theory that further postulates overuse of antibiotics and changes in life style leads to an overgrowth of staphylococcus and various microbials as pathophysiological mechanisms in AD.<sup>3–5,31–34</sup> According to the T Helper (T<sub>H</sub>) hypothesis, an imbalance of T-helper cell immunology is associated with AD pathogenesis. Children with AD have a high concentration of various T<sub>H</sub> cytokines and chemokines, such as T<sub>H</sub>17 IL-31 and IL-33 and antimicrobial peptides in the skin.<sup>35,36</sup> The interplay of these theories and hypotheses points to a complex mechanism of AD pathogenesis that cannot be explained by any sole theory or hypothesis alone.<sup>3–5,37</sup> Successful management of this disease demands a multipronged approach consisting of optimal skincare and pharmacotherapy.<sup>1,3–5</sup> To complicate matters, there are several cultural and psychosocial issues that make AD difficult to manage in some countries.<sup>38</sup>

We undertook a structured search of peer-reviewed research articles from PubMed and Google Scholar. Recent and up-to-date studies relevant to the topic were included. The Pubmed search was conducted in Clinical Queries using the key term “atopic dermatitis” and “eczema”. The search included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews. The search was restricted to English literature. The information retrieved from the above search was used in the compilation of the present article.

## Overview of Therapies for Atopic Dermatitis

### Emollients and Moisturizers

Many guidelines and practical recommendations have been developed for the management of AD.<sup>5,39–41</sup>

Emollients and moisturizers are integral parts of AD management but are often not considered as topical medications. There have been a proliferation of emollients and moisturizers in recent years. These emollients contain NMF and/or pseudoceramides that claim good barrier repair functions. They are marketed as proprietary products.<sup>42–47</sup> Key players in the skin barrier are the natural NMF and ceramides.<sup>48,49</sup> Few of these products have been subjected to trials to establish their efficacy.<sup>43,45,48,50</sup> A Cochrane review on emollient trials demonstrates that many moisturizers have some beneficial effects but none is superior to another.<sup>51</sup>

### Corticosteroids

Conventionally, topical corticosteroids (TCS) marked the beginning of modern therapeutics for the management of AD and is the mainstay of treatment.<sup>1,3</sup> The risk of side effects depends on the area being covered, strength of the medication, and the duration of treatment, with children being more prone to their adverse effects following inadvertent usage.<sup>1,52</sup> Chronic use of topical steroids may be problematic, especially in young children, due to potential adrenal axis suppression and the risk of growth retardation, as well as local steroid side effects, such as skin thinning and depigmentation. Described as steroid phobia, many parents are reluctant to use steroids on their children.<sup>38,53,54</sup>

### Topical Immunomodulators

Topical calcineurin inhibitors (TCI) are useful and safe topical medications as an alternative to corticosteroids. Tacrolimus (Protopic) and pimecrolimus (Elidel) are the two commercially available TCIs. These immunomodulators down-regulate inflammation, inhibit the activity of calcineurin and block the activation of T and natural killer cells. Both immunomodulators are efficacious and safe.<sup>1</sup> Generally, TCIs are less effective and cause more skin burning and irritating sensation than topical corticosteroids. In February 2005, the Pediatric Advisory Committee of the Food and Drug Administration (FDA) recommended that “black box warnings” be placed on tacrolimus and pimecrolimus because of the potential risk of cancer.<sup>55</sup> In March 2005, the FDA issued an alert to health-care providers concerning a potential link between these topical calcineurin inhibitors and malignancy (skin cancer and lymphoma).<sup>55</sup> Subsequently, a Joint Task Force of the American College of Allergy, Asthma, and Immunology and the American Academy of

Allergy, Asthma and Immunology concluded that the current data did not support the use of “black box warning” on these medications.<sup>55</sup>

## Systemic Medications

Most guidelines recommend systemic medications in the management of severe and recalcitrant AD.<sup>1,4,56,57</sup> These medications may be associated with significant systemic side effects.<sup>4,56,57</sup> In particular, azathioprine is associated with neutropenia and impaired hepatic function whereas cyclosporin is associated with hypertension and impairment of renal function.<sup>3–5,56,58,59</sup> These medications are therefore not accepted by parents and patients for long-term disease control.<sup>59</sup> Furthermore, current international guidelines place limits on the prolonged use of cyclosporine. Methotrexate is another widely used drug, especially in adults. However, in many countries, cyclosporine is the only licensed traditional systemic drug for AD.<sup>39,40</sup>

## Novel Treatments

Novel therapeutic agents targeting the complex pathophysiology have been developed. The new drugs are efficacious and with less side effect compared to conventional medications. The move towards personalized medicine appears to be the way forward in drug development programs in AD.<sup>60–64</sup> Many topical and systemic drugs were initially developed as experimental agents but have been subsequently successfully marketed. They include systemic Janus kinase (JAK) inhibitors, subcutaneous monoclonal antibodies and topical PDE4 inhibitors.<sup>44</sup>

Among these successfully launched products, the biologics drug class leads the market and has dominated the global drugs market for the treatment of AD since 2018.

Dupilumab (Dupixent) is a fully human monoclonal antibody that has been approved as an IL-4Ra targeting biologic and an IL-4/IL-13 inhibitor, which is administered subcutaneously for the treatment of moderately severe AD.<sup>65–68</sup> In Phase II and III randomized trials conducted on adult patients, dupilumab reduced the AD severity.<sup>67–72</sup> Dupilumab has been approved by the FDA for the treatment of severe AD and successfully marketed.<sup>73</sup> The drug is an immunoglobulin G4 antibody that inhibits interleukin-4 (IL-4) and IL-13 signaling by specifically binding to the IL-4 receptor alpha subunit, which is shared by the IL-4 and IL-13 receptor complexes.<sup>74</sup> IL-4 and IL-13 are initiators and drivers of the helper T-cell type 2 (TH2) axis.<sup>75</sup> In two Phase III trials, dupilumab improved signs and symptoms and the

quality of life of AD patients. The drug has an acceptable safety profile. The most common adverse effects are nasopharyngitis, upper respiratory tract infections, injection site reactions and conjunctivitis.<sup>75</sup> Real-life experiences in adults and in the elderly have now been reported.<sup>76,77</sup>

Topical therapy is an integral part of AD care.<sup>75</sup> For decades, the two primary classes of topical drugs used to treat AD include topical corticosteroids and calcineurin inhibitors. Overactive phosphodiesterase (PDE)-4 enzyme contributes to the signs and symptoms of AD.<sup>75</sup> Crisaborole is a PDE4 antagonist that inhibits the degradation of cyclic adenosine monophosphate (cAMP) by PDE4, and results in downstream modification of proinflammatory signaling pathways.<sup>75</sup> Crisaborole has demonstrated significant efficacy in a phase III clinical trial.<sup>78</sup> A Phase I, randomized, double-blind trial has also shown that the application of topical crisaborole to sensitive skin areas of healthy volunteers was well tolerated throughout treatment, thus supporting its potential role as an alternative topical treatment in AD patients.<sup>79</sup> However, crisaborole’s affinity for the 4 different PDE-4 isotypes is weak potentially explaining its modest efficacy in AD. Furthermore, it burns/stings at the site of application. On top of this, crisaborole is an ointment (which patients prefer less than creams) that requires twice daily application.<sup>80</sup> On the other hand, the drug does not cause thinning of the skin. In patients with mild-to-moderate AD, Crisaborole interrupts the itch-scratch cycle and helps improve quality of life within a short duration of treatment.<sup>78,81–85</sup> The US FDA has now approved the usage of crisaborole for children  $\geq 2$  years with mild to moderate AD.<sup>44,75,80,81,84</sup> Real-life experiences of crisaborole have been reported.<sup>86</sup> In summary, subcutaneous dupilumab and topical crisaborole are now available in the market. They are expensive drugs but have good safety profiles.

## Miscellaneous

The development of new moisturizers containing pseudoceramides and natural moisturizing factors generally lacks efficacy data.<sup>38</sup> Bleach bathing has been recommended as an adjuvant treatment for AD.<sup>87</sup> Bathing with water alone might be similarly useful.<sup>88</sup> Sodium hypochlorite bathing has not acquired popularity in Europe.<sup>88,89,90</sup> Recently, bathing with pine-tar has been demonstrated as a useful adjuvant practice for AD patients. Clinical improvement is associated with the reduction of IgE and skin *S. aureus*.<sup>91,92</sup>

In parallel to western medicine, traditional Chinese medicine, naturopathy, homeopathy, and many folklore treatments have been widely accepted by patients but many lack scientific evidence and have not been extensively studied.<sup>93–96</sup> Mismatch between parental expectations and treatment outcomes can hinder compliance and lead to treatment failure.<sup>94,96–100</sup> Research has failed to demonstrate that alternative therapies are consistently effective.<sup>93,95</sup>

Chinese herbs have been used to treat AD for many generations.<sup>94,96,101–104</sup> The efficacy of various forms of oral Chinese medicine in childhood AD has not been consistently shown.<sup>105–109</sup> Systematic reviews and meta-analyses have been performed which consistently demonstrated no conclusive evidence that most Chinese herbal concoctions could improve AD.<sup>110–114</sup> Generally, strength of evidence is low and the risks of bias are high in these studies. Mechanisms of action of herbal medicine have been reported.<sup>44,93,111–113,115</sup>

In the early 1990s, a decoction was reported to be useful for treating AD but a subsequent randomized trial involving the same decoction did not show any effects.<sup>108,116–119</sup> In Hong Kong, a series of trials on a herbal concoction for pediatric patients AD has demonstrated efficacy and improvement of quality of life.<sup>120–128</sup> The concoction is now commercially available.

In AD, the symptom of sleep disturbance and itch is prevalent due to reduced nocturnal melatonin secretion.<sup>3–5</sup> Oral melatonin is a safe and effective treatment to improve disease severity due to its antioxidative and immunomodulatory effects.<sup>129</sup> In a randomized trial, AD severity and sleep-onset latency were improved with melatonin.<sup>129</sup>

Naturopathy, homeopathy and osteopathy are several modalities of Complementary and Alternative Medicine (CAM) claiming their usefulness for the treatment of AD.<sup>93,126,130–132</sup> However, there is insufficient evidence of their efficacy. Alternatively, several Chinese herbal formulae have been used topically and orally in AD.<sup>96,110,112</sup> To date, there has been evidence that an oral Chinese herbal concoction ameliorates AD in pediatric patients.<sup>96</sup> Toxicity associated with herbs must simultaneously be investigated in clinical trials. Most importantly, control of herbal medicinals to be investigated and their quality assurance must be performed in double-blind, placebo-controlled clinical trials.<sup>125,126</sup> Well-designed, adequately powered clinical trials are mandatory to evaluate the efficacy and safety profile of herbal medicinals in the management of AD.<sup>110,113</sup>

## Experimental Drugs for Atopic Dermatitis

Experimental drugs that are being investigated include topical, subcutaneous and oral forms of medications.

### Topical Agents

Among the topical agents, a moisturizing cream containing Rhamnosoft, L-isoleucine (ILE) and ceramides has been developed for treating facial AD.<sup>132</sup> Topical ceramides in this pro-AMP cream restore the skin barrier, whereas topical L-isoleucine potentiates cutaneous  $\beta$ -defensin and stimulates AMP production. In a randomized, controlled trial, the pro-AMP cream was efficacious for children with mild-to-moderate chronic facial AD.<sup>50,132</sup>

A selective PDE4 inhibitor (OPA-15,406) ointment has been demonstrated to be efficacious in the treatment of AD. Adverse events are uncommon and usually mild.<sup>13,44</sup>

Other topical agents for the treatment of AD are the JAK inhibitors.<sup>75</sup> Several proinflammatory cytokines elicit their actions on the intracellular signaling pathway [JAK–signal transducer and activator of transcription (JAK–STAT)]. These agents work by inhibiting the activity of the JAK family of enzymes (JAK1, JAK2, JAK3, TYK2), thereby phosphorylating activated cytokine receptors. These phosphorylated receptors in turn activates the JAK–signal transducer and activator of transcription (STAT) transcription factors which modulate gene transcription.<sup>75</sup> Topical JAK inhibitor decreases IL-4 and IL-13 signaling and improves the barrier function of the skin.

Tofacitinib is a small-molecule JAK inhibitor approved for the treatment of rheumatoid arthritis that blocks multiple cytokine signaling, including interleukin IL-4, IL-5 and IL-13 implicated in immune response and inflammation.<sup>14</sup> Topical tofacitinib has shown efficacy in a phase IIa, randomized, double-blind controlled study with 69 adults with mild to moderate AD.<sup>15</sup> In another phase IIa trial, topical tofacitinib also demonstrated efficacy.<sup>15,44</sup> Further research is needed. Adverse effects, including infection, increased blood creatine phosphokinase and contact dermatitis, were mild in patients receiving tofacitinib.<sup>15</sup>

Histamine is a pruritogen. H<sub>1</sub> and H<sub>2</sub> receptor antagonists have shown poor efficacy in reducing pruritis associated with AD.<sup>91,92</sup> Nevertheless, a recent meta-analysis of three studies showed that topical 4% sodium cromoglycate emulsion was effective in the management of AD in the pediatric

age group.<sup>44,93</sup> Meanwhile, H<sub>4</sub> receptor antagonist has recently been developed which may reduce histamine-induced itch and eczema severity.<sup>94,95,115,133,134</sup>

Another systematic review of three databases on topical treatment with silver-coated fabrics or engineered silk concluded that recommendation for the functional textiles usage in AD is weak.<sup>36</sup>

As the therapeutic pipeline for AD is growing, several agents are coming closer to market. Two promising topical agents are tapinarof and roflumilast.

Tapinarof influences both Th17 and Th2 pathways, it has the potential to impact the pathways in both psoriasis and AD. It is believed that the aryl hydrocarbon receptor (AhR) modulation by tapinarof increases antioxidant activity via upregulation of NF-E2-related factor 2 (Nrf2) and promotes skin barrier restoration through upregulation of a number of epidermal barrier genes, including filaggrin, hornerin, and involucrin. Tapinarof, a Therapeutic Aryl hydrocarbon receptor Modulating Agent (TAMA), inhibits the IL-17A and IL-17F pathways implicated in psoriasis and IL-4, IL-5, and IL-13 in AD. It is a natural AhR agonist that resolves skin inflammation in mice and humans.<sup>135</sup> Tapinarof 1% cream applied once a day demonstrated statistically significant improvement in EASI75 and BSA compared to vehicle applied once a day at week 12.<sup>136</sup> Commonly reported adverse events include nasopharyngitis and folliculitis.<sup>136</sup>

ARQ-151 is a once-daily topical cream formulation of roflumilast. Roflumilast is a highly potent and selective PDE4 inhibitor that is under development for AD and psoriasis. The topical cream is used once daily and has shown greater potency (25- to 300-fold) than the two other FDA-approved PDE4 inhibitors for psoriasis.<sup>137,138</sup> In a Phase II proof-of-concept study, it was reported that roflumilast cream was well tolerated for psoriasis.<sup>137</sup> However, trial on the use of roflumilast for the treatment of AD has not materialized.<sup>139</sup> The safety and tolerability of ARQ-151 in AD is particularly important given that most AD subjects are young children. Also, because AD is a skin barrier defect, there is an increased risk of systemic exposure, even with topical treatment.<sup>97</sup>

## Subcutaneous Agents

IL-31 is an important interleukin in AD pathogenesis. Safety and efficacy of nemolizumab (CIM331) in AD have been shown in a randomized clinical trial.<sup>98</sup> Nemolizumab is a subcutaneously administered

humanized monoclonal antibody against IL-31 receptor A, IL-31 is a newly discovered cytokine that is involved in pruritus and inflammation in AD.<sup>14</sup> It has been shown that subcutaneous nemolizumab significantly improves pruritus in patients with moderate-to-severe AD. In a phase II clinical trial, monthly injections of nemolizumab significantly inhibited pruritus in patients with moderate to severe AD.<sup>98</sup> Nemolizumab also decreased the use of topical corticosteroid and ameliorated sleep efficiency in that trial.<sup>98</sup> The efficacy of nemolizumab in reducing pruritus was also evaluated in a 16 week, double-blind, phase III trial of 215 Japanese patients aged 13 years and older with AD who had moderate-to-severe pruritus.<sup>99</sup> Patients were randomized to receive subcutaneous nemolizumab (60 mg) or placebo every 4 weeks until week 16, with concomitant topical agents.<sup>99</sup> The mean percent change in the visual-analogue scale (VAS) score for pruritus was reduced by 42.8% in the nemolizumab group compared to 21.4% in the placebo group.<sup>99</sup> The incidence of injection site reactions was greater with nemolizumab than placebo. The authors suggested that longer and larger trials are necessary to determine whether nemolizumab has a durable effect and is safe for the treatment of AD.<sup>99</sup>

Lebrikizumab is a high-affinity, monoclonal antibody that binds specifically to the soluble IL-13 and prevents the formation of the IL-13Ra1/IL-4Ra heterodimer receptor signaling complex.<sup>100</sup> Lebrikizumab has also previously been investigated for the treatment of asthma with inconsistent results.<sup>140–142</sup> Lebrikizumab was studied in a proof-of-concept, randomized double-blind phase II trial of 209 adult patients with moderate to severe AD in combination with mandatory topical corticosteroids.<sup>143</sup> At week 12, significantly more patients achieved EASI-50 (reduction of Eczema Area and Severity Index by 50%)<sup>144</sup> with subcutaneous lebrikizumab 125 mg every 4 weeks than placebo (82.4% vs 62.3%). However, the protocol-mandated topical corticosteroids have limited the understanding of the efficacy of lebrikizumab as monotherapy and the short study duration did not enable long-term safety or efficacy evaluation.<sup>143</sup>

In a phase IIb double-blind, randomized, placebo-controlled trial, adults with moderate-to-severe AD were treated with dose-ranging lebrikizumab injections every 4 weeks or every 2 weeks. At week 16, the lebrikizumab groups showed dose-dependent, statistically significant improvement in Eczema Area and Severity Index (EASI) scores compared to the placebo group.<sup>75,100</sup> Common

adverse effects in the lebrikizumab groups included upper respiratory tract infection, nasopharyngitis, headache, pain at the injection site and fatigue.<sup>14</sup>

Tralokinumab for atopic dermatitis is another promising new therapy.<sup>145</sup> In a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study in adults with moderate-to-severe AD, patients received subcutaneous tralokinumab or placebo every 2 weeks for 12 weeks and topical corticosteroid cream or ointment at least once daily from the run-in to end of follow-up. Tralokinumab improved health-related QoL in patients with moderate-to-severe AD, providing further evidence of the value of targeting interleukin-13 in such patients.<sup>146</sup>

## Oral Agents

Among the oral agents, apremilast is an oral PDE-4 inhibitor proven effective for the treatment of psoriasis vulgaris and psoriatic arthritis. Apremilast has shown some efficacy in AD.<sup>44,147</sup>

A number of oral JAK inhibitors are being investigated for the treatment of AD.<sup>15,44</sup> JAK inhibitors are small molecules that exert their immunosuppressive and antiproliferative effects by inhibiting the JAK-STAT.<sup>148</sup> Current agents under investigation for use in AD include baricitinib (a JAK1 and JAK2 inhibitor), upadacitinib (JAK1 inhibitor) and abrocitinib (JAK1 inhibitor). The efficacy of oral baricitinib was evaluated in a phase II double-blinded trial of 124 adults with moderate-to-severe AD. Significantly more patients who received baricitinib (4 mg) achieved EASI-50 than patients receiving placebo (61% vs 37%) at 16 weeks.<sup>149</sup> Adverse effects relating to baricitinib included headache, increased blood levels of creatine phosphokinase, decrease in the neutrophil count and nasopharyngitis.<sup>149</sup>

The efficacy and safety of oral abrocitinib monotherapy has also been evaluated in a phase II and phase III trial and were found to be effective and well tolerated for short-term use in adults with moderate to severe AD.<sup>150,151</sup> It is an investigational oral once-daily JAK1 inhibitor. A phase III randomized placebo-controlled trial (JADEMONO-1) to assess the efficacy of oral once-daily abrocitinib showed improvements in pruritus and disease burden at week 2 of treatment and continued throughout the rest of the 12-week study.<sup>150</sup>

Upadacitinib also shows promising results in a phase II clinical for AD. In that study, 50% of the participants treated with 30 mg daily of upadacitinib, achieved EASI-

90 response at week 16.<sup>75,148</sup> However, ongoing studies are required to evaluate its safety profile.<sup>99</sup>

Along another line for oral agents for the management of AD is fecal transplants with commensal bacteria.<sup>152</sup> In a randomized double-blind trial, lysate of *Vitrosilla filiformis* bacterium reduced cutaneous *S. aureus* colonization, severity and pruritus of AD.<sup>155</sup> This implies the use of commensal strains to control biofilm formation and overgrowth of pathogenic staphylococci.<sup>156,157</sup> Transplantation of cutaneous commensal gram-negative rods from healthy individuals activates innate immunity and controls the growth of *S. aureus* in a mouse model.<sup>158</sup> When applied to human eczematous skin, *Staphylococcus hominis* and *S. epidermidis* from healthy non-atopic individuals decrease *S. aureus* colonization.<sup>159</sup> Studies of the topical application of gram-negative coccobacillus commensal and coagulase-negative *Staphylococcus* for AD are ongoing.<sup>159160161</sup>

## Intravenous Agents

IL-22 induces epidermal hyperplasia and plays a major role in barrier function disruption in model systems.<sup>154</sup> A randomized double-blind, placebo-controlled trial evaluated the efficacy and safety of intravenous fezakinumab, an anti-IL22 antibody, as monotherapy in adult patients with moderate to severe AD. At week 12, there was no significant decline in Scoring AD (SCORAD). Significant findings were only demonstrated in the subset of patients with severe AD.<sup>14</sup> The drug was well tolerated and the common adverse events were upper respiratory infections.

## Miscellaneous

Transient receptor potential (TRP) ion channels are involved in the transmission of somatosensory signaling, such as heat, pain and taste throughout the body.<sup>153</sup> TRP cation channel subfamily V member 1 or TRPV1, one of the members of this large family of ion channel, is expressed on diverse cells of this skin and is an important molecule in pruritus signaling in AD.<sup>154</sup> TRPV1 also appears to play a role in maintaining skin barrier function. Neurokinin antagonists may also affect similar pathway of pruritus signaling by blocking the substance P neuropeptide that mediates pruritus and affect neurogenic inflammation. Several trials that are undergoing evaluation of the efficacy and safety of this class of drugs include PAC-14,028 (TRPV1 channel inhibitor), CT327/SNA120 (TrkA kinase inhibitor), tradipitant

(Neurokini 1/SP antagonist) and serlopitant VPD-737 (Neurokinin antagonist).<sup>154</sup>

Given the role of prostaglandins and leukotrienes plays in the development of atopy in asthma pathogenesis, in vitro and in vivo studies of AD have suggested that these molecules may be important in the pathogenesis of AD.<sup>89</sup> Therefore, targeted therapy against these molecules may have a role in the management of AD. Several agents in development that targets the leukotriene/prostaglandin pathway include C000459, Q301 and ZPL-521.<sup>89</sup>

Two anti-alarmin drugs were investigated for AD, namely etokimumab and tezepelumab. The role of IL-33 inhibition was investigated in a phase 2a study of etokimab, an IgG1 anti-IL-33 monoclonal antibody, in 12 adult patients with moderate-to-severe AD who received a single intravenous administration of etokimab.<sup>162</sup> A sustained clinical benefit was observed with 83% achieving EASI-50 and 33% EASI-75, and with a reduction in peripheral eosinophils at day 29 after administration. Etokimab also inhibited neutrophil migration to skin interstitial fluid in vitro.

The role of an anti-thymic stromal lymphopoietin monoclonal antibody was investigated in a phase 2a study (NCT02525094) where adult patients were randomized to subcutaneous tezepelumab 280 mg or placebo every 2 weeks, plus class 3 topical corticosteroids (TCS).<sup>90,163</sup> The primary endpoint was the week 12 response rate in the EASI-50. Although not statistically significant, numerical improvements over placebo were demonstrated.

Alefacept (intravenous/intramuscular) and efalizumab (subcutaneous) are other biologics effective in the treatment of moderate to severe AD in adults but long-term administration of these agents are limited by their significant toxicity.<sup>152</sup> They are not currently marketed.

## Conclusions

This review summarizes AD medications in topical, subcutaneous and oral forms and explores novel and investigational drugs. Some have been successfully marketed whilst others remain experimental. PDE4 inhibitors are an effective topical treatment for mild-to-moderate AD whereas dupilumab is an effective subcutaneous agent for the treatment of moderate-to-severe AD with little minimal effects.

Experimental treatments in topical, subcutaneous and oral forms are ongoing and include antihistamine and biologics. The usage of biologics is a major advance in

the management of AD. Dupilumab is now available in the market. The drug has been subjected to extensive randomized controlled trials and confirmed to be useful and safe. The efficacy profile of crisaborole is comparable to topical steroid and calcineurin inhibitors but is a lot more expensive. Nevertheless, longer term follow-up studies are needed to evaluate potential adverse events. One disadvantage of using dupilumab is that the medication has to be administered subcutaneously twice weekly and is painful for children. Furthermore, dupilumab is a very costly medication.

Currently, the majority of novel and experimental medications have been developed and marketed for adults with AD. Only subcutaneous Dupilumet and topical Crisaborole have been successfully marketed for patients younger than 18 years of age.

There has been an exploding proliferation of many new antibodies, biologics and small molecules that are undergoing Phase II and III clinical trials. Eventually, some of these medications may be successfully marketed. However, it appears that there remains no cure for AD to date.

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