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Novel topical and systemic therapies in atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is the most common inflammatory skin disease driven by both terminal keratinocyte differentiation defects and type 2 immune responses, and this condition causes psychological and social morbidity. Although patients with severe AD require systemic immunotherapy, conventional agents including ciclosporin could not be used for several years due to side effects such as nephrotoxicity, hypertension and long-term risks of malignancy. It is well known that dupilumab, which blocks receptor binding of both IL-4 and IL-13, is remarkably efficacious in the treatment of AD. We have entered a new era when many novel topical and systemic agents that may have great potential in AD treatment are emerging through clinical trials. The purpose of this article is to summarize the efficacy and safety of the current topical and systemic therapies in AD by reviewing recently published papers regarding phase II/III clinical trials. It is revealed that topical phosphodiesterase 4 inhibitors and Janus kinase (JAK) inhibitors are promising treatments for AD. Moreover, systemic therapies such as biologics targeting IL-13 and oral JAK inhibitors show strong efficacy in AD.

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Atopic dermatitis; eczema; dupilumab; JAK inhibitor

1. Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease caused by interactions of genetic and environmental factors. AD, driven by both terminal keratinocyte differentiation defects and strong type 2 immune responses, affects 15%–30% of children and 5% of adults and causes functional, psychological and social morbidity [1–3]. Although mild and moderate AD can usually be managed with topical corticosteroids, topical calcineurin inhibitors and/or phototherapy, ~2% of patients with severe AD require systemic treatments to induce adequate symptom control [4,5].

Conventionally, the main systemic treatment for AD has been ciclosporin [6]. Ciclosporin is a calcineurin inhibitor that inhibits T-cell-dependent immune responses. It has a rapid onset of action with a significant improvement in disease severity that is often seen within a few weeks. However, relapse is frequently seen soon after treatment withdrawal. Moreover, nephrotoxicity and hypertension are the most significant side effects of ciclosporin. As a result, ciclosporin cannot be used for several years even when the patient's condition is under good control by the drug. Although other immunosuppressive drugs, such as methotrexate and azathioprine, have also been used to treat severe AD,

these agents have a relatively slow action compared to that of ciclosporin. Methotrexate is a folic acid antagonist, but its exact mechanism of action in inflammatory diseases, including AD, is not fully understood. Azathioprine can cause myelosuppression and carries an increased risk of infection, lymphoma and nonmelanoma skin cancers [7,8]. Therefore, the development of novel agents with improved long-term safety is essential.

In acute lesions, AD onset is characterized by T helper (Th) 2 cytokines, including IL-4, IL-5, IL-13, IL-31 and CCL18, and Th22 responses, such as IL-22 and S100A proteins [9,10]. These mediators have been demonstrated to downregulate terminal differentiation genes and tight junction products, leading to skin barrier dysfunction in patients with AD [11–16]. Among Th2 cytokines, IL-4 and IL-13 have been demonstrated to play important roles in AD pathogenesis. Genetically, AD has been shown to be associated with IL-4 and IL-13 polymorphisms [17–20], and eczema-like symptoms are induced in transgenic mice overexpressing these cytokines [21–24]. Keratinocytes differentiated in the presence of IL-4 and IL-13 exhibit significantly lower filaggrin gene expression [25]. Moreover, loricrin and involucrin are also downregulated by IL-4 and IL-13 in lesional and nonlesional AD skin [12]. The successful treatment of AD with dupilumab, which

Table 1. A summary of novel topical treatments for atopic dermatitis.

Agent	Target	Drug	Phase	Manufacturer	References
Crisaborole	PDE4	Topical PDE4 inhibitor	Phase III published	Pfizer, New York, NY	[29]
OPA15406	PDE4	Topical PDE4 inhibitor	Phase II published	Otsuka, Tokyo, Japan	[30]
Tofacitinib	JAK1/3	Topical JAK1/3 inhibitor	Phase II published	Innovaderm, Montreal, Quebec, Canada	[31]
JTE-052	JAK	Topical JAK inhibitor	Phase II published	Japan Tobacco Inc, Tokyo, Japan	[32]
Tapinarof	AhR	AhR modulating agent	Phase II published	GlaxoSmithKline, London, UK	[33]
PAC-14028	TRPV1	Topical TRPV1 antagonist	Phase II published	Amorepacific Corporation, Yongin, Korea	[34]

AhR: aryl hydrocarbon receptor; JAK: Janus kinase; PDE4: phosphodiesterase type 4; TRPV1: transient receptor potential vanilloid subfamily, member 1.

Table 2. A summary of novel systemic treatments for atopic dermatitis.

Agent	Target	Drug	Phase	Manufacturer	References
Dupilumab	IL-4R α	Anti-IL-4R α mAb	Phase III published	Regeneron, Tarrytown, NY	[35,36]
Lebrikizumab	IL-13	Anti-IL-13 mAb	Phase II published	Hoffmann-La Roche, Basel, Switzerland	[37]
Tralokinumab	IL-13	Anti-IL-13 mAb	Phase II published	MedImmune, Gaithersburg, MD	[38]
Nemolizumab	IL-31R	Anti-IL-31R mAb	Phase II published	Chugai, Tokyo, Japan	[39,40]
Ustekinumab	IL-12/23p40	Anti-p40 mAb	Phase II published	Janssen, Titusville, NJ	[41,42]
Apremilast	PDE4	PDE4 inhibitor: oral small molecule	Phase II published	Celgene, Summit, NJ	[43]
Fezakinumab	IL-22	Anti-IL-22 mAb	Phase II published	Pfizer, New York, NY	[44]
GBR830	OX40	Anti-OX40 mAb	Phase II published	Glenmark, Mumbai, India	[45]
Baricitinib	JAK1/2	JAK1/2 inhibitor: oral small molecule	Phase II published	Eli Lilly, Indianapolis, IN	[46]
ASN002	JAK/SYK	JAK/SYK inhibitor	Phase I published	Asana BioSciences, Bridgewater, NJ	[47]
ZPL-3893787	H4R	H4R antagonist	Phase II published	Ziarco Pharma, Sandwich, UK	[48]
Tezepelumab	TSLP	Anti-TSLP mAb	Phase II published	Amgen, Thousand Oaks, CA	[49]

H4R: histamine 4 receptor; IL-4R: IL-4 receptor; IL-31R: IL-31 receptor; JAK: Janus kinase; mAb: monoclonal antibody; PDE4: phosphodiesterase type 4; SYK: spleen tyrosine kinase; TSLP: thymic stromal lymphopoietin.

blocks receptor binding of both IL-4 and IL-13, proves their central role in disease pathogenesis [26–28].

Novel targeted biologics such as dupilumab and small molecule agents have recently emerged through clinical trials, which would provide us with an increasingly broad range of therapeutic options. The purpose of this paper is to review recently published clinical trials on novel topical and systemic therapies in AD (Tables 1 and 2).

2. Novel topical therapies

2.1 Crisaborole and OPA15406: topical PDE4-inhibitors

Phosphodiesterase 4 (PDE4) is a key regulator of inflammatory cytokine production in AD through the degradation of cyclic adenosine monophosphate [50,51]. PDE4 activity is increased in circulating inflammatory cells of patients with AD [52–55], and the inhibition of PDE4 in monocytes *in vitro* has been demonstrated to reduce the release of proinflammatory cytokines [56]. Crisaborole enhances the cellular control of inflammation by inhibiting PDE4 and its ability to degrade intracellular cyclic adenosine monophosphate [51,57]. The efficacy and safety of crisaborole ointment was assessed in two randomized, vehicle-controlled, double-blind phase III studies (AD-301 and AD-302) of patients with mild-to-moderate AD [29]. Patients aged 2 years or older with an Investigator's Global Assessment

(IGA) score of mild or moderate were assigned for twice-daily application for 28 days. The primary end point was an IGA score of 0 or 1 with a 2-grade or greater improvement from baseline at day 29. More crisaborole-treated patients achieved IGA score success than vehicle-treated patients (AD-301 trial: 32.8% vs. 25.4%, $p = .038$; AD-302 trial: 31.4% vs. 18.0%, $p < .01$). Moreover, crisaborole-treated patients achieved success in the IGA score and improvement in pruritus earlier than those treated with vehicle (both $p < .001$). Treatment-related adverse events were infrequent and mild-to-moderate in severity.

OPA15406 is another PDE4 inhibitor with high selectivity for PDE4B. A phase II randomized, double-blind, placebo-controlled study was performed on adult and adolescent patients with mild-to-moderate AD [30]. Patients received topical OPA15406 or vehicle twice daily for 8 weeks. The primary end point, an IGA score of 0 or 1 with a greater than or equal to 2-grade reduction, was met at week 4 in the OPA15406 group ($p = .0165$ vs. vehicle). The mean percentage improvement from the baseline Eczema Area and Severity Index (EASI) score for OPA15406 was notable in week 1 (31.4% vs. 6.0% for vehicle; $p = .0005$) and persisted for 8 weeks. OPA15406 levels in blood were negligible. Moreover, the incidence of adverse events was low, with most events mild in intensity. Taken together, topical PDE4 inhibitors demonstrated a favorable safety profile and remarkable improvement in efficacy, including overall disease severity and skin score.

2.2 Tofacitinib and JTE-052: topical JAK inhibitors

The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is utilized by numerous cytokines and growth factors for signal transduction [58]. Tofacitinib, a small-molecule JAK inhibitor, has been shown to inhibit cytokines such as IL-4 directly and leads to rapid attenuation of JAK–STAT signaling in keratinocytes [59]. Tofacitinib ointment was efficacious in a phase II study in patients with mild-to-moderate chronic plaque psoriasis [60].

Two phase II, randomized, double-blind, vehicle-controlled studies were performed to assess the efficiency and safety of topical JAK inhibitor therapy on AD patients [31,32]. In the first trial, patients with mild-to-moderate AD were randomized to 2% tofacitinib or vehicle ointment twice daily for 4 weeks [31]. The primary end point was the percentage change from baseline in the EASI score at week 4. The mean percentage change from baseline at week 4 in the EASI score was significantly greater for tofacitinib (81.7%) vs. vehicle (29.9%). In the tofacitinib-treated group, significant improvement in EASI was observed by week 1, and improvement in pruritus was observed by day 2. Safety and local tolerability were generally similar for both treatments. In the second trial, 327 Japanese patients with moderate-to-severe AD were randomized to JTE-052 ointment, a novel JAK inhibitor, or vehicle ointment or tacrolimus twice daily for 4 weeks [32]. The primary end point was the percentage change in EASI score from baseline. At week 4, the least-squares mean percentage changes from baseline in the modified EASI score for JTE-052 (3% dose), the vehicle ointment, and tacrolimus were 72.9%, 12.2%, and 62.0%, respectively. The JTE-052 group showed a significant reduction in the modified EASI score compared to the vehicle group ($p < .001$). The JTE-052 group also showed significant improvement in other parameters; notably, the pruritus score was reduced as early as day 1 at night-time. Regarding safety, JTE-052 ointment at doses up to 3% was safe and well tolerated. These results from two clinical trials suggested that topical JAK inhibition through topical delivery would potentially be a promising therapeutic target for AD.

2.3 Tapinarof: AhR modulator

Tapinarof is a nonsteroidal topical agent representing a unique class of anti-inflammatory compounds called therapeutic aryl hydrocarbon receptor (AhR) modulating agents. Tapinarof activity is mediated primarily through AhR, which affects Th2 cytokine and skin barrier gene expression [61]. Moreover,

tapinarof exhibits inherent antioxidant properties through activation of the nuclear factor, erythroid 2-like 2 pathway. The anti-inflammatory effects of coal tar extracts, which have been used topically for AD for decades, may also result from activation of AhR/nuclear factor, erythroid 2 like 2 [61]. A double-blind, vehicle-controlled, randomized trial was performed in patients aged 12–65 years, with body surface area involvement of at least 5%–35% and an IGA score of 3 or 4 at baseline [33]. Primary end points included an IGA score of clear or almost clear and a minimum 2-grade improvement (treatment success) at week 12. Secondary analyses included a 75% or greater improvement in EASI score. The rates of treatment success at week 12 were 53% (1% tapinarof twice daily), 46% (1% once daily), 37% (0.5% twice daily), 34% (0.5% once daily), 24% (vehicle twice daily) and 28% (vehicle once daily). The rate with a concentration of 1% tapinarof twice daily (53%) was statistically higher than the rate with vehicle twice daily (24%). Treatment success was maintained for 4 weeks after the end of tapinarof treatment. Although the rate of treatment-emergent adverse events was higher with tapinarof (93 of 165: 56%) than with vehicle (34 of 82: 41%), the events were mild-to-moderate in intensity. In summary, tapinarof cream was efficacious and tolerated in adolescent and adult patients with AD.

2.4 PAC-14028: topical TRPV1 antagonist

Transient receptor potential vanilloid subfamily member 1 (TRPV1) is expressed not only on sensory nerves but also on keratinocytes, dendritic cells (DCs) and sebocytes in the skin [62]. It is directly activated by pain-producing stimuli such as capsaicin, heat, and acid or activated when intracellular signal transduction is conducted by pruritogens [63]. In AD-like murine models, the selective TRPV1 antagonist PAC-14028 has shown antipruritic effects, improved skin barrier function and suppressed allergic inflammation by blocking the secretion of neuropeptides, modulating epidermal differentiation markers and suppressing Th2 cytokines [64–66]. A phase IIb, randomized, double-blind and vehicle-controlled trial of PAC-14028 cream was conducted in patients with mild-to-moderate AD [34]. A total of 194 patients were randomized to receive PAC-14028 cream or vehicle cream twice daily for 8 weeks. The primary efficacy end point was the IGA success rate, defined as the percentage of patients with an IGA score of 0 or 1 at week 8. The success rate at week 8 was 57.45% for PAC-14028 cream 1.0%, which was significantly higher than that for vehicle cream (14.58%),

$p < .001$). The 75% or 90% reduction of the EASI score from baseline (EASI-75/90), sleep disturbance score and pruritus visual analog scale tended to be improved in the treated group but did not reach significant difference. No significant safety issues were reported. In conclusion, PAC-14028 cream may be an effective and safe treatment modality for the treatment of patients with mild-to-moderate AD.

3. Novel systemic therapies

3.1 Dupilumab: anti-IL-4R α mAb

Dupilumab is a human monoclonal antibody (mAb) against IL-4 receptor alpha. Because the IL-4 receptor and an IL-13 receptor share the alpha chain, the antibody inhibits signaling of IL-4 and IL-13. Dupilumab proved to be efficacious in two randomized, placebo-controlled, phase III trials of identical design (SOLO 1 and SOLO 2) with ~1400 patients published in 2016 [67]. The primary outcome was the proportion of patients with an IGA score of 0 or 1 and a reduction of 2 points or more in that score from baseline at week 16. The primary outcome was met in 36%–38% of all patients who received dupilumab compared with 8%–10% in patients who received placebo in both studies. Dupilumab was also associated with improvement in other clinical endpoints, including reduction in the EASI score.

In a more recently published 1-year, randomized, double-blinded, placebo-controlled, phase III study entitled 'LIBERTY AD CHRONOS', 740 adults with moderate-to-severe AD and inadequate response to topical corticosteroids were enrolled [35]. All patients were given concomitant topical corticosteroids with or without topical calcineurin inhibitors. Topical corticosteroids could be applied on the basis of disease activity. The findings after 16 weeks were similar to those in the SOLO studies and proved to be stable over the extension period of 52 weeks.

In a further study, the efficacy and safety of dupilumab was studied in combination with concomitant topical corticosteroids in adults with AD showing an inadequate response to or intolerance of cyclosporine or in adults for whom cyclosporine treatment was medically inadvisable [36]. The primary endpoint, EASI-75 at week 16, was achieved by ~60% in the treatment groups, whereas ~30% of patients who received topical steroids in combination with placebo injections reached this endpoint. Only local injection site reactions and conjunctivitis occurred as a specific side effect of dupilumab significantly more often in treatment groups than in the group treated with placebo.

3.2 Lebrikizumab and tralokinumab: anti-IL-13 mAb

IL-13, a major type 2 cytokine secreted from T lymphocytes, is highly elevated in AD both in blood and in skin [68]. Additionally, IL-13 is considered to be a key cytokine of type 2 inflammation with a number of effects on a variety of cells, excluding T lymphocytes [69]. Two antibodies against IL-13 have been studied in AD so far.

Lebrikizumab was studied in different doses in a randomized, placebo-controlled, double-blind, phase II study of adults with moderate-to-severe AD in combination with topical corticosteroids twice daily [37]. The rate of patients achieving EASI-50 at week 12 was significantly higher with lebrikizumab than with placebo, although the difference was not very large because of a pronounced placebo response (82.4% in the treatment group vs. 62.3% in the placebo group). Adverse events were similar between groups and were mostly mild or moderate.

Tralokinumab, a fully human anti-IL-13 mAb, was studied in different doses in 204 adults with moderate-to-severe AD in a phase IIb study with concomitant topical glucocorticoids [38]. Coprimary endpoints were change from baseline in EASI and the percentage of participants with an IGA response with 0 or 1 score and reduction of two grades or more from baseline at week 12. Here, the highest applied dose of tralokinumab (300 mg) led to significant improvement from baseline in EASI vs. placebo, and a greater percentage of participants (26.7% vs. 11.8%) achieved an IGA response. Interestingly, greater responses were found in participants with higher concentrations of biomarkers of increased IL-13 activity in this study. Taken together, the anti-IL-13 mAb treatment showed strong efficacy in AD.

3.3 Nemolizumab: anti-IL-31R mAb

Nemolizumab is an antibody targeting IL-31 receptor A. In a phase II, randomized, double-blind 12-week trial, 216 adult patients with moderate-to-severe AD inadequately controlled by topical treatments were treated with subcutaneous nemolizumab at different doses [39]. The primary endpoint was improvement from baseline in the score on the pruritus visual analog scale at week 12. Changes on the pruritus visual analog scale were between -44% and -63% (depending on the nemolizumab dose) vs. -21% in the placebo group. Changes in the severity score of EASI were lower and varied between -23% and -42% in the nemolizumab groups versus -27% in the placebo group. Furthermore, the results of a long-term extension study have been published [40]. Improvement from baseline in the pruritus visual

analog scale was maintained/increased from weeks 12–64 depending on the nemolizumab dose. Improvement from baseline in EASI was also maintained/increased to week 64 (percentage changes in EASI were between –68.5 and monoclonal antibody 78.9 depending on the nemolizumab dose). Common side effects were worsening of AD, nasopharyngitis, infections of the upper respiratory tract, peripheral edema and elevation of the creatine phosphokinase. These results suggested that nemolizumab would be a good choice for treating AD patients with severe pruritis.

3.4 Ustekinumab: anti-p40 mAb

Ustekinumab is an IL-12/IL-23p40 antagonist that suppresses Th1, Th17 and Th22 activation and has been approved in the treatment of psoriasis [27]. In a phase II, double-blind, placebo-controlled study, 33 patients with moderate-to-severe AD were treated with either ustekinumab or placebo [27], with subsequent crossover at 16 weeks. The ustekinumab group tended to achieve higher improvements of the Scoring Atopic Dermatitis (SCORAD) compared to the placebo group, which did not reach statistical significance. Likewise, in another placebo-controlled, phase II study, 79 Japanese patients with severe AD received ustekinumab or placebo subcutaneous injections at weeks 0 and 4, with follow-up until week 24 [41]. Ustekinumab treatment showed similar levels of EASI score improvement at week 12 compared to that of placebo [41]. In all, ustekinumab proved to have limited efficacy in AD.

3.5 Apremilast: PDE4 inhibitor

Apremilast, an orally available PDE4 inhibitor that is approved for the treatment of adults with moderate-to-severe psoriasis and active psoriatic arthritis, regulates a number of the proinflammatory signals involved in AD, including IL-17, IL-22, IL-13, IL-31, IL-33, IL-5 and the alarmins S100A7, S100A8 and S100A12 [70,71]. A phase II, double-blind, placebo-controlled study was performed to evaluate the efficacy, safety and pharmacodynamics profile of apremilast for the treatment of adult patients with moderate-to-severe AD [43]. Patients were randomly assigned to receive placebo, apremilast 30 mg twice daily (APR30), or apremilast 40 mg twice daily (APR40) for 12 weeks. Among 185 randomly assigned intention-to-treat patients at week 12, a dose-response relationship was observed; APR40, but not APR30, led to statistically significant improvements (vs. placebo) in EASI (mean percent change from baseline = –31.6% vs. –11.0%, $p = .04$). Regarding adverse events, safety with APR30 was

largely consistent with apremilast's known profile: nausea, diarrhea, headache and nasopharyngitis. With APR40, adverse events were more frequent, and cellulitis occurred in 9.5% of the group. Therefore, an independent safety monitoring committee discontinued the APR40 dosage. Taken together, these findings indicate that apremilast cannot be considered a novel therapeutic treatment for AD at this point.

3.6 Fezakinumab: anti-IL-22 mAb

IL-22 is a T-cell cytokine that acts mainly on epithelial cells and in the skin is related to epidermal hyperplasia, keratinocyte apoptosis, and inhibition of antimicrobial peptide production relevant to AD [72]. The anti-IL-22 specific antibody fezakinumab was studied in a randomized, double-blind, placebo-controlled trial of intravenous monotherapy every 2 weeks for 10 weeks [44]. At 12 weeks, the mean declines in the severity score SCORAD were not significant, with a mean reduction of 14 points in the fezakinumab arm and 8 points in the placebo arm. During the observation phase until week 20, further improvements were observed in the fezakinumab treatment group. Future studies are necessary to confirm whether anti-IL-22 treatment will be primarily indicated in AD.

3.7 GBR830: anti-OX40 mAb

GBR830 is a humanized mAb against OX40, a costimulatory receptor on activated T cells [45]. OX40 ligand (OX40L) is expressed on activated antigen-presenting cells, including DCs and endothelial cells. OX40-OX40L engagement is key to potentiating T-cell responses triggered through the T-cell receptor [73]. In patients with AD, the numbers of OX40L⁺ DCs were highly increased compared with those in psoriatic and normal skin, with greater expression of OX40 in AD lesions [74–76]. GBR830 is an investigational, first-in-class, humanized IgG1 mAb specifically inhibiting OX40 to treat autoimmune and chronic inflammatory disorders. The efficacy and safety of GBR830 was investigated in patients with moderate-to-severe AD in a randomized, double-blind, placebo-controlled trial [45]. GBR830 or placebo was intravenously administered on days 1 and 29. At day 71, the proportion of intention-to-treat subjects achieving 50% or greater improvement in EASI score was significantly greater with GBR830 (76.9%) vs. placebo (37.5%). Regarding efficacy, GBR830 was well tolerated, with equal treatment-emergent adverse event distribution (both, 63.0%). Taken together, GBR830 administration 4 weeks apart induced significant progressive clinical changes

until day 71 (42 days after the last dose), highlighting the potential of targeting OX40 in patients with moderate-to-severe AD.

3.8 Upadacitinib, baricitinib and ASN002: JAK inhibitors

JAKs are critically involved in signal transduction via cytokine receptors. JAKs are promising targets for both topical and systemic treatment of AD. Several press releases on successful treatment with systemic JAK inhibitors such as upadacitinib (JAK1 inhibitor) and PF-04965842 (JAK1 inhibitor) are available [77]. A randomized, double-blind, placebo-controlled multicenter phase IIb study was performed to assess the efficacy and safety of upadacitinib in patients with moderate-to-severe AD. For patients receiving upadacitinib, the mean percent improvement from baseline in the EASI score was 48/44/69% for the 7.5/15/30 mg doses, respectively, compared to 34% for patients receiving placebo. Among patients receiving placebo in Period 1 (week 0–16) and rerandomized to receive the upadacitinib 30 mg dose in Period 2 (week 17–32), the mean percent improvement from baseline in the EASI score was 97% at week 32 [77].

Baricitinib is an oral inhibitor of JAK1 and JAK2 and has already been approved for the treatment of rheumatoid arthritis in several countries. In a recently published controlled phase II study, 124 patients with moderate-to-severe AD received placebo or baricitinib in two doses for 16 weeks [46]. The use of topical corticosteroids was obligatory before the study and permitted during the study. The primary outcome was the proportion of patients achieving EASI-50 compared to placebo. A rapid significant improvement of eczema was observed with both doses of baricitinib compared to the placebo at week 4. Because topical corticosteroids were allowed in the study, improvement of eczema was also seen in the placebo group over time. After 16 weeks, a significantly higher rate of patients receiving a 4 mg dose of baricitinib achieved EASI-50 compared to that of the placebo-group (61% vs. 37%). The drug also improved pruritus and sleep loss.

Spleen tyrosine kinases (SYKs) are involved in the release of cytokines during the proinflammatory process, including IL-1 β , IL-10 and IL-17, and regulate DCs, B lymphocytes and keratinocyte differentiation, suggesting that SYK inhibitors could improve inflammatory skin diseases with aberrant differentiation, such as AD [78,79]. ASN002 is a potent, dual inhibitor of JAK and SYK kinases [47]. The efficacy of ASN002 was assessed by a randomized double-blind, placebo-controlled study in patients with

moderate-to-severe AD. On day 28, ASN002 was superior to placebo with respect to the proportion of patients achieving EASI-50 (40 mg: 100.0%, $p = .003$; 80 mg: 83.3%; $p = .03$; placebo: 22.2%) and the change from baseline in pruritus (40 mg: -3.1 ± 2.7 , $p = .27$; 80 mg: -4.7 ± 2.1 , $p = .01$; placebo: -1.6 ± 1.8). Adverse events were generally mild and similar across all groups [47]. Taken together, JAK/SYK inhibitors showed strong efficacy with a rapid onset of action and associated improvements in AD.

3.9 ZPL-3893787: histamine H4R antagonist

Histamine H4 is the most recently discovered histamine receptor subtype, and its role in mediating histamine-induced inflammation and pruritus is well documented [80,81]. H4 mediates proinflammatory functions in a number of cell types involved in allergic inflammation, including T cells, mast cells, eosinophils and DCs. Selective H4 receptor antagonists have shown anti-inflammatory and antipruritic efficacy in various preclinical animal models, supporting the concept that they might represent a novel treatment for inflammatory skin diseases, including AD.

In the first clinical trial, the H4R antagonist JNJ 39758979 reduced inflammation and pruritus in Japanese patients with AD but unfortunately led to nonfatal agranulocytosis in two patients, which led to early termination of that study with this antagonist [82]. Recently, a randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate ZPL-3893787, another selective histamine 4 receptor antagonist [48]. The oral drug or placebo was given once daily to 98 adult patients with moderate-to-severe AD. At week 8, treatment with ZPL-3893787 showed a 50% reduction in the EASI score compared to 27% for placebo and a 41% reduction in SCORAD with ZPL-3893787 vs. 26% with placebo at week 8. Regarding side effects, ZPL-3893787 was well tolerated, without any reductions in circulating granulocytes. These results showed that a selective histamine 4 receptor antagonist was able to improve inflammatory skin lesions in patients with AD, suggesting that the H4 receptor antagonist could be one choice of oral anti-histamine blockers in AD.

3.10 Tezepelumab: anti-TSLP mAb

Thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine, is produced in response to proinflammatory stimuli. TSLP-activated DCs induce the production of Th2 cytokines, IL-4, IL-5 and IL-13 and tumor necrosis factor- α [83]. TSLP could be a key target to control AD-associated

inflammation and skin barrier disruption, the pathogenesis of which is associated with these downstream Th2 cytokines and immunomodulating proteins. Tezepelumab is a fully human immunoglobulin G2 λ mAb that specifically binds TSLP and prevents interaction with its receptor complex. In the phase IIb PATHWAY study, tezepelumab demonstrated significant reductions in the annual asthma exacerbation rate vs. that of placebo in patients with uncontrolled asthma, irrespective of baseline biomarker status [84]. The efficacy and safety of tezepelumab in adults with moderate-to-severe AD were evaluated in a randomized, double-blind, placebo-controlled study [49]. In the phase IIa study, 113 patients were randomized 1:1 to receive subcutaneous tezepelumab or placebo every 2 weeks, plus class 3 topical corticosteroids. The primary endpoint was the week 12 response rate for EASI-50. A numerically greater percentage of tezepelumab achieved EASI-50 (64.7%) vs. placebo (48.2%), which did not reach a significant difference ($p = .091$). Future studies should be performed to confirm the efficacy of tezepelumab in AD.

3.11 MOR106: anti-IL-17C mAb

IL-17C is one of the six members of the IL-17 cytokine family, which consists of IL-17A through IL-17F, which is believed to play a role in the pathogenesis of psoriasis. In contrast to IL-17A, which is produced by Th17 cells and innate immune cells such as $\gamma\delta$ T cells and invariant natural killer T cells [85], the main source for IL-17C appears to be epithelial cells [86]. It was reported that IL-17C expression was increased and localized to keratinocytes and infiltrating immune cells in the lesional skin of AD patients as well as in that of individuals with psoriasis [87]. MOR106, a human IgG1 antibody identified from the MorphoSys Ylanthia library [88], binds both human and mouse IL-17C. MOR106 potently blocks the interaction of human and mouse IL-17C with its high affinity receptor IL-17RE. No binding was observed to other human and mouse IL-17 family members [87]. A randomized, double-blind, placebo-controlled phase I trial evaluating single ascending doses of MOR106 in healthy volunteers and multiple ascending doses in patients with moderate-to-severe AD was conducted [89]. Twenty-five AD patients were enrolled and received four infusions once weekly of either MOR106 (at doses of 1, 3 and 10 mg/kg body weight) or placebo in a 3:1 ratio. Patients were followed for 10 weeks after the end of the treatment period. At the highest dose level of MOR106 (10 mg/kg), 83% of patients (5 out of 6) achieved EASI-50 at week 4. Pooled data across dose cohorts showed that patients

treated with MOR106 achieved an EASI improvement compared to baseline of 58%, 62%, 72% and 64% at weeks 4, 8, 12 and 14, respectively. For patients receiving placebo, the EASI improvement was 32%, 40%, 38% and 50%, respectively. For safety, all adverse drug reactions observed were mild-to-moderate and transient in nature. No serious adverse events and no infusion-related reactions were recorded. Future studies are ongoing to confirm the efficacy of MOR106 in AD.

4. Conclusion

In this review, recently published clinical trials on AD were highlighted. Many novel biologic and small molecule agents that are clinically effective in AD treatment have emerged. Although the performance of dupilumab is outstanding, anti-IL-13 mAb and oral JAK/SYK inhibitors might have potential to be comparable with dupilumab in terms of EASI score improvement. More data regarding ongoing development programs can be expected in the future for other biologics and small molecule inhibitors. In addition to the ability to alter the natural history of AD, drug safety and cost-effectiveness should be considered. Although we have entered an exciting era in AD treatment, further studies are required before the promise of a therapeutic revolution becomes reality.

Disclosure statement

The authors declare no conflict of interest.

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