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REVIEW ARTICLE

Therapeutic New Era for Atopic Dermatitis: Part 1. Biologics

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Atopic dermatitis (AD) is a chronic, inflammatory cutaneous disease driven by immune dysregulation and skin barrier dysfunction. We are currently experiencing a new era of understanding of the pathogenesis of AD and, as a consequence, a new era of innovation in therapeutics, including small molecules and biologic therapy. Recently, advances in translational research have challenged the traditional AD pathogenesis paradigm of AD being solely a Th2-dominant disease. Other immune pathways seem to play a role in the complex AD pathophysiology, although the clinical relevance of these additional immune pathway abnormalities is unclear. Type 1, type 22, and type 17 pathway activation (with related cytokines/chemokines) have been demonstrated in the skin and blood of AD patients. Type 2 (interleukin [IL]-4, IL-13), IL-31, and type 22 (IL-22) pathway cytokines are increased in AD acute lesions. IL-22 induces both an epidermal hyperplasia at the onset of acute AD and a marked increase in the terminal differentiation S100 genes. This understanding of pathogenesis corresponds to a historic increase in therapeutic development in AD. The extreme clinical heterogeneity and the chronic progression of AD establish the need for newer, safer, and more effective treatments, control the disease, and improve the quality of life of affected patients. **(Ann Dermatol 33(1) 1～10, 2021)**

-Keywords-
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BIOLOGICS

Atopic dermatitis (AD) is one of the most common inflammatory diseases in medicine, not just skin, associated with a broad patient burden of skin lesions, pruritus, and both allergic and non-allergic comorbidities. The clinical presentation is heterogeneous, and various phenotypes can be identified; however, for all patients, the main symptom is pruritus[1]. Most cases of AD occur in early childhood that follows a recurrent and chronic course that can resolve in childhood. However, in up to half of patients, it may re-emerge or persist into adulthood becoming a lifelong condition[2]. The term adult-onset AD has been used to describe patients in whom the disease presents *de novo* during adulthood, and persistence into adulthood often reflects the more severe cases. Up to 25% of AD cases in adulthood may be adult-onset[3], and such patients often have added skin problems such as recalcitrant pruritus and lichenification that resist topical medications. Management is difficult for most adult cases, and attention to the classification of the disease should not be diverted by questionable labels[4]. Furthermore, as the population grows and old, poorly-classified elderly chronic eczemas are emerging that may represent elderly AD with a significant impact on the quality of life[5]. In these points, AD is no longer a childhood specific problem.

Recently, advances in translational research have challenged the AD pathogenesis paradigm shft[6-9], and this knowledge leads to the development of AD treatment. Biologics

are protein-based therapies such as monoclonal antibodies that target cytokines or cytokine receptors that initiate and maintain abnormal inflammatory pathways; several antibodies targeting cytokines have been developed or are in development as therapeutic agents for AD.

Dupilumab, the first biologic drug approved for AD, filled a large void for a safe and effective therapy for long-term use. Since the advent of dupilumab, several biologics are now being developed and investigated to provide alternatives to dupilumab (Table 1). Several antibodies targeting cytokines and cytokine receptors have been developed as therapeutic agents against AD.

Th2 cell inhibition

1) IL-4 and IL-13 inhibition

Interleukin (IL)-4 and 13 are two critical cytokines in normal Th2 responses for combating parasitic infections and play essential roles in the differentiation of Th2 cells and the production of immunoglobulin E (IgE). IL-4 acts on Th0 cells to promote differentiation and growth into Th2 cells, and the newly dispersed and proliferating Th2 cells produce more IL-4; thus amplifying and sustaining Th2 reactions. IL-4 receptors are expressed in T cells, B cells, and macrophages, and when IL-4 binds to these receptors, low-affinity IgE receptors are displayed on the surface of B cells, monocyte, and macrophages[10-12]. In B cells, Janus Kinase-1 and 3 are activated when IL-4 stimulates IL-4 receptors, which induces activation of signal transducer and activator of transcription 6 (STAT6) and increases IgE production.

IL-4 and IL-13 were shown to impair epidermal barrier integrity by suppressing major terminal differentiation proteins: filaggrin, loricrin, and involucrin expression which were reduced in the presence of these two Th2 immune mediators. In isolated keratinocytes, IL-4 decreases the expression of genes in the epidermal differentiation complex (EDC) that contribute to the barrier function and innate immune defense[9]. This epidermal barrier dysfunction, together with IL-4 and IL-13 ability to inhibit skin production of antimicrobial peptides (AMP), predispose AD skin to infections[9]. Cell culture studies to reveal increased IL-4/IL-13 levels that lead to the recruitment of additional inflammatory cells and disturb skin barrier function by inhibiting the production of barrier structural proteins like filaggrin, lipids, and AMP, and encourage *Staphylococcus aureus* colonization[9].

Moreover, IL-4 and IL-13 also induce the expression of thymic stromal lymphopoietin (TSLP), which contributes to linking the barrier abnormality and Th2 activation responses. TSLP activates dendritic cells and induces OX40L to appear on the surface of the activated dendritic cells; Keratinocyte-derived TSLP activates dendritic cells to induce the production of Th2 immunity cytokines such as IL-4, IL-5, IL-13, and tumor necrosis factor (TNF)-α. IL-33 appears to amplify TSLP's effect of inducing expression of OX40 ligand on dendritic cells[9]. IL-13, specifically, appears to be one of the key cytokines driving AD pathology. In a recent study, Tsoi et al.[13] conducted a large-scale transcriptomic study of AD with deeply sequenced RNA-sequencing samples using long (126-bp) paired-end reads. They described disease-specific molecular and cellular features, with AD skin showing the dominance of IL-13 pathways with near undetectable IL-4 expression. In addition, IL-13 is highly elevated in the skin and the blood of AD patients and correlates with disease severity.

(1) IL-4 and IL-13 inhibition: Dupilumab is a human monoclonal antibody (mAb) against IL-4 receptor α (Fig. 1). The IL-4 receptor α subunit is shared between both the IL-4 and IL-13 receptors. The randomized, placebo-controlled, phase 3 trials (SOLO 1 and SOLO 2) confirmed the efficacy and safety of dupilumab in adults with moderate to severe AD[1]. In this study, the primary outcome was 0 (clear) or 1 (almost clear) on the Investigator's Global Assessment (IGA) score and a reduction of 2 points or more from baseline at week 16. The primary outcome was achieved by 36%～38% of all patients who received dupilumab compared with 8%～10% in patients who received

Table 1. Novel systemic biologics; targeted therapies of atopic dermatitis

Category	Target	Name	Development Status
Th2 inhibitors	IL-4Rα	Dupilumab	Approved
	IL-13	Tralokinumab	Ph III on-going
		Lebrikizumab	Ph II completed
	IL-33	Etokimab	Ph II on-going
		REGN3500	Ph II completed
		PF-067817024	Ph I on-going
Others	IL-31	Nemolizumab	Ph III on-going
		BMS-981164	Ph I completed
		KPL-716	Ph II on-going
	TSLP	Tezepelumab	Ph II on-going
	OX40	KHK4083	Ph II on-going
		GBR830	Ph II on-going
	IL-5	Mepolizumab	Ph II completed
Th1/17/22 inhibitors	IL12/23	Ustekinumab	Ph II completed
	IL-17	Secukinumab	Ph II on-going
		MOR106	Ph II on-going
	IL-22	Fezakinumab	Ph II completed

IL: interleukin.

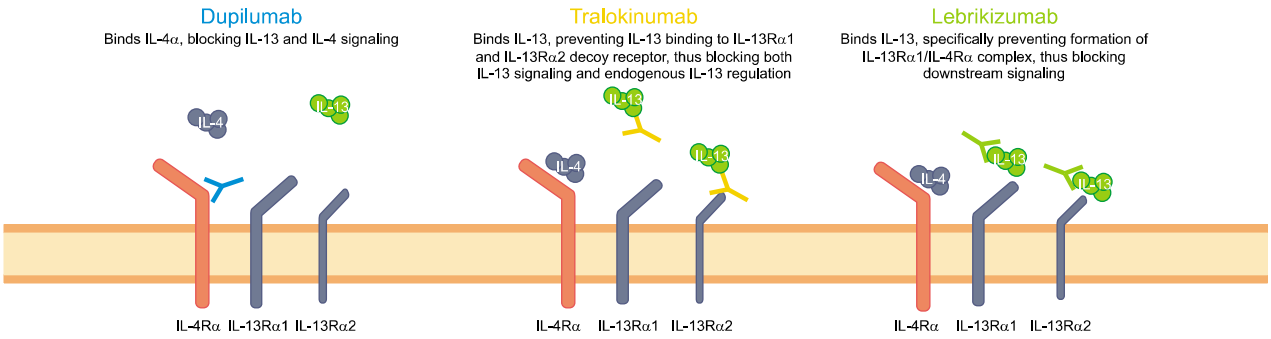

Fig. 1. Mechanism of dupilumab, tralokinumab, and lebrikizumab. IL: interleukin.

a placebo ($p<0.0001$). Patients also experienced a reduction in itch as early as week 2[1]. This study showed that there were no significant differences between every two-week dosing of dupilumab in IGA scores, Eczema Area and Severity Index (EASI), Numerical Rating Scale (NRS), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI) compared with weekly dosing[1].

A more recently published 1-year, randomized, double-blinded, placebo-controlled, phase 3 study (CHRONOS), 740 adults with moderate-to-severe AD and inadequate response to topical corticosteroids (TCS) were enrolled[14]. Unlike SOLO trials, patients used concomitant TCS with or without topical calcineurin inhibitors (TCI). The results after 16 weeks were similar to those in the SOLO studies and proved to be stable over the 52 weeks[15]. This study showed that dupilumab with standard TCS treatment for one year improved AD with acceptable safety.

The CAFÉ study, another Phase 3 study, sought to answer whether dupilumab provides adequate treatment outcomes for patients previously exposed to cyclosporin (CsA) or in patients whose CsA treatment was needed. In this 16-week, double-blind, randomized, placebo-controlled, phase 3 trial, patients were randomized 1:1:1 to subcutaneous dupilumab 300 mg weekly (*qw*) or every 2 weeks (*q2w*) or placebo. This study evaluated dupilumab on a background of treatment with TCS[15]. Significantly more patients in the dupilumab *qw*+TCS and *q2w*+TCS groups achieved EASI 75 at week 16 vs. the placebo+TCS group (primary endpoint) (59.1% and 62.6% vs. 29.6%, respectively; $p<0.001$ vs. placebo+TCS, both doses). No new safety signals were reported[16]. Thus, dupilumab presented effectiveness in a potentially highly-refractory patient population with most previously treated CsA.

The most common adverse events in clinical trials were the deterioration of AD[1,14,15] and reported adverse effects were nasopharyngitis, conjunctivitis, headache, herpes simplex infection, and injection site reaction. But the overall incidence of adverse events was similar in the dupilumab groups and the placebo groups in the clinical study. Serious adverse events were uncommon[16].

Overall, dupilumab appears to be a safe therapy suitable for long-term use. Laboratory monitoring is not required as no end-organ damage has been observed[17]. Dupilumab does not appear to be immunosuppressive, and vaccination responses are not affected.[17] Further, studies reveal a significantly reduced risk of serious or severe infections compared to placebo[18].

To determine the effects of dupilumab on *S. aureus* colonization and microbial diversity on the skin, bacterial DNA was analyzed from swabs collected from lesional and non-lesional AD skin. During dupilumab treatment, microbial diversity increased, the abundance of *S. aureus* decreased, and so pronounced changes were showed in both nonlesional and lesional skin. Also decreased *S. aureus* correlated with clinical improvement of AD and biomarkers of type 2 immunity[19].

The most common adverse event reported in higher rates on treatment compared to placebo was conjunctivitis. A significant proportion (8.6%～22.1%) of patients receiving dupilumab for AD in clinical trials developed conjunctivitis[20], and conjunctivitis occurred more often in patients who had severe AD or coexisting allergic conjunctivitis. In the SOLO trials, only 1 discontinued study treatment because of conjunctivitis, however. Interestingly, dupilumab didn't have a higher rate of conjunctivitis than placebo in asthma or nasal polyposis clinical study, which suggests that this adverse event is a specific disease-drug interaction[20].

Clinical characteristics of the conjunctivitis were that it was presented mostly bilaterally and was mild-to-moderate, associated with pruritus, a burning sensation, increased lacrimation, and a foreign body sensation[21,22]. The cause of dupilumab-associated conjunctivitis is currently unclear. Pathogenetic hypotheses are inhibition of IL-4 and IL-13 signaling pathways, which lead to increased activity of ligands such as OX40L and developed of atopic kerato-

conjunctivitis[16]. Another hypothesis is based on the transient dupilumab-induced increase in eosinophils, which play a part in the development of allergic conjunctivitis[23]. A recent study described the histopathological characteristics of a patient with severe, new-onset conjunctivitis during dupilumab treatment and four months after discontinuation of dupilumab. In conjunctiva biopsy, there are goblet cell (GC) scarcity with a median density of 2～4 goblet cells/mm with a CD4-/CD8-positive (mainly CD4-positive) T-cell infiltrate at the interface, partially migrating into the epithelium. After discontinuation of dupilumab, follow-up conjunctival biopsy showed a normal GC density of 24～28 cells/mm with significantly fewer T cells[24]. They explained that blocking IL-13 leads to a reduction of GCs and mucin production, resulting in irritative conjunctivitis. Affected patients should be examed an ophthalmologist to rule out other types of conjunctivitis (e.g., bacterial or viral).

Corticosteroid preparations such as fluorometholone 0.1% eye drops are commercially available for the treatment of dupilumab related conjunctivitis. Eye drops containing CsA are also suitable for the treatment of severe conjunctivitis, and another option is tacrolimus 0.03% compounded eye ointment. A key advantage of tacrolimus compared to corticosteroids is the fact that the former can be used long term, as there is no increased risk of developing glaucoma or cataracts[25].

Currently, dupilumab is prescribed to AD patients in many countries, and real-word data is reported allowing for an assessment of real-world effectiveness and safety. In a French multicenter adult cohort, a ≥75% improvement in SCORAD was shown in 27 of 163 (16.6%) patients, and EASI75 was 40 of 82 (48.8%) patients, and it was consistent with a previous clinical trial. They reported conjunctivitis in 84 of 241 (34.9%) patients, 100/177 (56.5%) had blood eosinophilia[26]. In a Japanese cohort, the EASI score significantly decreased by 44% on average at 1 month and by 69% at 3 months; however, no significant decrease in the EASI scores for the head and neck was found at 1 month after starting dupilumab. They explained the treatment of the head and neck needs 3 months after starting dupilumab[27]. In Italy, EASI 50, EASI 75, and EASI 90 were achieved by 59.6%, 28.4%, and 9.3% of patients at 4 weeks and by 87.2%, 60.6%, and 32.4% of them at 16 weeks, respectively. Adverse events were experienced by 19.3% (21/109) of the patients, and conjunctivitis was the most common side effect[28]. And also, Netherland multicenter data shows disease severity-related serum biomarkers (TARC, PARC, periostin, and IL-22), eotaxin-1, and eotaxin-3 significantly decreased during dupilumab treatment[29].

In Korea (National Medical Center), a total of 101 patients was reported[30] EASI 50 and EASI 75 were 92.7% and 63.6% at 16 weeks. Factors affecting the therapeutic response of dupilumab are no well-known not yet. In the Korean study, the only possible therapeutic biomarker was gender, with an odds ratio for female achieving EASI 75 is 5.4 ($p=0.04$) than male. This study also showed that hypereosinophilia might negatively affect the treatment response. Patients with persistent hypereosinophilia up to 16 weeks of evaluation during the treatment of dupilumab were not as effective as those who did not. When total eosinophil count (TEC)≥1,500 at 16 weeks, the mean percent change of EASI was 62.82 and when TEC<1,500 was 76.16 ($p=0.014$)[30]. However, TEC is a non-specific marker and can be elevated due to comorbid allergic diseases. Additional studies regarding the relationship between eosinophil counts and dupilumab treatment responses are needed. Usually, baseline predictive biomarkers are likely more useful than severity-base biomarkers.

As expected, some rare adverse events not captured in trials have emerged during real-world use. Facial dermatitis, inflammatory arthritis, severe keratitis, and psoriasiform dermatitis have been reported. Facial erythema is emerging as a significant problem in a small subset of patients with AD, although the etiology is unclear[27,31-34]. Facial erythema in a patient with AD can be caused by refractory AD lesions, contact dermatitis, topical steroid withdrawal syndrome, and possibly a newly-described side effect; dupilumab-induced facial dermatitis. Dupilumab-induced psoriasiform dermatitis has been reported in various locations on the body. The facial eruption may be one manifestation of this as the facial erythema can often have a well-demarcated morphology with less itch than typical AD[26,35].

Dupilumab also is approved for use in adolescents aged ≥12 years with inadequately controlled moderate-to-severe AD. Dupilumab significantly improved AD signs/symptoms in a 16-week, randomized, placebo-controlled phase 3 trial in adolescents. The phase 2a study and phase 3 open-label extension were the earliest studies of dupilumab in adolescents to characterize its PK and long-term safety and efficacy profile. The results from these studies support the dupilumab for the long-term management of moderate-to-severe AD in adolescents[36].

(2) IL-13 inhibition: Tralokinumab, an IgG4 λ anti-IL-13 mAb derived from a human phage display library, prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2 (Fig. 1)[37,38]. IL-13Rα2 has a short cytoplasmic tail different from IL-13Rα1 and no known signaling motifs and may function as a decoy receptor to modulate IL-13 levels via internalization of excess IL-13[38]. The biologic effects of blocking IL-13 binding to the decoy receptor are unknown in hu-

mans, but a loss of function of the IL-13 decoy receptor was shown to be deleterious in a mouse model of cutaneous inflammation[39]. Tralokinumab can prevent both IL-13-mediated signalings downstream of IL-4Rα/IL-13Rα1 hetero-dimerization (type 2 receptor) and endogenous regulation of IL-13 that is mediated by IL-13Rα2.

Tralokinumab was studied in different doses in adults with moderate-to-severe AD in a phase 2b study with concomitant TCS42. At week 12, 300 mg of tralokinumab significantly improved change from baseline in EASI score (adjusted mean difference, -4.94; 95% confidence interval [CI], −8.76 to −1.13; $p=0.01$), and a higher percentage of participants achieved an IGA response (26.7% vs. 11.8%)[39]. The highest applied dose of tralokinumab (300 mg) showed significant improvement. Moreover, improved responses were observed in higher concentrations of IL-13 activity and IL-13 related biomarkers, DDP-4, and periostin[39].

Recently the press released a phase 3 clinical trial results from the ECZTRA studies. The studies assessed tralokinumab as monotherapy in adults with moderate to severe AD. The randomized, double-blind, placebo-controlled, multinational 52-week studies included 802 adults in ECZTRA 1 and 794 adults in ECZTRA 2, and ECZTRA 3 is a 32-week study of 380 adults to evaluate tralokinumab in combination with TCS for patients with AD. The detailed results will be submitted for presentation at scientific congresses and peer-reviewed publications.

(3) IL-13 inhibition: Lebrikizumab is a humanized, IgG4κ mAb that also binds soluble IL-13, but at a different epitope compared with tralokinumab (Fig. 1)[40]. Lebrikizumab selective inhibition of the IL-4Rα/IL-13Rα1 signaling complex, it does not prevent IL-13 from binding to IL13Rα2, thus leaving endogenous regulation of IL-13 levels through IL-13Rα2 intact. The two antibodies interfere with IL-13–mediated signaling by different mechanisms. Tralokinumab prevents access of the IL-13Rα1 and IL-13Rα2, while lebrikizumab interferes with IL-13 binding to IL-13Rα1, not IL-13Rα2. Lebrikizumab was studied in different doses in a randomized, placebo-controlled, double-blind, phase 2 study of adults with moderate-to-severe AD in with TCS twice daily. Achieving EASI 50 at week 12 was significantly higher with lebrikizumab than with placebo (82.4% in the treatment group vs. 62.3% in the placebo group)[40]. In a recent, a phase 2b monotherapy trial evaluating higher doses and more frequent dosing, and at the 250 mg dose every 2 or 4 weeks showed significant dose- and frequency-dependent improvements in EASI scores compared to placebo at 16 weeks[41]. Compared with placebo (EASI least-squares mean [standard deviation] percentage change, −41.1% [56.5%]), lebrikizumab groups showed dose-dependent, statistically significant improvement in the primary endpoint at week 16: 125 mg every 4 weeks (−62.3% [37.3%], $p=0.02$), 250 mg every 4 weeks (−69.2% [38.3%], $p=0.002$), and 250 mg every 2 weeks (−72.1% [37.2%], $p<0.001$)[41]. IGA 0 or 1 rates were higher for 250 mg of lebrikizumab versus placebo at week 16. Dose-dependent differences between placebo-treated patients and lebrikizumab-treated patients were defined as early as the first visit (week 4)[41].

2) IL-33 inhibition

IL-33 is an IL-1 family cytokine produced by innate immune cells, produced by stimuli by allergen or microbes. IL-33 acted on Th2 cells in the in vitro experiment to produce IL-5 and IL-13 and *in vivo* experiment increased the number of eosinophils and immunoglobulin in the peripheral blood. IL-33 also stimulates the mast cell to create cytokines and chemokines such as IL-5, IL-6, IL-10, IL-13, CXCL8, and CCL1[42].

There was a study about the role of IL-33 inhibition in phase 2a study of etokimab (ANB020), an IgG1 anti-IL-33 mAb, in AD. Twelve adult patients with moderate to severe AD received a single systemic administration of etokimab. Ten patients (83%) achieved Eczema EASI 50, and 33% EASI 75, with a reduction in peripheral eosinophils at day 29[42]. However, a subsequent study has been prematurely stopped for lack of efficacy.

IL-31 inhibition

IL-31 is implicated in the disruption of the physical skin barrier[43], and it seems mainly involved in pruritus induction in AD patients. The receptor for IL-31, a heterodimer of IL-31 receptor α-chain (IL-31RA) and oncostatin M receptor β-chain (OSMRβ), are expressed by immune cells (macrophages, dendritic cells, eosinophils, and basophils), epidermal keratinocytes but also by cutaneous peripheral sensory neurons[44].

1) Nemolizumab

Nemolizumb is a humanized mAb that targets the IL-31 receptor alpha subunit; it binds to the IL-31 receptor on a spectrum of cells and neurons, thus relieves pruritus. In phase 2 clinical study, nemolizumab improved EASI, IGA, NRS with 30 mg dose being most effective. The 30 mg dose reduced EASI scores versus placebo at 24 weeks (−68.8% vs. −52.1%, $p<0.016$). NRS scores were improved at 16 weeks (−68.6% vs. −34.31%, $p<0.0001$). And, it was safe and tolerated; common adverse events were nasopharyngitis and upper respiratory tract infection[45]. In long term extension phase2 studies, they reported the long-term effi-

cacy and safety of nemolizumab injected every four weeks or every eight weeks for 52 weeks, and concluded nemolizumab for up to 64 weeks was effective and well-tolerated[45]. Recently, a 2b trial revealed that nemolizumab with TCS significantly improved EASI and IGA and itch scores at week 24 and was well tolerated, with the 30 mg dose being most effective[44]. A 30 mg of nemolizumab reduced EASI scores versus placebo at week 24 (−68.8% vs. −52.1%, $p=0.016$), IGA 0 or 1 rates were higher for 30 mg of nemolizumab versus placebo at week 16 (33.3% vs. 12.3%, $p=0.008$) but not week 24 because of an increased placebo/TCS effect (36.8% vs. 21.1%, $p=0.06$). NRS scores were improved for 30 mg of nemolizumab versus placebo at week 16 (−68.6% vs. −34.3%, $p<0.0001$) and week 24 (−67.3% vs. −35.8%, $p<0.0001$), and NRS response rates (≥4-point decrease) were greater for 30 mg of nemolizumab versus placebo at week 16 ($p\leq0.001$) and week 24 ($p\leq0.01$)[44].

2) BMS-981164

BMS-981164 ended phase I clinical trials, but no results were reported[46].

3) KPL-716

KPL-716 is an anti-oncostatin M receptor beta mAb (anti-OSMR β) inhibiting IL-31 and oncostatin M signaling, an inflammatory signal implicated in pruritus, Th2 inflammation, and fibrosis. KPL-716 showed good safety and tolerability as well as an anti-pruritic effect in patients with moderate-to-severe AD in a phase1a/1b study[47]. Additional phase 2 studies (NCT03858634, NCT03816891) for chronic pruritic diseases and prurigo nodularis are currently underway.

Thymic stromal lymphopoietin inhibition

A TSLP, an epithelial cell-derived cytokine, is produced in response to proinflammatory stimuli. TSLP has been identified as the "master switch" of allergic inflammation because of its role as the trigger of the downstream cascade of Th2 inflammation in asthma and AD. TSLP can activate dendritic cells, inducing Th2 polarization, and the production of Th2 cytokines.

Tezepelumab is a human anti-TSLP mAb that blocks the binding of TSLP to its receptor. In the phase 2a study, 113 patients were randomized 1:1 to subcutaneous tezepelumab 280 mg or placebo every two weeks with class 3 TCS. A higher percentage of tezepelumab treated patients achieved EASI 50 (64.7%) versus placebo plus TCS for 12 weeks (48.2%; $p=0.091$)[48]. Results are difficult to interpret given the heavy TCS use allowed in the study. Future monotherapy studies would help clarify the true efficacy of this molecule which could be a helpful addition given the positive results seen in asthma trials[49].

OX40 inhibition

OX40 (CD134), a costimulatory molecule of TNF receptor, is expressed predominantly on T cells, including effector cells and forkhead box P3 ($Foxp^3$)$^+$ regulatory T cells. OX40 ligand (OX40L; CD252) is expressed on activated antigen-presenting cells. OX40-OX40L engagement is critical to potentiate T-cell response (Fig. 2). In AD patients, numbers of OX40L$^+$ DCs are highly increased[50].

1) GBR830

GBR830 is a humanized mAb against OX40. In the phase 2a study, two doses of GBR830 administered four weeks apart were well tolerated and induced significant progressive tissue and clinical changes until day 71 (42 days after the last dose)[51].

2) KHK4083

KHK4083 is a humanized mAb against OX40, showed a continuous reduction in EASI score with every 2-week dosing for 6 weeks, and an additional phase 2 trial (NCT03703102)

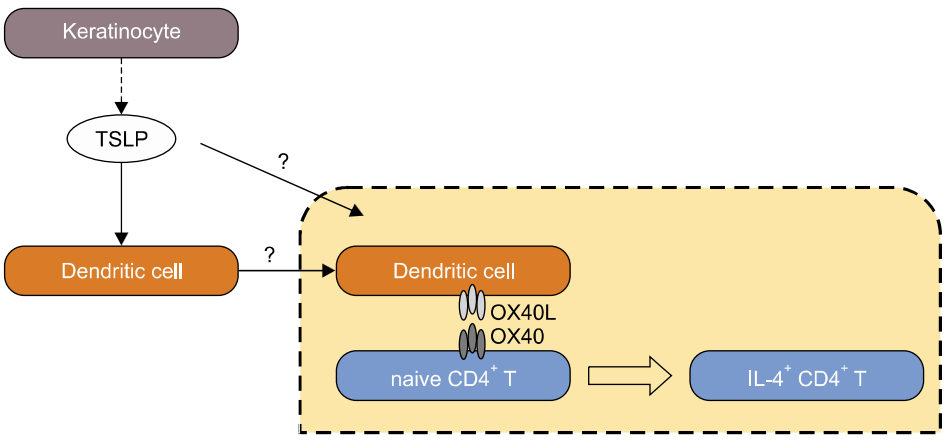

Fig. 2. TSLP-OX40 axis. Keratinocyte-derived TSLP activates dendritic cells to induce the production of Th2 immunity cytokines, IL-33 appears to amplify TSLP's effect of inducing expression of OX40 ligand on dendritic cells. TSLP: thymic stromal lymphopoietin, IL: interleukin.

is underway.

IL-5 inhibition

IL-5 is another Th2-related cytokine involved in AD, by recruiting and activating eosinophils[52].
Mepolizumab is a fully-humanized monoclonal anti-IL-5 antibody approved for the treatment of severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis[53]. In a phase 2 study, there was no meaningful difference in IGA and NRS score with placebo group[54].

Th1/Th17/Th22 cell inhibition

AD is well known to be a Th2 mediated disease. However, also non-Th2 cytokines may play a role in the pathogenesis of the disease. Although an intense polarization of Th2 identified in the general AD population, there appear to be relatively dominant Th17 subtype patients of Asian descent, and patients with intrinsic AD (low IgE). African-American patients with AD and pediatric patients with AD also appear to have higher relative contributions of Th17 inflammation[55].

1) IL12/23 inhibition

Ustekinumab is an IL-12/IL-23p40 antagonist that suppresses Th1, Th17, and Th22 activation, commonly used for patients with psoriasis. The ustekinumab group achieved numerically higher SCORAD 50 responses at 12, 16 (the primary endpoint), and 20 weeks compared to the placebo, but the difference between groups was not significant. Ustekinumab had apparent clinical and molecular effects, but a profound placebo effect might have obscured clinical outcomes, most likely due to background TCS and possibly insufficient dosing for AD[56].

2) IL-17 inhibition

(1) Secukinumab: Secukinumab is a humanized anti-IL-17A mAb. Since secukinumab is well established in the therapy of psoriasis with a highly favorable benefit to risk ratio, IL-17 has now been described in AD therapy. In a phase 2 study, randomized, placebo-controlled, multicenter, double-blinded study to evaluate the efficacy and safety of subcutaneous secukinumab compared to placebo in 45 adults with AD[57]. However, no results have been reported.

(2) MOR106: MOR106 is IL-17C neutralizing Ab, which can inhibit both Th2 cells and Th 17/22-skewed inflammatory loops that drive different features of AD and psoriasis. The therapeutic potential of IL-17C antagonism in AD is supported by a small phase 1 clinical trial[58]. However, an additional study was stopped for lack of efficacy.

3) IL-22 inhibition

In vivo human and animal studies suggest that IL-22, the Th22 cytokine, promotes hyperplasia and inhibits keratinocyte differentiation and skin barrier formation, two hallmarks of AD[59].
Fezakinumb is an IL-22 antagonist, and in phase 2a study in adult patients with AD, at 12 weeks, the mean declines for SCORAD for the entire study population were 13.8 ± 2.7 in the fezakinumab arm and 8.03 ± 0.1 in the placebo arm ($p = 0.134$). All scores showed progressive improvements after the last dosing (10 weeks) until the end of the study (20 weeks). Upper respiratory tract infection was reported more than in placebo groups[59].
Part 2. be continued about small molecules of the AD treatment.

CONFLICTS OF INTEREST

There are no conflict of interest for Jiyoung Ahn and Yusung Choi.
Dr. Simpson reports salary from AbbVie Inc., salary and honorarium from Eli Lilly Co., salary from Genentech, salary and honorarium from Leo Pharmaceutical, salary from Merck, salary and honorarium from Pfizer, salary and honorarium from Regeneron Pharmaceuticals, honoraria from AbbVie, honoraria from Boehringer-Ingelheim, honoraria from Dermavant, honoraria from Dermira, honorarium form Glaxo Smith Kline, honorarium form Incyte, honorarium from Sanofi Genzyme.

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