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REVIEW ARTICLE

Therapeutic New Era for Atopic Dermatitis: Part 2. Small Molecules

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Atopic dermatitis (AD) is a chronic, inflammatory cutaneous disease driven by immune dysregulation and skin barrier dysfunction. Currently, we are 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. In contrast to biologics, small molecules are similar to conventional pharmacologic chemical agents used as drugs and are generally prepared by chemical synthesis. Unlike biologics, these drugs often are taken orally or formulated for topical use. The purpose of this review is to summarize the efficacy and safety of the current topical and systemic new therapies in AD by reviewing recently published papers on therapies currently in phase 2 or 3 clinical trials. In this review, it is important to note the characteristics of the study population, the primary endpoints, and whether or not there was concomitant topical therapy allowed. These study design elements may significantly alter the results of studies and should be taken into account. Targeted therapy help push AD treatment into a new era of personalized medicine. **(Ann Dermatol 33(2) 101～107, 2021)**

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SMALL MOLECULE

Beyond biologics, several small molecule inhibitors are in various stages of clinical development. The use of small molecules follows a different approach since they usually block the intracellular signal transduction upon the activation of cytokine receptors. Considering their potential for inhibition of multiple atopic dermatitis (AD) immune pathways in a selective way, small molecule could be useful in reducing side effects compared to other traditional systemic agents (Table 1).

Janus kinase inhibitor

The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) and spleen tyrosine kinase (SYK) pathways are involved in signaling of several cytokines, mediating downstream inflammation, and related other inflammatory diseases (Fig. 1, 2). This signal transduction pathway is from the cell membrane to the nucleus, and it regulates the immune system through mediating the effects of proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13, IL-31, and thymic stromal lymphopoietin). There are four mammalian JAKs (JAK1, JAK2, JAK3, and tyrosine kinase 2) and seven STATs (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6). The binding of ligands to receptors on the cell membrane leads to JAK-STAT activation and its translocation to the nucleus for gene transcription initiation. Thus, blocking JAKs can reduce proinflammatory cytokine signaling. The well-established efficacy of JAK inhibitors in other inflammatory disorders, particularly rheumatoid arthritis and ulcerative colitis, suggests the positive effects in

AD. In AD, JAK-STAT signaling induces Th2 and eosinophil activation, B-cell maturation, up-regulation of epidermal chemokines, and down-regulation of anti-microbial peptides. The safety of JAK inhibitors is well known from studies in other inflammatory diseases, such as rheumatoid arthritis. These are also well-tolerated with limited adverse severe events to date. The most common serious adverse events are infections such as herpes zoster and tuberculosis[1], and other common adverse events include headache, diarrhea, upper respiratory infection, decreased lymphocyte or neutrophil count, and elevated lipids, creatinine phosphate kinase, or liver enzymes. Creatine phosphokinase elevations are a pharmacologic effect of JAK inhibitors and are not associated with muscle-related side effects, as previously reported with other studies[2]. Hematologic abnormalities (neutropenia, anemia, thrombocytopenia) may also be seen with JAK inhibitors[3]. The theoretical risk of malignancy in JAK inhibitors is another concern, although malignancy risks in rheumatoid arthritis patients on tofacitinib do not appear higher than patients not on JAK inhibitors[3]. The safety of topical JAK inhibitors has been reported for topical tofacitinib, ruxolitinib, and delgocitinib[4]. But some studies have shown a more favorable safety profile in topical than in oral. Especially SNA-125, a newer topical JAK inhibitor, was designed to minimize systemic toxicity[3].

Table 1. Small molecules; targeted therapies of atopic dermatitis

Category	Target	Name	Formulation	Development status
JAK inhibitors	JAK1	Upadacitinib	Oral	Ph III on-going
		Abrocitinib	Oral	Ph III completed
	JAK1/2	Baricitinib	Oral	Ph III completed
		Ruxolitinib	Topical	Ph III on-going, completed
	JAK1/3	Tofacitinib	Oral/ topical	Ph II completed (topical)
	Pan JAK	ASN002	Oral	Ph II completed
		Delgocitinib	Topical	Ph II on-going
PDE4 inhibitors	PDE4	Apremilast	Oral	Ph II completed
		Roflumilast	Topical	Ph II completed
		Crisaborole	Topical	Approved
		Opa-15406	Topical	Ph III on-going
		DRM-02	Topical	Ph II completed
		LEO29102	Topical	Ph II completed

JAK: Janus kinase, PDE4: phosphodiesterase enzyme 4.

1) JAK1 inhibition

(1) Upadacitinib: Upadacitinib was initially developed for the treatment of rheumatoid arthritis. The first generation of JAK inhibitors, tofacitinib, and ruxolitinib, lacked sub-

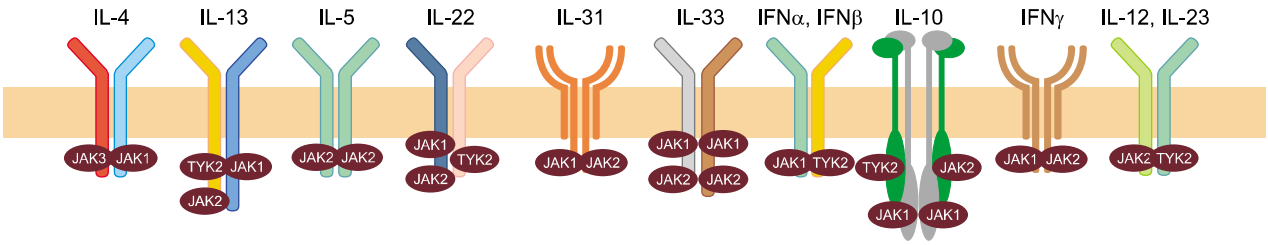

Fig. 1. Signaling JAKs for cytokines in immune homeostasis and immune-mediated disease. JAK: Janus kinase, TYK: tyrosine kinase, IL: interleukin, IFN: interferon.

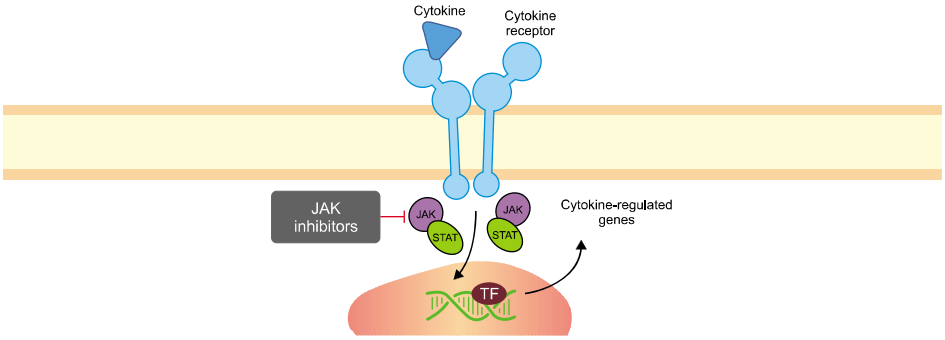

Fig. 2. JAK-STAT pathway, A cytokine binds to its cell surface receptor. A JAK family of receptor-associated kinases phosphorylate intracellular receptors and increase the production of a group of STAT. Phosphorylated STATs dimerize and translocate to the nucleus, leading to the activation of targeted gene expression. JAK: Janus kinase, STAT: signal transducer and activator of transcription, TF: tissue factor.

type selectivity, affecting JAK1/JAK3 and JAK1/JAK2, respectively. It has led to dose-limiting side effects. Upadacitinib is a second-generation JAK inhibitor that is selective for the JAK1 subtype of this enzyme over the JAK2 (74-fold), JAK3 (58-fold) and tyrosine kinase 2 subtypes[5]. A phase 2b trial in adults AD revealed upadacitinib 30 mg was superior to placebo in Eczema Area and Severity Index (EASI) score improvement and pruritus reduction ($p<0.001$)[6]. Upadacitinib 30 mg once daily (QD) was associated with the most significant reduction in EASI and appeared to present the best benefit/risk profile; the EASI 90 and Investigator's Global Assessment (IGA) 0/1 results with upadacitinib 30 mg (both end points, 50.0% at week 16) are significant[6]. Adverse effects were reported in 71% (30 of 42), 74% (31 of 42), and 79% (33 of 42) of patients receiving upadacitinib 7.5 mg, 15 mg, and 30 mg, respectively, versus 63% (25 of 40) of placebo[6]. The most frequently reported adverse events were upper respiratory tract infection, AD worsening, and acne (all reported as mild or moderate in severity). There was no relationship between the dose of upadacitinib and the occurrence of particular adverse effects. Currently, a phase 3 study is underway[7]. Additional studies, including younger patients, are also being performed.

(2) Abrocitinib: Abrocitinib is an oral JAK1 selective inhibitor under investigation for the treatment of AD. In this randomized, double-blinded, phase 2b clinical trial, including 267 participants, the proportion of patients achieving substantial improvement from baseline was significantly higher for those receiving 200 mg and 100 mg of abrocitinib compared with placebo. Dose-related decreases in platelet count were observed for all doses higher than 10 mg, but platelet values trended upward toward baseline after the maximum decrease at week 4, and despite ongoing treatment with abrocitinib; most adverse events were mild and considered unrelated to treatment[8]. The top-line results detailed in a presentation of two phase 3 trials of abrocitinib showed statistically significant results with clinically-meaningful effect sizes and rapid onset of action with good tolerability and no unexpected safety events[8]. In the MONO-1 study, IGA 0/1 was 43.8% (abrocitinib 200 mg, n=154), 23.7% (abrocitinib 100 mg, n=156), and 7.9% (placebo, n=77) at 16 weeks[8].

2) JAK 1/2 inhibition

(1) Baricitinib: Baricitinib is a selective JAK1 and JAK2 inhibitor that currently approved for the treatment of rheumatoid arthritis. The phase 2 trial included a standardization period with the use of topical corticosteroid (TCS) to identify individuals whose AD was inadequately controlled by TCS, EASI 50 higher than the placebo group (61% vs. 37%, $p=0.027$) at 16 weeks. The phase 3 trials BREEZE-AD1 and AD2 confirmed significant clinical efficacy in both baricitinib doses of 2 mg and 4 mg with a good safety profile for patients with moderate-to-severe AD[9]. At week 16, more patients achieved the primary endpoint of validated IGA of AD (0, 1) on baricitinib 4 mg and 2 mg compared with placebo in BREEZE-AD1 (n=624; baricitinib 4 mg 16.8% [$p<0.001$], 2 mg 11.4% [$p<0.05$], 1 mg 11.8% [$p<0.05$], placebo 4.8%), and BREEZE-AD2 (n=615; baricitinib 4 mg 13.8% [$p=0.001$], 2 mg 10.6% [$p<0.05$], 1 mg 8.8% [$p=0.085$], placebo 4.5%). Improvement in itch was achieved as early as week 1 for 4 mg and week 2 for 2 mg[9].

(2) Ruxolitinib: Ruxolitinib is another selective inhibitor of JAK-1 and JAK-2. In the phase 2 study, 307 adult patients with AD, an IGA score of 2 or 3 (mild or moderate), and 3%～20% affected body surface area, were equally randomized for eight weeks of double-blind treatment to topical ruxolitinib cream (1.5% twice daily [BID], 1.5% QD, 0.5% QD, 0.15% QD), vehicle, or triamcinolone cream (0.1% BID for four weeks then the vehicle for four weeks)[10,11]. All ruxolitinib regimens demonstrated therapeutic benefit at week 4; 1.5% BID provided the most considerable improvement in EASI (71.6% vs. 15.5%; $p<0.0001$) and IGA responses (38.0% vs. 7.7%; $p<0.001$) versus vehicle[11]. Recently, two phase 3 studies revealed that the application of ruxolitinib cream brought about rapid (within 12 hours of initiation of therapy), substantial, and sustained reduction in itch, and ruxolitinib cream showed superior efficacy vs. vehicle in IGA, EASI-75, and ≥4-point reduction in itch Numerical Rating Scale (NRS) score[12]. No serious side effects were observed in patients treated with ruxolitinib cream and well tolerated[12]. Currently, a phase 1 study in children aged 2 to 17 years and two phase 3 studies in patients older 12 years is underway[13].

3) JAK 1/3 inhibition

(1) Tofacitinib: Tofacitinib is an oral small molecule JAK1/JAK3 inhibitor approved for the treatment of rheumatoid arthritis. In AD, it has been studied in adults only. A case series described six patients (2 male, 4 female; age range, 18～55 years) with moderate to severe AD, treated with oral tofacitinib citrate 5 mg BID (n=5) and QD (n=1). After 8 to 29 weeks of treatment, the Scoring Atopic Dermatitis Index significantly decreased by 66.6%[14]. It is important to note that tofacitinib has been associated with solid organ malignancy and lymphoma in rheumatoid arthritis patients[3]. It is unclear whether it will have the same effects in AD, and further long-term studies will need to be completed[15]. In 2019, the safety committee of the European

Medicines Agency (EMA) began a review of tofacitinib, and they recommended that doctors temporarily not prescribe the 10 mg twice-daily dose to people at high risk for pulmonary embolism.

4) Pan JAK inhibition

(1) Gusacitinib: Gusacitinib is a potent, dual inhibitor of JAK and SYK kinases. A total of 36 patients with moderate-to-severe AD were randomized (3:1) to gusacitinib or placebo in the phas1b study. Three dosage cohorts were studied over 28 days (20 mg, 40 mg, and 80 mg QD)[16,17]. Gusacitinib was superior to placebo for the proportion of patients achieving EASI 50 (20 mg 20%, $p=0.093$; 40 mg 100%, $p=0.0003$; 80 mg 83%, $p=0.003$; placebo 22%), EASI 75 (20 mg 0%, $p=0.027$; 40 mg 71%, $p=0.006$; 80 mg 33%, $p=0.065$; placebo 22%). Adverse events were generally mild and similar across all groups. Gusacitinib showed dose-dependent plasma exposure with low interpatient variability, significantly downregulated several serum biomarkers involved in Th1, Th2, and Th17/Th22 immunity, and decreased the atherosclerosis-associated biomarker E selectin/SELE[16,17]. There is a phase 2, extension study to evaluate the long-term safety, tolerability, and efficacy of gusacitinib in subjects with moderate to severe AD until 2021[11]. A recent press release was reported regarding the phase 2b study (RADIANT) evaluating efficacy and safety of gusacitinib in 244 adult patients with moderate-to-severe AD. In the RADIANT trial, gusacitinib achieved the primary endpoint of a statistically significant reduction in EASI at the 60 mg and 80 mg doses compared to placebo at week 12. Gusacitinib also met the key secondary endpoint in the proportion of subjects to achieve an NRS reduction of ≥ 4 points with all doses statistically significant from placebo. And gusacitinib also is expected an effective treatment for chronic hand eczema. Phase 2, randomized, double-blind, placebo-controlled, parallel-group study evaluating two doses (40 mg and 80 mg QD) of gusacitinib over 32 weeks in moderate-to-severe chronic hand eczema has completed enrollment (NCT03728504).

(2) Topical delgocitinib: Delgocitinib is a pan JAK inhibitor, which has inhibitory effects on all types of JAK family kinase (JAK1, 2, 3, and tyrosine kinase 2). In nonclinical studies, the topical application of delgotinib suppressed skin inflammation in animal dermatitis model; improved skin barrier dysfunction by promotion production of terminal differentiation proteins, including filaggrin; and suppressed pruritus.

In a phase 2 study showed significant improvement in the overall symptoms of AD by week 4, and decreased modified EASI (mEASI) and IGA scores with a favorable safety profile[18]. Improvements in pruritus were also observed by day 1, which was likely due to the inhibition of IL-31 signaling mediated by the JAK-STAT pathway or possibly via a direct effect of JAK inhibition on itch transmission by neurons[19]. Improvements in mEASI score with the higher doses of delgocitinib were similar to the tacrolimus 0.1% ointment active control arm, although there were no statistical comparison[20]. A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study was recently published. In part 1, Japanese patients aged 16 years or older with moderate or severe AD were randomly assigned in a 2:1 ratio to delgocitinib 0.5% ointment or vehicle ointment for 4-week. Eligible patients extended part 2, to receive delgocitinib 0.5% ointment for 24-week. The primary efficacy endpoint was the percent change from baseline in the mEASI score at the end of treatment, at the end of treatment in part 1, the primary efficacy endpoint was significantly higher in the delgocitinib group than in the vehicle group (-44.3% vs. 1.7%, $p<0.001$), the improvement was maintained in part 2. Most adverse events were mild and unrelated to delgocitinib[21].

Phosphodiesterase enzyme 4 (PDE4) inhibition

A class of small molecule inhibitors, which have been investigated for the treatment of AD, include those targeting PDE4, an enzyme involved in chronic inflammatory pathways. PDE4 is a critical regulator of intracellular cyclic adenosine monophosphate (cAMP) levels expressed within inflammatory cells, including T lymphocytes and eosinophils. Inhibition of PDE4 increases levels of cAMP, resulting in the inhibition of production and secretion of proinflammatory cytokines and chemokines (e.g., IL-2, IL-4, IL-31) thought to contribute to the manifestations of AD[22].

1) Apremilast

Apremilast, an orally available PDE4 inhibitor that is approved for the treatment of adults with moderate to severe psoriasis and active psoriatic arthritis, regulates several proinflammatory signals involved in AD, including IL-17, 22, 13, 31, 33, 5, and S100A7/A8. Patients were randomly assigned to receive a placebo, apremilast 30 mg BID (APR30), or apremilast 40 mg BID (APR40) for 12 weeks. APR40, but not APR30, led to statistically significant improvement (vs. placebo, n=64) in EASI (-31.6% vs. -11.0%; $p<0.04$) mRNA expression of Th17/22 related markers (IL17, 22, and S100A7/A8; $p<0.05$) showed the highest reduction with APR40[23]. Although apremilast at a dose of 40 mg showed clinical efficacy and decreased Th17/Th22 related biomarkers, it was discontinued due to serious adverse events like cellulitis.

2) Roflumilast

Roflumilast is a topical PDE4 inhibitor; there was a phase 2 clinical trial, but showed no benefit in AD[24].

3) Crisaborole

Crisaborole is mainly acting on PDE4B, an isoenzyme important in promoting inflammation in AD[25]. Inhibition of PDE4B appears to suppress the release of tumor necrosis factor alpha (TNF α), IL-12, IL-23, and other cytokines, proteins believed to be involved in the immune response and inflammation. Two-phase 3, vehicle-controlled, double-blind studies that enrolled 1,527 patients with mild (Investigator's Static Global Assessment [ISGA] score 2) to moderate (ISGA score 3) AD at baseline, aged two years and older. Most subjects (87%) were children and adolescents (2～17 years old), with approximately (33%) 2 to 6 years old. In these studies, more crisaborole- than vehicle-treated patients achieved ISGA success (clear/almost clear with ≥2-grade improvement) at the end of the 28 days of twice-daily application. They also experienced improvements in pruritus sooner than the control group. Adverse events were infrequent, with the most common being application-site pain affecting 4.4% of patients on crisaborole compared with 1.2% of controls[26]. They suggested it suitable for steroid-phobic patients and as a steroid-sparing agent, and it can be used as first-line treatment or for long durations of maintenance therapy instead of topical steroids and thus avoiding potential steroid side effects. In infants (aged 3 to <24 months) with mild-to-moderate AD (A Phase 4 Open-Label Study; CrisADe CARE 1), crisaborole was well tolerated and effective in infants with mild-to-moderate AD[27]. Furthermore, another study showed that the respective mean changes in Atopic Dermatitis Severity Index score and body surface area on day 29 were (crisaborole vs. vehicle) −3.52 vs. −2.42 ($p<0.0001$) and −7.43 vs. −4.44 ($p<0.0001$)[28]. A commentary by Ahmed acknowledged the efficacy of crisaborole compared to placebo but questioned the utility in practice given the relatively high number needed to treat (mild-to-moderate AD) or one success over a vehicle. The cost-effectiveness of crisaborole is still in question, although crisaborole can provide a non-steroidal option for patients with AD of any age[29].

4) OPA15406

OPA15406 is a highly selective inhibitor of the PDE4 subtype, also subtype B. In a phase 2 study, IGA of Disease Severity Score of 1 or 1 with greater than or equal to 2-grade reduction, was met at 4 weeks in the OPA15406 1% group ($p=0.016$ vs. vehicle)[30]. Incidence of adverse events mild in intensity. A phase 3 study is underway[31].

5) LEO29102

It is also topical PDE4 inhibitor; phase 2 clinical trials are currently underway[32,33].

CONCLUSION

The extreme clinical heterogeneity and the chronic progression of AD support the need for additional safe and effective treatments to control the disease and improve the quality of life of affected patients. Dupilumab, the first approved monoclonal antibody for the treatment of AD and the other monoclonal antibodies and small molecules currently under investigation, aims to improve the clinical management of AD.

Many novel biologic and small molecule agents that are clinically effective in AD treatment have emerged, even though effective management of AD is complicated due to its multifaceted pathophysiology, variable clinical manifestations, and chronic course of the disease. More data emerging from ongoing development programs will be published for other biologics and small molecule inhibitors, providing clarity on treatment algorithms and risk-benefit ratios. The ability to change the disease progress, drug safety, and cost-effectiveness should be essential factors for all the treatments. Real-world registries will also shed light on the real clinical effectiveness and possibly comparative effectiveness and safety of these promising agents.

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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