



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Invited Review Article

Innovation in the treatment of atopic dermatitis: Emerging topical and oral Janus kinase inhibitors

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ARTICLE INFO

Article history:
Received 5 August 2021
Available online xxx

Keywords:
Atopic dermatitis
Baricitinib
Dergocitinib
JAK-STAT
Upadacitinib

ABSTRACT

Atopic dermatitis (AD) is characterized by chronic, eczematous, severe pruritic skin lesions. The knowledge on the pathogenesis of AD is driving the development of new drugs. From the research results, it has been revealed that Th2 cell-mediated immunity, skin barrier dysfunction, and pruritus cause a vicious cycle of AD. On the other hand, the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway are one of the essential signaling pathways in various inflammatory diseases including AD. In particular, TSLP, IL-4, IL-13 and IL-22 occupy an important position for Th2 cell-mediated immune reaction. Moreover, experimentally pan-JAK inhibitor suppress the STAT3 activation and improved the skin barrier function. Furthermore TSLP, IL-4, IL-13 and IL-31 contribute a lot to chronic pruritus of AD, and transmitted via JAK-STAT pathway. Therefore, JAK inhibitors are promising candidates for the treatment of severe AD. Here we review clinical trials of topical dergocitinib; a pan-JAK inhibitor, ruxolitinib; a JAK1 and JAK2 inhibitor, and tofacitinib; a JAK1, JAK2, and JAK3 inhibitor and oral baricitinib; a JAK1 and JAK2 inhibitor, abrocitinib and upadacitinib; JAK1 inhibitor. Significant improvements in the symptoms were obtained by each drug with low frequency of adverse events. In particular, oral JAK inhibitors have the ability to improve the pruritus and skin symptoms quickly. Therefore, the emergence of these topical and oral JAK inhibitors would be regarded as an innovation in the treatment of atopic dermatitis.

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Introduction

Atopic dermatitis (AD) is characterized by chronic, eczematous, severe pruritic skin lesions caused by skin barrier dysfunction and Th2 cell-mediated immunity. A mutation in the gene that encodes filaggrin (FLG), a natural moisturizer, is one of the most well-known causal factors of barrier dysfunction.¹ Various studies have suggested that barrier dysfunction causes the unregulated activation of proteases in the epidermis, leading to the production of Th2-type immune-inducing factors, such as TSLP.² A recent study demonstrated that epithelial cells directly stimulate cutaneous sensory neurons via TSLP to promote pruritus.³ In addition, peripheral nerves in the skin express IL-4 receptor (R) α , which directly induces pruritus via IL-4/13.⁴ Because IL-4/13 attenuates the FLG expression, skin barrier dysfunction, pruritus, and Th2 reaction cause a vicious cycle of AD. Therefore, dupilumab, a

humanized monoclonal antibody against IL-4R α , has been approved in 2018. Dupilumab treatment in adults with moderate-to-severe AD resulted in a marked improvement of eczema and associated biomarker levels such as TARC/CCL17, in several trials.⁵ One commonly used outcome measure is the Eczema Area and Severity Index (EASI), which was designed to mimic the Psoriasis Area and Severity Index and ranges from 0 to 72. Based on a 12-week study of dupilumab, 85% of treated patients achieved a 50% reduction in EASI scores compared to the 35% in the control group ($P < 0.001$).⁵

IL-31 is a potent pruritogenic cytokine primarily produced by Th2 cells. Both IL-31 transgenic mice and wild-type mice treated with IL-31 exhibit AD-like skin lesions and scratching behavior. Nemolizumab is a subcutaneously administered humanized monoclonal antibody against IL-31 receptor A, which is involved in pruritus and inflammation in AD. A recent study demonstrated that the use of subcutaneous nemolizumab and topical agents for AD resulted in a greater reduction in pruritus than the use of placebo and topical agents.⁶ The mean percent change in EASI scores was -45.9% in the nemolizumab group and -33.2% in the placebo group. In addition, the mean percent change in visual

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Peer review under responsibility of Japanese Society of Allergology.

<https://doi.org/10.1016/j.alit.2021.10.004>

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analog scale scores was -42.8% in the nemolizumab group and -21.4% in the placebo group.⁶ Since the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway is one of the important signaling pathways downstream of these Th2 cytokine receptors, JAK inhibitors are promising candidates for the treatment of severe AD.

The role of JAK- STAT pathway in the pathogenesis of AD

JAK-STAT pathway

The JAK-STAT signaling pathway is the major intracellular signaling pathway for cytokines. It is related to various body functions and is involved in important biological processes, including cell proliferation, differentiation, apoptosis, immune regulation, and hematopoiesis.⁷ Mammals have four types of JAK family proteins: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), and seven types of STAT family proteins are known: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6.⁸ There are also more than 50 cytokines signals via the JAK-STAT pathway. The JAK-STAT pathway is involved in the signaling of IL-2, IL-3, IL-6, and IL-10 families, hematopoietic growth factors, and type 1 and type 2 interferons (Table 1).

For interferons and interleukins, the receptor subunits are heterodimers. First, a cytokine binds to a receptor and induces its dimerization. For signal propagation through heterodimers, JAK is associated with cytoplasmic domain of cytokine receptors via JAK binding site. Then, JAK activation occurs upon cytokine-mediated receptor dimerization, because two JAKs are brought into close proximity allowing trans-phosphorylation. Secondly, the activated JAKs subsequently phosphorylate the residues on the cytokine receptors to create the docking sites for recruitment of downstream proteins with Src homology 2 (SH2) domains including STAT family of proteins. Then, the STAT proteins with SH2 domains are recruited to the docking site of the receptors. JAKs also phosphorylate STATs. These phosphorylated STATs are activated and dimerized. Finally, the dimerized STATs are transferred into the nucleus to induce the expression of cytokine-related genes (Fig. 1).⁷

T cell subsets in AD

The etiology of AD is complex and involves Th2-mediated immune reaction, skin barrier, and pruritus. In the acute phase, the JAK-STAT pathway mediates the signaling of several important cytokines in the pathogenesis of AD, including IL-4, IL-5, IL-13, and IL-31. In the chronic phase or in Asian patients with AD, Th17 and Th22 cytokine profiles predominate.⁹

Th2 cytokines

Th2 immune reactions are essential for the pathogenesis of AD. In particular, the JAK-STAT pathway is involved in the signaling of Th2 cytokines (IL-4, IL-13, and IL-31), which are important for Th2-type immune responses.⁸ There are two types of IL-4 receptors: type I IL-4 receptors, which consist of an IL-4R α chain and a common γ chain, and type II IL-4 receptors, which consist of IL-4R α and IL-13 receptor $\alpha 1$ (IL-13R $\alpha 1$) chain. Type II IL-4 receptors also function as IL-13 receptors. IL-13 receptor $\alpha 2$ chain is also an IL-13 receptor,¹⁰ but it is a decoy receptor that does not transmit signals.

In the type I IL-4 receptor-mediated pathway, JAK1 and JAK3 are activated, followed by STAT6 activation. On the other hand, in the pathway mediated by type II IL-4 and IL-13 receptors, JAK1 and TYK2 are activated, followed by STAT6 and STAT3 activation.¹¹ (Fig. 2). STAT6 is a transcription factor that is essential for the biological activity of IL-4 and IL-13. IL-4R α and IL-13R $\alpha 1$ are widely expressed in both immune and non-immune cells, but IL-13R $\alpha 1$ is

Table 1

List of cytokines that signal through the JAK-STAT pathway.

Cytokines	Major Functions
IL-2 family	
IL-2	Immune response, T-cell differentiation
IL-4	Th2 differentiation
IL-7	T-, B-cell growth factor
IL-9	Pleiotropic, Stimulates T-, B-, and NK cells
IL-15	Stimulates, T-, and NK cells
IL-21	Stimulates T-, B-, and NK cells
IL-3 family	
IL-3	Multi-lineage hematopoietic growth factor
IL-5	B-cell development, eosinophils
GM-CSF	Multi-lineage hematopoietic growth factor, especially monocytes, neutrophils, eosinophils, and basophils
IL-6 family	
IL-6	Pleiotropic, haematopoiesis, acute phase response, lymphoid differentiation
LIF	Pleiotropic, blastocyte implantation, bone remodelling, CNS
CNTF	Neuronal growth factor
CT1	Cardiac myocytes growth factor
CLC	Neurological growth factor
OSM	cone formation
IL-31	Inflammatory, cell-mediated immunity
NP	Neural growth factor
IL-10 family	
IL-10	Anti-inflammatory, inhibits macrophage activation
IL-19	Inflammatory, acts on dermal cells
IL-20	Inflammatory, acts on dermal cells
IL-22	Inflammatory, secreted by Th1 and Th17 cells, acts on dermal cells
IL-24	Inflammatory, acts on dermal cells
IL-26	Antimicrobial, Th17 cytokine
Homodimeric	
G-CSF	Stimulates granulocyte production, mobilises stem cells
EPO	Stimulates formation of erythrocytes
TPO	Stimulates formation of megakaryocytes/platelets
GH	Growth
PRL	Milk production
LEP	Regulates appetite
Interferon	
IFN α	Anti-viral, secreted by lymphocytes, fibroblasts, and monocytes
IFN β	Anti-viral, ubiquitously expressed
IFN γ	Pro-inflammatory, secreted by T- and NK- cells, activates macrophages/monocytes
Others	
IL-12	Stimulates T- and NK- cells
IL-13	Pleiotropic, airway epithelia, allergic disease
IL-23	Inflammation
TSLP	Inflammatory, stimulates T- and B- cells

IL, Interleukin; GM-CSF, granulocyte/macrophage colony stimulating factor; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic growth factor; CT1, cardiotrophin 1; CLC, cardiotrophin-like cytokine; OSM, oncostatin M; NP, neuropoietin; G-CSF, granulocyte colony stimulating factor; EPO, erythropoietin; TPO, thrombopoietin; GH, growth hormone; PRL, prolactin; LEP, leptin; IFN, interferon; TSLP, thymic stromal lymphopoietin; NK, natural killer.

not expressed in T cells.¹² In murine models, a previous report demonstrated how the JAK-STAT pathway is involved in the pathogenesis of AD using NC/Nga mice, which have spontaneous AD-like dermatitis when they are raised under conventional conditions.¹³ The topical application of JAK inhibitors attenuated the Th2-mediated cutaneous reactions, pruritus, and repaired the skin barrier dysfunction.^{13,14}

IL-31 receptors consist of a heterodimer of IL-31 receptor α -chain (IL-31RA) and oncostatin M receptor β -chain (OSMR β).¹⁵ The intracellular signaling that involves the binding of IL-31 to IL-31 receptors is transmitted by JAK-STAT, phosphatidylinositol-3 kinase (PI3K)/AKT (also known as protein kinase B or PKB), and mitogen-activated protein kinase (MAPK) pathways.¹⁶ (Fig. 3). The phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) alone is insufficient to activate JAK1/JAK2 and STAT3.¹⁶

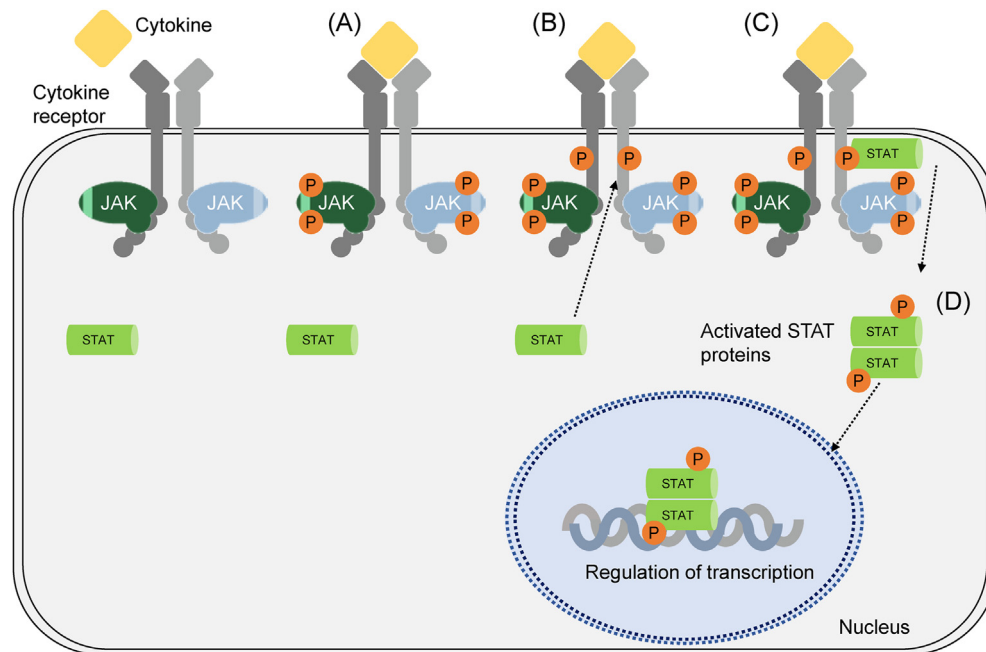


Fig. 1. JAK-STAT signal pathway. (A) Cytokines bind to receptors, leading to the dimerization of receptors. JAKs are associated with cytoplasmic domain of cytokine receptor via JAK binding site and are phosphorylated. (B) Activated JAKs then phosphorylate tyrosines on the intracellular domains of the receptor. (C) STAT proteins are recruited to the docking site of the receptors and are phosphorylated. (D) Activated STAT–STAT dimers translocate to the nucleus and regulate the gene expression.

Th17 and Th22

Although AD seems to be unanimously characterized by a strong activation of Th2 immune responses, the Th1, Th17, and Th22 cytokine pathways likely play a role in some AD types.¹⁷ Th17 cells are characterized by the production of inflammatory cytokines including IL-17A and IL-17F. Th17-associated molecules are consistently upregulated in patients with acute or chronic AD. In particular, the number of Th17 cells correlates with matrix metalloproteinase (MMP)-9-expressing eosinophils, which are involved in tissue remodeling.¹⁸ Therefore, Th17 cells might play some roles in tissue remodeling in chronic AD. The receptor complex of IL-17,

which includes IL-17RA and IL17RC, is widely expressed on epithelial, mesenchymal and hematopoietic cells.¹⁹ The binding of IL-17 to its receptor leads to the recruitment of the adaptor protein Act1, which interacts with the scaffold proteins tumor necrosis factor receptor-associated factor 6 and transforming growth factor- β -activated kinase 1 to activate nuclear factor (NF)- κ B and p38/MAPKs.²⁰ Thus, that Th17 does not depend on the JAK/STAT signaling.

Th22 is significantly increased in AD skin. Th2 and Th22 responses are intensified in chronic AD lesions. IL-22, which is a glycoprotein belonging to the IL-10 family, has been identified as a

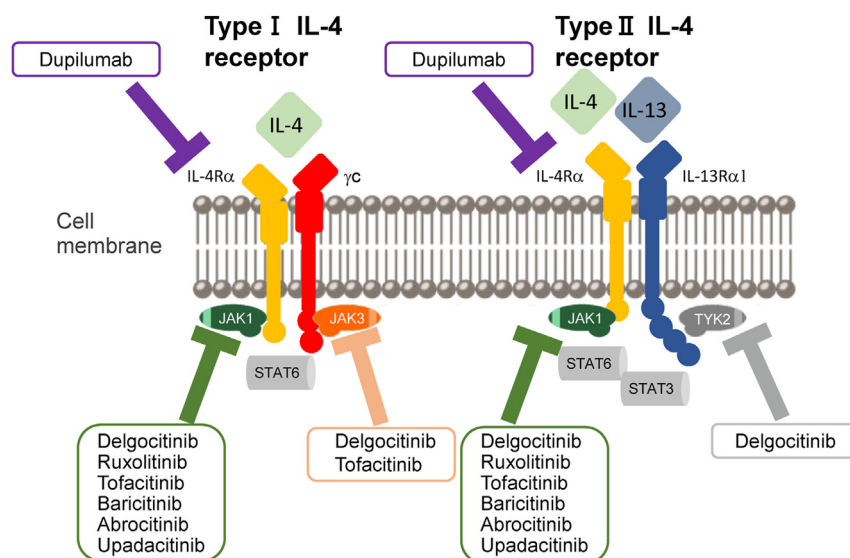


Fig. 2. IL-4/13 receptor. IL-4 and IL-13 play a critical role in the development of AD. Their effects depend on their binding to and signaling through a receptor complex. There are two types of IL-4 receptors: Type I IL-4 receptors, which consist of IL-4R α and common γ chain, and type II IL-4 receptors, which consist of IL-4R α and IL-13R α 1. Type II IL-4 receptors also act as IL-13 receptors.

key mediator of epidermal hyperplasia. Human IL-22 receptors are composed of IL-22R and IL-10Rb. IL-22R is expressed in epithelial cells, such as the skin, gut, and lungs. When IL-22 binds to its receptor, it induces the phosphorylation of JAK1 and Tyk2, activating STAT3.²⁰

Barrier dysfunction

The skin barrier protects the body against mechanical, chemical, and microbial injuries by forming terminally differentiated keratinocytes.²¹ It was previously reported that the JAK-STAT pathway plays a critical role in skin barrier function. The pan-JAK inhibitor delgocitinib suppressed the STAT3 activation and improved the skin barrier function, permitting the increase in the levels of terminal differentiation proteins, such as FLG, and natural moisturizing factors (NMFs) in a murine dry skin model treated with acetone/ether/water (Fig. 4).¹³ Another study showed that delgocitinib did not cause skin atrophy nor decrease the immunohistochemical staining intensity for epidermal claudins, which are common safety concerns associated with topical corticosteroids.²²

Pruritus

Pruritus is defined as an unpleasant cutaneous sensation resulting in an urge to scratch.

Th2 cytokines including IL-4, 13, 31, which are involved in the chronic pruritus of AD, are transmitted via JAK-STAT pathway. We previously reported that delgocitinib suppressed the pruritus and nerve elongation in an AD murine model (Fig. 4).¹⁴ Ruxolitinib, a JAK1 and JAK2 inhibitor, was also highly effective in ameliorating the disease symptoms in murine Th2-mediated dermatitis models, resulting in a reduced skin thickening and decreased pruritus.²³

Ointment JAK inhibitors

JAK inhibitors are often classified into first generation and newer JAK inhibitors. First-generation JAK inhibitors are less selective and therefore demonstrate activity against three or all four members of the JAK enzyme family, whereas newer JAK inhibitors display more selectivity for specific JAKs.²⁴ Some JAK inhibitors were developed for the treatment of AD (Table 2).²⁵ Delgocitinib, a

small molecule (molecular weight, 310.35), is a diazospiroalkane derivative topical JAK inhibitor developed in Japan.²⁶ It is a first-generation pan-JAK inhibitory profile that inhibits all the JAK activities in enzyme assays.²⁷ It inhibits the activation of inflammatory cells, such as T cells, B cells, monocytes, and mast cells, and improves skin barrier dysfunction.¹³

Phase 1 clinical studies were performed to assess its safety by patch testing and photo testing, tolerability, and pharmacokinetics by treating Japanese healthy volunteers and patients with AD with delgocitinib ointment.²⁸ Phase 2, multicenter, randomized, double-blind, vehicle-controlled clinical studies were also performed for children aged ≤ 16 years.²⁹ These showed that the least-squares mean percentage changes in modified EASI (mEASI) scores from baseline were -54.2% in the 0.25% delgocitinib group, -61.8% in the 0.5% delgocitinib group, and -4.8% in the vehicle group. In phase 3, randomized, double-blind, vehicle-controlled study for patients aged ≥ 16 years,³⁰ the mEASI scores improved by 44.3% from baseline in the 0.5% delgocitinib group and by 1.7% in the vehicle group after four weeks of treatment. The pruritus numeric rating scale (NRS) score significantly decreased from baseline. In a 52-week, long-term, open-label study for patients aged ≥ 16 years with mild-to-severe AD,³¹ the proportion of patients with mEASI-50 was 51.9%, while those with mEASI-75 was 27.5% at week 52. Adverse events (AEs) and treatment-related AEs were reported in 69.0% and 15.4% of the patients, respectively. Study interruption due to AEs occurred in 3.4% of the patients, and the most common AEs leading to study discontinuation were contact dermatitis and application site irritation in 1.0% and 0.6% of the patients, respectively.

On the other hand, 0.25% and 0.5% delgocitinib ointments were effective for Japanese pediatric patients with AD. A phase 3, randomized, double-blind, vehicle-controlled study and subsequent open-label, long-term study were performed in Japanese pediatric patients with AD aged 2–15 years. The mEASI scores improved by 39.3% from baseline in the 0.25% delgocitinib group and by 10.9% in the vehicle group after four weeks of treatment. A numerical reduction in pruritus scores was noted immediately after the start

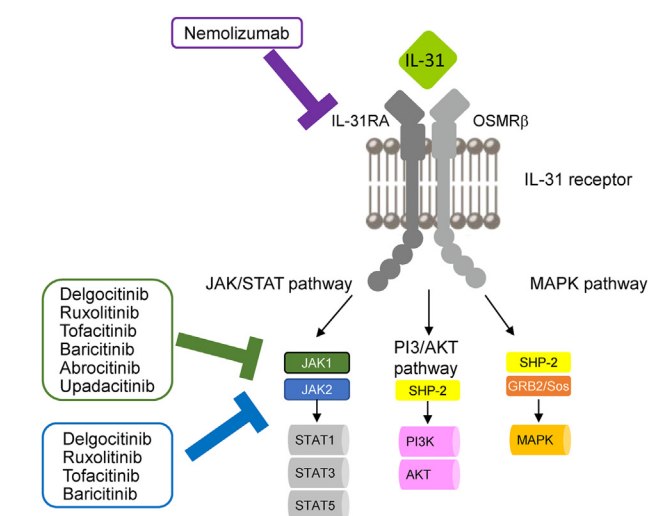


Fig. 3. IL-31 signal transduction. IL-31 mediates three signal transduction pathways: JAK-STAT, PI3K/AKT, and MAPK.

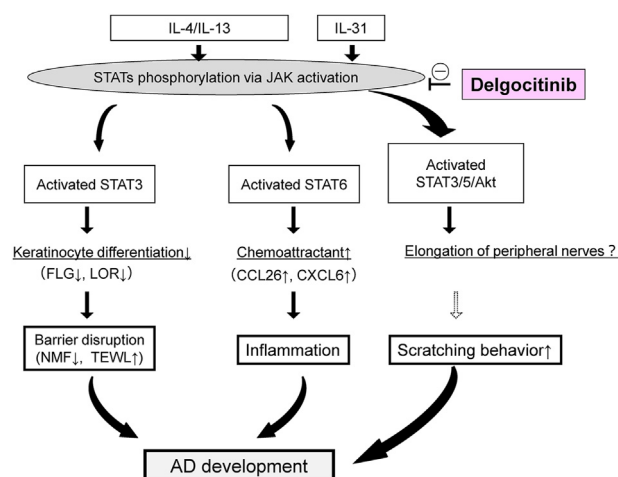


Fig. 4. Model of the mechanism of JAK-STAT in AD skin. Th2 cytokines induce the phosphorylation of STATs proteins via JAK activation. Activated STAT3 downregulates keratinocyte differentiation, causing barrier disruption. Activated STAT6 upregulates chemoattractants, leading to skin inflammation. In addition, activated STAT3/5 and Akt proteins induce peripheral nerve elongation, which may be related to the scratching behavior. The topical application of delgocitinib inhibits the phosphorylation of STAT proteins and contributes to the improvement of AD symptoms. This is a modified version of the figure in Reference 13. A permission for the use has been obtained.

Table 2

The list of latest clinical trials of JAK inhibitor for atopic dermatitis.

	Investigational agent (Synonyms)	Inhibition target	Acronym	Number of patient (Age)	Phases	Endpoint	Interventions (Arm)	Result
oral JAK inhibitor	Upadacitinib (ABT-494)	JAK1	AD Up	810 (12–75 y)	3	Week 16	Topical corticosteroids plus Upadacitinib 15 mg Topical corticosteroids plus Upadacitinib 30 mg Placebo	EASI-75 response rate: 65%/77%/26% vIGA-AD ≥ 2 improvement rate: 40%/59%/11%
			Measure Up 1	905 (12–75 y)	3	Week 16	Upadacitinib 15 mg Upadacitinib 30 mg Placebo	EASI-75 response rate: 70%/80%/16% vIGA-AD ≥ 2 improvement rate: 48%/62%/8%
			Measure Up 2	918 (12–75 y)	3	Week 16	Upadacitinib 15 mg Upadacitinib 30 mg Placebo	EASI-75 response rate: 60%/73%/13% vIGA-AD ≥ 2 improvement rate: 39%/52%/5%
			Rising Up	272 (12–75 y)	3	Week 141	Upadacitinib Placebo for upadacitinib Topical Corticosteroids	not available
	Abrocitinib (PF-04965842)	JAK1	JADE MONO-1	485 (18–75 y)	3	Week 52	Upadacitinib	not available
				387 (≥ 12 y)	3	Week 12	Abrocitinib 100 mg Abrocitinib 200 mg Placebo	IGA ≥ 2 improvement response rate: 24%/44%/8% EASI-75 response rate: 40%/63%/
			JADE EXTEND	3000 (≥ 12 y)	3	Week 92	Abrocitinib 100 mg Abrocitinib 200 mg Placebo	not available
			JADE MONO-2	391 (≥ 12 y)	3	Week 12	Abrocitinib 100 mg Abrocitinib 200 mg Placebo	IGA ≥ 2 improvement response rate: 28.4%/38.1%/9.1% EASI-75 response rate: 44.5%/61.0%/10.4%
				1235 (≥ 12 y)	3	Week 12	Abrocitinib 100 mg Abrocitinib 200 mg Placebo	not available
			JADE Compare	838 (≥ 18 y)	3	Week 12	Abrocitinib 100 mg Abrocitinib 200 mg Dupilumab 300 mg subcutaneously	IGA ≥ 2 improvement response rate: 36.6%/48.4%/36.5% EASI-75 response rate: 58.7%/70.3%/58.1%
			JADE TEEN	287 (12–17 y)	3	Week 12	Abrocitinib 100 mg Abrocitinib 200 mg Placebo	not available
	Gusacitinib (ASN002)	JAK/SYK	RADIANT	250 (18–75 y)	2	Week 12	Gusacitinib Placebo	not available
	Baricitinib (LY3009104)	JAK1, 2	BREEZE-AD7	168 (18–75 y)	2	Week 104	Gusacitinib	not available
				329 (≥ 18 y)	3	Week 16	Baricitinib 4 mg Baricitinib 2 mg Placebo	vIGA-AD ≥ 2 improvement response rate: 31%/24%/15%
topical JAK inhibitor	Ruxolitinib	JAK1, 2	TRuE AD1	631 (≥ 12 y)	3	Week 8	0.75% Ruxolitinib Cream	IGA ≥ 2 improvement response rate: 50.0%/39.0%/15.1%
			TRuE AD2	618 (≥ 12 y)	3	Week 8	1.5% Ruxolitinib Cream Vehicle	IGA ≥ 2 improvement response rate: 39.0%/51.3%/7.6%
	Tofacitinib	JAK1, 2, 3		69 (18–60 y)	2	Week 4	2% Tofacitinib Ointment Vehicle	EASI change from baseline: –81.7%/-29.9%
	Ifidancitinib (ATI-502)	JAK1, 3		22 (≥ 18 y)	2	Week 4	Ifidancitinib Topical Solution	PGA ≥ 2 grade improvement from baseline: 41.2% EASI percent change from baseline: 40% SPA percent change from baseline: 31%
	Delgocitinib (LEO 124249)	JAK1, 2, 3/Tyk2		44 (≥ 2 y)	1	Week 8	Delgocitinib Cream	not available
	Delgocitinib (JTE-052)	JAK1, 2, 3/Tyk2		158 (≥ 18 y)	3	Week 4	Delgocitinib 0.5% Ointment Vehicle	mEASI change from baseline: –44.3%/1.7%
	Brepocitinib (PF-06700841)	JAK1/Tyk2		292 (12–75 y)	2	Week 6	Brepocitinib Cream Vehicle	not available

of the treatment. The improvement in ease and pruritus score were also seen through week 56.³²

A topical agent of ruxolitinib, which inhibits JAK1 and JAK2 selectively, was developed.³³ Two phase 3 studies, TRuE-AD1 and TRuE-AD2, were carried out for patients aged ≥ 12 years with AD under a primary endpoint of IGA 0/1 and ≥ 2 -grade improvement from baseline at week 8. Each study was different in target areas of the world. In each study, the treatment success rates of 0.75% ruxolitinib cream, 1.5% ruxolitinib cream, and vehicle were 50.0%/39.0%/15.1% and 53.8%/51.3%/7.6%, respectively. Significant itch reductions relative to the vehicle were reported within 12 h of the first application of 1.5% ruxolitinib cream.³⁴ In both studies, the patients achieved EASI-90 at week 8, and a significant reduction in itch scores compared to the vehicle group was reported within 12 h of the first application of 1.5% ruxolitinib cream ($P < 0.05$).

Tofacitinib is the first authorized JAK inhibitor that inhibits JAK1, JAK2, and JAK3.³⁵ Its oral preparations were approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis. A phase 2a study on adult patients with mild-to-moderate AD using 2% tofacitinib ointment was performed.³⁶ The mean percentage change in EASI scores from the baseline was significantly greater ($P < 0.001$) for tofacitinib (-81.7%) compared to the vehicle group (-29.9%) at week 4. Meanwhile, patients treated with tofacitinib ointment showed significant improvements in physician global assessment and body surface area by week 1 and significant improvements in pruritus by day 2.

Therefore, it is thought that topical JAK inhibitors rapidly improve the AD rash and symptoms relatively safely.

Oral JAK inhibitors

Several clinical trials support the use of JAK inhibitors in AD (Table 2). In these trials, a greater proportion of patients taking oral baricitinib, abrocitinib, or upadacitinib achieved a Validated Investigator's Global Assessment of AD score of clear or almost clear when compared to placebo. Baricitinib is an orally administered selective and reversible inhibitor of JAK1 and JAK2 with less affinity for JAK3 and TYK2.³⁷ It inhibits the signal transduction of the IL-6, IL-12, IL-20, IL-22, IL-23, and IFN- γ , and it is approved in many countries as a treatment for rheumatoid arthritis. While inhibiting JAK1 and JAK2, baricitinib suppresses Th2 cytokines, such as IL-4, IL-5, and IL-13, and suppress IL-22 and IL-31, which are involved in the pathophysiology of AD. In phase 2 trials, significantly more patients who received 4 mg baricitinib achieved EASI-50 than did patients receiving placebo after 16 weeks of using topical corticosteroids.³⁸ Several phase 3 studies were also conducted. BREEZE-AD1 and BREEZE-AD2 used baricitinib as a monotherapy,³⁹ while BREEZE-AD3 was a 52-week, long-term trial.⁴⁰ In BREEZE-AD4, baricitinib was used in combination with topical corticosteroids for patients with moderate-to-severe AD who experienced failure or intolerance to cyclosporine. Lastly, to assess the efficacy and safety of 4 mg and 2 mg of baricitinib in combination with topical corticosteroids in adults with moderate-to-severe AD who previously had an inadequate response to topical corticosteroids therapy, BREEZE-AD7 was performed.⁴¹ In this study, the proportion of patients who achieved EASI-75 was 48%, 43%, and 23% in the 4 mg group, 2 mg group, and placebo group at week 16. Notably, the percentage of patients who achieved a four-point or better improvement in pruritus NRS was also measured at day 2; it was 8% in the 4 mg group; 5% in the 2 mg group, and 2% in the placebo group. Moreover, in the ADSS Item2 trial, skin pain and sleep disturbance due to itch were rapidly and remarkably improved compared to the placebo group. Treatment-emergent AEs were reported in 58%, 56%, and 38% of the patients in the 4 mg group,

2 mg group, and placebo group, respectively. Serious AEs were reported in 4%, 2%, and 4% of the patients in the 4 mg group, 2 mg group, and placebo group, respectively. The most common AEs were nasopharyngitis, upper respiratory tract infections, and folliculitis.

The oral JAK1 selective inhibitor abrocitinib demonstrated its efficacy and safety in a phase 3 monotherapy trial to patients aged ≥ 12 years with moderate-to-severe AD.⁴² In the trial, greater rates of patients in the 200 mg (61.0%) and 100 mg abrocitinib groups (44.5%) compared to the placebo group (10.4%) achieved EASI-75 ($P < 0.001$) at week 12. AEs were reported in 65.8%, 62.7%, and 53.8% of the patients in the 200 mg group, 100 mg group, and placebo group, respectively. Serious AEs, including decreases in platelet count and laboratory values indicating thrombocytopenia, were reported in the 200 mg group. Another phase 3 trial randomly assigned patients with AD to receive 200 mg or 100 mg of abrocitinib and dupilumab subcutaneous injections or placebo⁴³; 200 mg of abrocitinib was superior to the dupilumab group with respect to itch response at week 2.

The oral use of upadacitinib, a selective JAK1 inhibitor, proved its efficacy for pruritus in moderate-to-severe AD in a phase 2b trial.⁴⁴ In a global phase 3 study on adult and adolescent patients with moderate-to-severe AD, an EASI-75 response rate was observed in 38.1% and 50.6% of the patients in the 15 mg group and 30 mg group, respectively.^{45,46} The most common AEs were nasopharyngitis (12%) and acne (10%).

In summary, oral JAK inhibitors have the ability to quickly improve the pruritus and rash of patients with AD, with minimal risk of bacterial infection.

Conclusion

The studies reviewed here show that JAK-STAT plays an important role in the pathogenesis of AD. AD is driven by barrier dysfunction, pruritus, and abnormal immune activation of Th2, Th22, and varying degrees of Th17. JAK-STAT pathways are involved in the signaling of several AD-related cytokines, including IFN- γ , IL-4, IL-13, IL-22, and IL-31. Therefore, several topical and oral JAK inhibitors have been shown to improve the severity and symptoms of AD. Currently, topical delgocitinib, a pan-JAK inhibitor, and oral baricitinib, a JAK1 and JAK2 inhibitor, are approved in Japan. In addition, 0.25% delgocitinib ointment has been shown to be effective and safe in pediatric patients with AD and is now available for use in pediatric patients aged ≥ 2 years.

The efficacy and safety of oral JAK inhibitors, including abrocitinib, baricitinib, and upadacitinib, for the treatment of AD were also evaluated. Significant improvements in the symptoms of AD were obtained by each drug. In particular, an improvement in pruritus scores was detected in early stages after the administration of these drugs. A low frequency of AEs will make these agents additional therapeutic options for the treatment of moderate-to-severe AD.

The monoclonal antibody dupilumab that targets IL-4R α , which blocks IL-4 and IL-13, is approved for moderate-to-severe AD. The development of biologics is also progressing, and more drugs are expected to be approved in the future. It will be a major concern to determine which JAK inhibitors and biologics are appropriate for each patient and how to select these drugs.

JAK inhibitors are expensive; at the same time, the economic loss due to AD is also enormous. Although it is necessary to simultaneously consider the effects of high medication prices on patients with moderate-to-severe AD who were not able to obtain sufficient relief from existing treatments, the treatment options discussed here represent a paradigm shift in terms of treatment approaches.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan (to A. Otsuka).

Conflict of interest

AO received honoraria from Novartis, Sanofi, Torii, Abbvie, Eli Lilly, Maruho, Janssen. The rest of the authors have no conflict of interest.

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