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Review Article

Janus Kinase Inhibitor as novel treatment of atopic dermatitis: A review

Felix Hartanto, Sylvia Anggraeni

Departement of Dermatology and Venereology, Dr. Soetomo General Hospital/ Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Abstract

Known as a multifactorial illness, atopic dermatitis (AD) affects up to 20% of children and 10% of adults and is characterized by chronic inflammatory skin conditions. However, the whole pathophysiology of AD has not yet been completely understood. Janus kinase (JAK) inhibitors have recently become a novel therapeutic approach for the treatment of AD. The STAT (signal transducer and activator of transcription) transcription factor is phosphorylated after the transphosphorylation of the JAK receptor, which activates the JAK receptor. Following dimerization, STAT moves into the cell nucleus to alter gene transcription. Inhibition of JAK receptors prevents their transphosphorylation, which in turn prevents STAT's phosphorylation and dimerization, eventually prevents the production of inflammatory cytokines and dampens the inflammatory response as a whole. Differing JAK inhibitors with various isotype specificities have been created recently. By focusing on JAK signaling molecules downstream, JAK inhibitors in the context of AD can target a number of pruritogenic pathways. Consequently, oral and topical JAK inhibitors are viewed as novel AD treatments, particularly for individuals with persistent pruritus. In conclusion, JAK inhibitor are a potential new therapy option for AD and have been shown in several trials to be successful in symptom relief, improving quality of life, and enhancing psychological well-being of patients. Despite the encouraging results, further research is required to gauge the effectiveness and safety of JAK inhibitors.

Key words
Atopic dermatitis; Janus kinase inhibitor; JAK-STAT pathway; Psychological well-being.

Introduction

Up to 20% of population are affected with atopic dermatitis (AD), a recurring and chronic inflammatory skin disorder. A common symptom of AD is pruritus that can affect quality of life, lowering both physical and emotional well-being. AD is considered a multifactorial disease, although its complete pathophysiology has not been fully elucidated to date. Various factors that cause AD are a combination of genetic and environmental factors such as damage to skin barrier, infection, stress, and others.[1]

Topical calcineurin inhibitors, topical corticosteroids, and/or topical PDE-4 are all possible treatments for acute AD. Phototherapy and systemic immunosuppressants may be useful in moderate-severe instances of AD. Although there are several pharmacological options for the treatment of AD, controlling the illness still presents a number of obstacles. According to a poll by the National Eczema Association, 86% of patients were unhappy with their care.[2-4]

Recently there is emerging new therapeutic modalities for the management of AD, such as

Address for correspondence
Dr. Sylvia Anggraeni
Departement of Dermatology and Venereology, Dr. Soetomo General Hospital/ Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
Ph: +6281229999011
Email: sylvia.anggraeni@fk.unair.ac.id

probiotic supplementation, with the hope of altering the gut-skin axis, and Janus Kinase (JAK) inhibitors that are assessed for their effect on patients. JAK inhibitors are well-known for helping AD patients immediately relieve itching and can greatly reduce the amount of inflammatory lesions on their skin.[2,3,5-7] It is hoped that this review will help clinically to understand the great potential of JAK inhibitors as a new treatment option for AD cases, so that the quality of life of AD patients can be improved.

The JAK-STAT Pathway

The STAT (signal transducer and activator of transcription) transcription factor is phosphorylated as a result of the transphosphorylation of JAK receptor. In order to alter gene transcription, STAT dimerizes and moves from the cytosol into the cell nucleus. The downstream effects on cytokine signaling of the four JAK receptors (JAK1, -2, -3, and TYK2) differ from one another. The STAT transcription factors, STAT1, -2, -3, -4, -5A, -5B, and -6, are tightly connected to JAK function. This interaction is called the "JAK-STAT signaling pathway". This pathway carries extracellular signals to the nucleus, where it triggers transcription process.[8,9]

By preventing JAK receptor phosphorylation, STAT's phosphorylation and dimerization are also prevented by JAK receptor inhibition. As a result, the overall inflammatory response is suppressed and STAT dimerization's ability to operate as a transcription factor for inflammatory cytokines is inhibited. Chronic pruritus is regulated by the IL-4R and JAK1 signaling pathways. JAK1 is also necessary for the signaling pathway of the cytokine IL-31, which plays a significant role in pruritus. JAK2 influences myelopoiesis, erythropoiesis, and platelet activation; as a result, JAK2 suppression is linked to unfavorable haematological outcomes such anemia and thrombocytopenia. Since B and T cells are the major cell types that produce JAK3, JAK3 inhibition is linked to CD8+ cluster differentiation, T cell malfunction, and reduced Natural Killer (NK) cell generation. Numerous interleukins and interferons are regulated by TYK2, and TYK2 inhibition suppresses the production of a number of cytokines.[8,9]

Pathophysiology of atopic dermatitis focusing on the JAK-STAT pathway

One of the mysteries surrounding AD is its pathogenesis. However, several studies have demonstrated that immunological dysregulation and skin barrier disruption play roles in the pathobiology of AD. The most prominent pathological finding is skin barrier disruption, which is essential as a physical barrier. The main proteins in charge of epidermal function include filaggrin (FLG), transglutaminase, keratin, and intercellular proteins. These proteins' flaws make it easier for allergens and microorganisms to enter the skin.[10]

Physical disruption of skin barrier, which is played primarily by the stratum corneum, plays a significant role in AD. The stratum corneum is a variety of cells arranged in layers, consisting of corneocytes surrounded by intercellular/ intercellular lipid-filled spaces formed by lamellar bodies. These lipids contain ceramides, cholesterol, and free fatty acids, are hydrophobic and function as inhibitors of water evaporation.[10]

Allergen invasion and microbial colonization on the skin of AD patients will be made easier by damage to the skin barrier. Keratinocytes are stimulated to secrete IL-1, -25, -33, MDC, TARC, and TSLP, which activate langerhans and dendritic cells in response to environmental cues and skin barrier disruption. Th2 cells are induced by activated dendritic cells to generate IL-4, -5, -13, -31, and -33, which compromises

barrier function, lowers AMP synthesis, impairs keratinocyte differentiation, and causes feelings of itching. Recruitment of Th1, Th22, and Th17 causes aberrant keratinocyte proliferation and epidermal thickening in chronic AD. Scratching and microbial toxins will also cause increase in pro-inflammatory cytokines, which will cause the synthesis of adhesion molecules and promote inflammatory responses.[10]

IL-4 and -13, which are generated by Th2, are expressed at considerably greater amount in AD lesions. Downregulation of filaggrin (FLG), loricrine (LOR), and involucrine (IVL) is also linked to barrier dysfunction in AD. Normal individual epidermal keratinocytes have an IL-4Rα/IL-13Rα1 receptor shared by IL-4 and I-13, which activates the JAK1/JAK2/TYK2-STAT6 and STAT3 pathways and inhibits the production of FLG, LOR, and IVL.[11]

Mechanism of action of JAK inhibitors

JAK inhibitors have immunomodulatory, antiproliferative, and anti-inflammatory actions in relation to JAK's activity.[12] Different JAK inhibitors with varying isotype specificity have been developed in recent years. Tofacitinib and peficitinib are examples of less selective JAK inhibitors. Selective JAK inhibitors include upadacitinib (JAK1 inhibitor), abrocitinib (JAK1 inhibitor), and deucravacitinib (TYK2 inhibitor). Many more JAK inhibitors are now being researched in clinical studies in dermatology, however the first generation of JAK inhibitors was created and employed in the domains of hematology and rheumatology. JAKi can provide patients hopeful therapy alternatives for a variety of disorders in a variety of sectors. **Table 1** lists the many kinds of JAK inhibitors that are currently available and being studied.[13,14]

Th1, Th2, Th17, and Th22 immunological pathways, which are implicated in the pathophysiology of AD, are known to be modulated by the JAK-STAT signaling pathway and spleen tyrosine kinase (SYK). JAK receptors are made up of four groups: JAK1, -2, -3, and TYK2. TYK2 mediates cytokine-

Table 1 Various types of JAK inhibitors currently available.

Name	*Sub-specificity*	*Approved indication*	*FDA approved*	*EMA approved*
Non-selective JAK inhibitor				
Tofactinib	JAK 1/2/3	RA, PsoA, UC	Yes	Yes
Ruxolitinib	JAK 1/2	RA, MF, PV, GvHD	Yes	Yes
Baricitinib		RA, DA	Yes	No
Peficitinib	Pan JAK	-	No	No
Delgocitinib		-	No	No
Gusacitinib		-	No	No
Ifidancitinib	JAK 1/3	-	No	No
Selective JAK inhibitor				
Upadacitinib	JAK 1	RA, DA	Ya	Yes
Filgotinib		RA	No	Yes
Itacitinib		-	No	No
Solcicitinib		-	No	No
Abrocitinib		DA	No	No
Deucravacitinib	TYK 2	-	No	No
Brepocitinib		-	No	No
PF-06826647		-	No	No
Ritlecinitib	JAK 3	-	No	No

Abbreviation: RA, rheumatoid arthritis; PsoA, psoriatic arthritis; UC, ulcerative colitis; MF, myelofibrosis; PV, polycythemia vera; GvHD, graft versus host disease.

stimulated transcriptional alterations by phosphorylating the transcription factors STAT (STAT1, -2, -3, -5A, -5B, and -6).[3]

JAK inhibitors work by blocking the JAK-STAT signaling pathway, to have immunosuppressive and antiproliferative effects. It has been established that the JAK-STAT signaling system, which is driven by cytokines, is a key modulator of AD-related symptoms. The prevalence of pruritus in AD has been demonstrated to be significantly influenced by thymic stromal lymphopoietin (TSLP), IL-4, -3, and -31 via the JAK receptor.[3] By focusing on JAK signaling molecules downstream, JAK inhibitors attack a number of pruritogenic pathways in AD, including those already outlined above. Therefore, oral and topical JAK inhibitors are known to target various cytokines of the JAK-STAT signaling pathway and are considered as new therapies in AD, especially for patients with persistent pruritus.

Both as a monotherapy and in conjunction with topical corticosteroids, JAK inhibitors have demonstrated great efficacy in the management of AD. According to studies, topical tofacitinib can improve baseline EASI scores by roughly 80% after just four weeks of therapy.[15] Another research discovered that after four weeks of therapy, 10% patients had an IGA score of 0 or 1 while receiving 1,5% ruxolitinib cream daily.[16]

Topical corticosteroids and calcineurin inhibitors are still regarded as highly efficient first-line treatments for AD, even though topical JAK inhibitors are studied to be efficacious drugs for AD.[17,18] Topical JAK inhibitors can be used as an additional therapy option when a patient fails to respond to numerous first-line topical medicines. For those who are afraid of corticosteroids, topical JAK inhibitors might be a helpful option.[9]

For patients with moderate-severe atopic dermatitis, oral JAK inhibitors have also been demonstrated to be useful in treating the condition. According to studies, upadacitinib resulted in a 75% improvement in EASI scores after four months.[19] Another research discovered that when oral baricitinib was combined with topical corticosteroids, patients who achieved EASI-50 and EASI-75 was higher than topical corticosteroids monotherapy.[20] Numerous research have attempted to determine the efficacy of utilizing JAKi as a treatment for AD, both topically and orally. Some of these previous studies can be seen in **Table 2**.

Side Effects of JAK Inhibitors

The most often reported adverse effects of JAK inhibitors in clinical trials for AD were headache, nausea, and mild- severe infection, most frequently nasopharyngitis. The major adverse effects associated with JAK inhibitors likely to be less common in the younger and generally healthier group of AD patients.

Table 2 Previous studies of JAK inhibitor in atopic dermatitis.

JAK Inhibitor	*Target*	*Study*	*Clinical Phase*
Delgocitinib	JAK1,2,3 TYK2	Nakagawa, et al.	III
Ruxolitinib	JAK1,2	Kim, et al.	II
		TruE-ADI	III
Tofacitinib	JAK3 and/or JAK1	Bissonnette, et al.	II
Abrocitinib	JAK1	Silverberg, et al. (JADE MONO-2)	III
Baricitinib	JAK1,2	Simpson, et al. (BREEZE-AD4)	III
Gusacitinib	JAK1,2	Bissonnette, et al.	Ib
Upadacitinib	JAK1	Guttman-Yassky, et al.	IIb

Although percentage of serious adverse events associated with oral JAK inhibitor for AD is generally low, studies point to a potential heightened risk of more severe side effects, including herpes zoster reactivation, thromboembolic and cardiovascular events.[21,22]

Because JAK2 is known to be correlated with myelopoiesis, erythropoiesis, and platelet activation, possible risks associated with JAK2 receptor inhibition include thromboembolism, thrombocytopenia, anemia, and neutropenia. Ruxolitinib, tofacitinib, and baricitinib have been linked to an increased risk of thromboembolic events in studies evaluating JAK inhibitor therapy for rheumatoid arthritis patients, despite the fact that this result has not been seen in studies with AD patients. Despite the fact that JAK1 is specifically inhibited by upadacitinib, research has demonstrated that JAK2 depends on JAK1 for its transphosphorylation and activation. Observed adverse effect of upadacitinib usage, neutropenia, may be explained by these interconnected JAK pathways.[19,21-23] Contraindications to using JAK inhibitors include having a history of reactions to other JAK inhibitors, being pregnant, having liver or renal illness, having blood abnormalities, having some types of cancer, having active infections, or having a history of active tuberculosis.

Conclusion

Atopic dermatitis can greatly interfere with the quality of life of patients. Often in a small number of cases, recalcitrant cases do not give satisfactory results using conventional treatments available, which can have clinical implications that greatly affect the patient's quality of life.

Janus kinase inhibitor is a promising new modality for atopic dermatitis treatment, which has been proven to be effective in various studies, either as a monotherapy or in conjuction with corticosteroids to reduce symptoms in the long term. Despite promising results in atopic dermatitis patients, further studies through clinical trial phase are needed to evaluate the efficacy and safety aspects of JAK inhibitors in atopic dermatitis cases. To date, several JAK inhibitors (delgocitinib, ruxolitinib, abrocitinib, and baricitinib) have entered the clinical phase III phase with satisfactory results. Studies of JAK inhibitor in various other diseases, both in dermatology and non-dermatology fields, gives promising results as well. Several JAK inhibitors have also been designated by the FDA as one of the therapeutic options that can be used in autoimmune diseases.

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