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Review Article

Janus Kinase Inhibitors - A next generation treatment in Dermatology

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Abstract

Over the past few decades, drugs targeting cytokines and their receptors have been researched and developed. These agents act on molecular targets at the subcellular level. The Janus Kinases family is a group of receptor-associated signaling molecules which are essential to the signal cascade originating from Type 1 and Type 2 cytokine receptors. Janus kinase inhibitors, also known as Jakinibs/ JAK inhibitors, are molecules developed against this class of kinases. Initially developed for use in different inflammatory conditions, such as rheumatological problems, JAK inhibitors are emerging as new agents in dermatology. Although biologics have proved to be effective and safe in various disorders, not all patients respond to this therapy. Jakinibs are also being seen as an alternative oral therapy for such patients. This article will review the basic principles of mode of action, efficacy and safety of JAK inhibitors in autoimmune conditions such as psoriasis, alopecia areata, atopic dermatitis, lupus erythematosus, dermatomyositis and vitiligo.

Key words
JAK inhibitors, cytokine receptors, autoimmune.

Introduction

The Janus kinase inhibitors are taking the dermatologic therapeutic world by storm.[1] The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway largely mediates local and systemic inflammation that characterizes autoimmune skin diseases. Advanced research has led to the development of inhibitors that specifically target the Janus kinase pathway.[2]

As the name suggests, this class of medications blocks cytokine-mediated signalling via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, which plays an important role in immunoregulation and normal cell growth.[3] Due to their anti-inflammatory properties, JAK inhibitors have been approved in various countries across the globe for the treatment of rheumatoid arthritis (tofacitinib, baricitinib) and myelofibrosis or polycythemia vera (ruxolitinib).[4]

Multiple JAK inhibitors have been recognized. Broadly, they have been classified into first and second generations. First-generation JAK inhibitors comprises of tofacitinib, ruxolitinib, baricitinib, and oclacitinib while second-generation JAK inhibitors includes decernotinib, peficitinib, filgotinib, fedratinib, momelotinib, and lestaurtinib.[5] Both generations of Janus kinase inhibitors have become promising treatment modalities for multiple dermatologic conditions which include psoriasis, atopic dermatitis, alopecia areata, vitiligo, dermatomyositis, and graft-versus-host disease.[6] Upcoming trials include use of JAK inhibitors in treatment of cutaneous lupus, cutaneous T-cell lymphoma, melanoma, allergic contact dermatitis, and lichen planus.[3]

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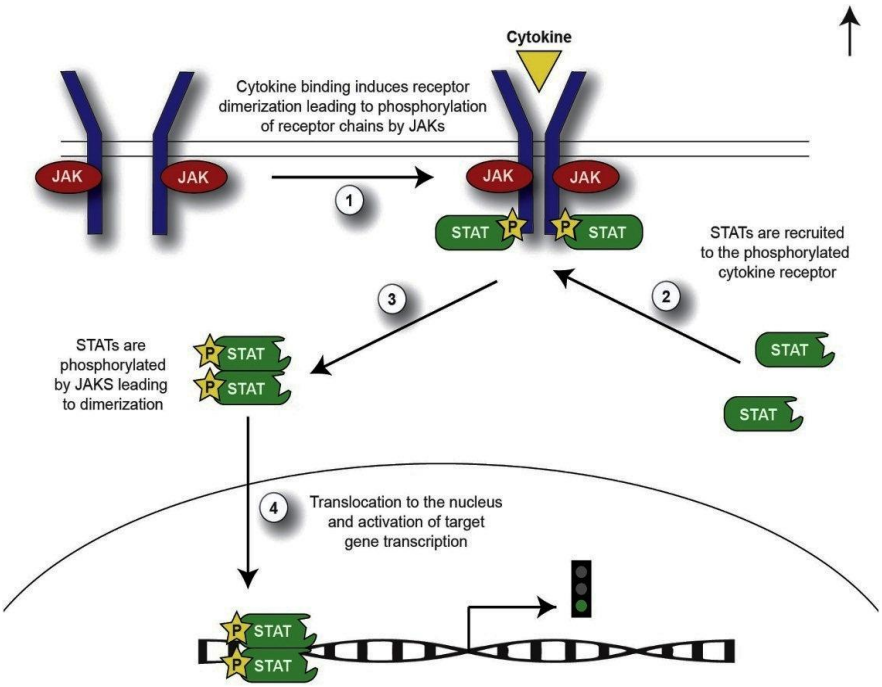

Figure 1[7]

Other than systemic preparations, topical JAK inhibitors have been explored too and have proved effective in Atopic Dermatitis, psoriasis, Alopecia areata, and vitiligo. Multiple studies are ongoing in this area.[7]

JAK-STAT pathway

As previously mentioned, cytokine receptor signaling involves pathways such as the JAK-STAT pathway **(Figure 1)** and the MAP kinase cascade.[8] The four members of the JAK family include: JAK1, JAK2, JAK3, and TYK2. When cytokines bind to the receptors, the latter oligomerize and recruit intracytoplasmic JAKs to bind in pairs. This dimerization follows autophosphorylation of JAKs which are subsequently activated. The activated JAKs modify the receptors, allowing STAT proteins to bind. The activation of STATs is followed by dimerization and translocation into the cell nucleus to influence DNA transcription, thus regulating gene expression.[9]

There are six different types of STAT proteins recruited by different combinations of JAK pairs and this permits the wide range of downstream activities seen in the JAK-STAT pathways.[10] There is a wide array of genes including SOCS, Nmi, Bcl-XL, p21, MYC, and NOS2 that are suppressed or activated by the JAK-STAT pathway ultimately affecting cell growth and apoptosis. However, JAKs associate with specific cytokine receptors hence influencing different aspects of immune cell development and function.

JAK1 is associated with IFN, IL-6, IL-10 receptors, and receptors containing common chains. JAK2 is primarily involved in hematopoietic receptors as well as IL-12 and IL-23. JAK3 dimerized with JAK1, acts selectively on receptors containing the common chain, which include IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, which are crucial to lymphocyte function. TYK2 is associated with IFN, IL-12, and IL-23 receptors in conjunction with JAK2.[11]

Mutations in JAK have been associated with myeloproliferative diseases including polycythemia vera, essential thrombocytopenia, and myelofibrosis along with inherited immunodeficiencies like severe combined immunodeficiency and hyperimmunoglobulin E syndrome[12] and in autoimmune diseases.[11]

Clinical uses in Dermatology

Psoriasis and Psoriatic Arthritis

Pathogenesis of psoriasis includes various cytokines that operate through the JAK-STAT signaling pathway. Tofacitinib is the most popular drug used in the majority of studies conducted in psoriasis patients. Tofacitinib inhibits the expression of interleukin (IL)-23 and the differentiation of T helper type 1 (Th1) cells. IL-23 essentially controls Th17 cells, therefore by inhibting IL-23, Tofacitinib reduces Th17 cell differentiation consequently decreasing the production of IL-17.[9] Several phase III randomized controlled trials (RCTs) have demonstrated that compared to placebo, patients taking tofacitinib not only significantly achieved 75 percent reduction in the Psoriasis Area and Severity Index (PASI 75) but also that there was a dose-dependent improvement of PASI 75 on tofacitinib 10 mg twice daily as compared to 5 mg twice daily.[13,14]

A phase III non-inferiority trial revealed that tofacitinib 10 mg twice daily and etanercept 50 mg twice weekly showed comparable results.[15] A post hoc analysis of the patients included in the above RCTs demonstrated significant improvements in Nail Psoriasis Severity Index (NAPSI) scores on tofacitinib 10 mg twice daily.[16]

Two newer JAK inhibitors, baricitinib and solcitinib have achieved fruitful results against psoriasis. A study of baricitinib demonstrated significantly more patients achieved PASI 75 as compared with placebo.[17] A multi-center study found solcitinib 400 mg twice daily to have similar efficacy to both tofacitinib and baricitinib, with 57% of patients achieving PASI 75.[18] However, further developments in solcitinib have been discontinued.

Topical JAK inhibitors for mild-moderate psoriasis have also been researched upon. Tofacitinib showed variable results in a phase IIa trial. Differences in efficacy were speculated to be due to variability in moisturizing properties of the formulations tested.[19] Ruxolitinib (INCB018424) studied in a non-blinded and non vehicle- controlled trial and was found to be effective by reducing the mean area and severity of psoriatic lesions.[20]

In December 2017, FDA approved tofacitinib for the treatment of psoriatic arthritis in adult patients not responding to or unable to tolerate methotrexate or other disease-modifying antirheumatic drugs.[3,21] This was based on the results of two phase III trials, which showed that patients on tofacitinib 5 mg and 10 mg twice daily demonstrated statistically significant improvements in American College of Rheumatology 20 (ACR20) response and change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at 3 months, as compared to placebo.[22,23]

Atopic Dermatitis

The complex pathogenesis of atopic dermatitis involves increased helper T cell type 2 (TH2) immunity driven from JAK/ STAT signaling from cytokines, such as IL-4, IL-5, and IL-13. Tofacitinib 5mg once or twice a day portrayed a 66.6% reduction in the severity scoring of AD Index and a 69.9% reduction in pruritus and sleep loss scores in patients with moderate to severe AD who were not responding to other treatment options.[24] In a phase 2 study

comparing topical tofacitinib 2% with vehicle, tofacitinib exhibited significant reduction in the area and severity of eczema as compared to placebo.[25]

Alopecia Areata

Alopecia areata (AA) is a chronic, autoimmune disorder that targets hair follicle epithelium and restricts hair growth in localized patches without scarring.[26] In alopecia areata (AA), JAK-STAT-dependent cytokines along with interferon (IFN) γ and IL-15 activate autoreactive T-cells. JAK inhibitors prevent the release of these inflammatory cytokines, thereby ending the pathogenetic process.

The immune-mediated process in alopecia areata occurs due to major histocompatibility complex class 1 expression which presents self-antigen to autoreactive T cells.[27] Histopathology shows a peribulbar T-cell infiltrate of the hair follicle which is predominantly CD8+ natural killer cell receptor D (NKG2D)+ T cells.[28] In addition to cellular infiltration, there is also an increase in inflammatory mediators, most notably interferon (IFN)-γ and interleukin (IL)-15, which are cytokines dependent on the JAK-STAT pathway for activation and proliferation of autoreactive T cells. The attack on the follicular epithelial cells results in dystrophy of the follicle and early transition into the catagen phase, resulting in hair shedding and the clinical presentation of alopecia.[29] Importantly, the stem cells are not usually targeted so the follicle maintains the ability to regrow hair in the future, through spontaneous remission or effective therapy.

Multiple studies have reported the use of baricitinib (JAK 1/2), ruxolitinib (JAK 1/2), and tofacitinib (JAK 1/3) in Alopecia Areata. JAK inhibition has shown potential as an effective AA therapy when used in case studies, case series, and open-label trials.

Vitiligo

IFN-γ utilizes the JAK/STAT pathway to mediate targeted destruction of melanocytes by CD8+ T cells. Generalized vitiligo showed near complete repigmentation of affected areas of the face, forearms, and hands over 5 months of treatment with tofacitinib (5mg every other day for 3 weeks followed by 5 mg daily). Following treatment discontinuation, however, loss of repigmentation was observed.[30] It was proposed that JAK1/JAK2 was involved in INF-γ signal transduction. They also indicated that the use of the JAK1/3 inhibitor blocked the INF-γ signaling and decreased C-X-C motif chemokine 10 (CXCL10) expression. The expression of CXCL10 in keratinocytes is induced by INF-γ, and it has been found to be an intermediate of depigmentation in vitiligo.

It has been demonstrated that IFN γ-induced expression of C-X-C motif chemokine 10 (CXCL 10) in keratinocytes mediates depigmentaion in vititligo. As IFN γ signal transduction occurs through JAK 1 and 2, blockade of JAK with tofacitinib inhibits IFN γ signaling, thereby downregulating CXCL 10 expression, leading to return in pigmentation.[5]
JAK-STAT inhibitors have shown valuable results in the treatment of vitiligo, including successful repigmentation outcomes. These molecules have been tried in both topical and systemic formulations. Pan JAK inhibitor, tofacitinib and JAK-1,2 inhibitor, ruxolitinib, have been found successful in causing repigmentation in vitiligo.[31]

Dermatomyositis

Dermatomyositis is an uncommon autoimmune disorder with distinctive cutaneous manifestations that are frequently challenging to manage. Treatment options include hydroxychloroquine, methotrexate,

mycophenolate mofetil, and intravenous immunoglobulins. However, in case of failure to respond, very few alternative options are available. In dermatomyosisits, there is abnormal upregulation of interferon signaling which is suppressed by tofacitinib.

In one series, three patients with refractory dermatomyositis observed clinical response after treatment with oral tofacitinib at a dose of 5–10 mg/day. The mean treatment period was 9.6 months. By the end of one month, there was significant clinical improvement in pruritus and muscle strength.[32]

Lichen planopilaris

Lichen planopilaris (LPP) is an inflammatory cicatricial alopecia for which many different therapies are attempted with varying success. In a case series, oral tofacitinib was used to treat 10 patients with recalcitrant LPP. 80% patients developed significant clinical improvement after treatment with tofacitinib used alone or in combination. Tofacitinib was well tolerated by all patients. There were two patients who did not improve on the 10 mg daily dose and, then, did respond after the dose was increased to 15 mg.[33]

Lupus erythematosus

In a case report by Wenzel *et al*., ruxolitinib dosed at 20 mg PO Q12H for 4 months in a 69-year-old patient with chilblain lupus was associated with complete remission of the condition.[34]

Miscellaneous

There are some case reports showing the efficacy of tofacitinib in chronic actinic dermatitis, erythema multiforme, hypereosinophilic syndrome, palmplantar pustulosis, graft versus host disease and polyarteritis nodosa.[5]

Contraindications

Absolute

- Hypersensitivity to the drug

Relative

- Liver impairment
- Stage IV kidney disease
- Active infections
- Pregnancy (category C)

Adverse effects

- Risk of infections: urinary tract infection, nasopharyngitis, and upper respiratory tract infections
- Varicella-zoster virus reactivation
- Impaired response to vaccination
- Thrombocytopenia, anemia
- Diarrhea, fatigue, dizziness, and headache
- Increased risk of malignancies
- DRESS[35]

Monitoring Guidelines

At baseline

- Complete blood count
- Renal function tests
- Liver function tests
- Fasting lipid profile
- HBsAg
- Anti-HCV
- Testing for tuberculosis
- HIV status

On followup

CBS, RFTs, LFTs and Fasting Lipid Profile should be repeated at one month after starting treatment and then after every 3 months.

Annual testing for Tuberculosis

Availability in Pakistan

- Tofacitinib is marketed as a 5 mg tablet.
- Ruxolitinib is marketed as 5, 15, and 20 mg tablets.

Conclusion

Overall, JAK inhibitors is a relatively safe class of drugs which has showed promising results and is comparable with biologics in efficacy. With future advances, it may be included amongst the first line of treatments.

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