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The Emerging World of JAK Inhibitors

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Abstract

The Janus Kinase inhibitors are a new emerging class of small molecules. These target the Janus Kinase proteins located on the cell membrane. Janus Kinase proteins regulate the cellular transcription of several proteins and act as mediators in several cytokine pathways. Dysregulation in these cytokine pathways is responsible for disorders like alopecia areata, psoriasis, vitiligo, lichen planus, and more in dermatology. Contrary to the injectable biologics, these Janus kinase inhibitors can be taken per oral route and have greater patient acceptability. In this review, we seek to discuss the various indications of Janus Kinase inhibitors and their side effects. We also strive to discuss the monitoring for this class of drugs.

Key words: Alopecia Areata; Atopic Dermatitis; JAK Inhibitors; Lichen Planus; Pruritus; Psoriasis; Vitiligo

The emerging world of Jak Inhibitors

The Janus kinase (JAK) proteins are tyrosine kinase proteins that, along with the signal transducer and activator of transcription (STAT) proteins, form the JAK STAT pathway. The JAK family has four members: JAK1, JAK2, JAK3, and TYK2; the STAT family has 7 members. The JAK proteins are located on the intracellular part of the transmembrane protein as homo or heterodimers. When the signalling molecule attaches to the transmembrane protein, it undergoes structural change with the phosphorylation of the JAK molecule. These JAK molecules then form the docking site for the STAT protein. The STAT protein then undergoes phosphorylation, translocates to the cellular nucleus, and regulates gene transcription.[1] JAK pathway dysregulation is implicated in various autoimmune disorders.

JAK inhibitors (JAKi)s are small molecules with wide roles due to their selective targeted role in immunopathogenesis. These molecules are available as oral or topical drugs, increasing their acceptability and convenience. JAKi have been approved by the FDA to treat atopic dermatitis (oral abrocitinib, oral upadacitinib, and topical ruxolitinib), alopecia areata (oral baricitinib), psoriasis (oral deucravacitinib), and vitiligo (topical ruxolitinib). New avenues are being constantly explored. Currently, oral tofacitinib is the only JAKi available in Nepal.

Tofacitinib is a first-generation nonselective JAKi. It is mainly metabolized by the liver and excreted by the kidney. Tofacitinib has been approved to treat psoriatic arthritis, rheumatoid arthritis and ulcerative colitis. It has been tried as an off-label indication on psoriasis, alopecia areata (AA), vitiligo, prurigo nodularis, atopic dermatitis, and others. The safety of tofacitinib in pregnancy, breastfeeding, and people less than 18 years of age is not yet established. Tofacitinib is not considered safe for active infections or severe hepatic or hematological impairment.[2]

In this editorial, we shall discuss the various emerging indications of JAKi's in dermatology and their adverse effects.

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Alopecia areata and JAKi

The pathogenesis of alopecia areata (AA) revolves around the INF-Y producing CD8+ T cells. These INF-Y producing CD8+ cells are responsible for the collapse of immune privilege of the hair follicle, and ensuing AA.[3] INF-Y acts via the JAK-STAT pathway in modulating cellular response. The first JAKi to be used in AA was tofacitinib.[4] The JAKi's approved for AA are baricitinib (JAK1/JAK2 inhibitor) and ritlecitinib (JAK3/TEC inhibitor). Baricitinib is the first JAKi to be approved for AA, and it is approved for adults with AA, whereas ritlecitinib is approved for children above 12 years of age. The indication to start using JAKi's in AA are in cases with noticeable eyebrow/eyelash involvement, when the AA has a significant psychosocial impact, or even in cases of diffuse AA where the hair pull test is diffusely positive all through the scalp. Though JAKi induces hair growth in AA of over 10 years, the response is more favorable when started early.[5] Patients with some amount of hair on their scalp respond better than those without any hair at the beginning of therapy.[5] Though currently unavailable in Nepal, combining JAKi's to low-dose oral minoxidil (2.5mg or 5 mg) improves response in some patients.[6]

Psoriasis and JAKi

The pathogenesis of psoriasis focuses on the IL12/IL23 axis and further activation of Th17 and TNF alpha.[7] Hence, most of the biologicals are centered around these cytokines. The TYK2 and JAK pairing is responsible for activating IL12 and IL23. Hence, JAKi's have found their place in the treatment of psoriasis. Currently, oral deucravacitinib is approved for psoriasis. Deucravacitinib is a selective inhibitor of TYK2 with minimal JAK1/2/3 cross-reactivity. Oral tofacitinib and oral upadacitinib are approved for psoriatic arthritis but not for cutaneous psoriasis. Tofacitinib, as an off-label indication has been used both as topical and oral agents in chronic plaque psoriasis, palmoplantar pustular psoriasis, and nail psoriasis with good results.[8-10]

Vitiligo and JAKi

In vitiligo, IFN -Y secreting CD8+ cells mediated destruction of the melanocytes. The main cytokines involved in vitiligo are INF-Y and IL-15. Both these cytokines act via the JAK pathway. Ruxolitinib 1.5% cream, is the only approved therapy for vitiligo for adults and children above 12 years of age.[11] Ruxolitinib 1.5% has shown good facial repigmentation starting as early as 4 weeks irrespective of duration or disease activity at the start of therapy.[12] Oral tofacitinib has shown significant repigmentation in cases of vitiligo, and the results have improved when combined with phototherapy.[13] Tofacitinib has also been tried in cases with psoriasis, alopecia areata, and vitiligo, all presenting in single patients and has shown improvement in all three conditions.[14]

Lichen Planus and JAKi

In the pathogenesis of lichen planus (LP), the INF-Y producing CD8+ T cells induce apoptosis of the keratinocytes. INF-Y utilizes JAK2/STAT pathway as its main signal transducer.[15] Inhibiting the JAK2 STAT pathway can help in the treatment of LP. Most of the studies on LP and JAKi have been done with tofacitinib.[16] Few studies have been done with ruxolitinib, baricitinib, deucravacitinib, and upadacitinib. JAKi's have been tried in all variants of LP including cutaneous lichen planus, lichen plano pilaris, lichen planus pigmentosus, nail lichen planus, and oral erosive lichen planus.[17-19] Most studies have shown favorable responses with minimal adverse effects. However, most of the studies have been case reports or case series, and proper randomized controlled trials have yet to be published.

Pruritus and JAKi

Various histaminergic and non-histaminergic pathways mediate pruritus. Antihistamines are not effective in controlling non histaminergic urticaria. Nonhistaminergic pathways of pruritus are often activated in chronic pruritus, such as prurigo nodularis, atopic dermatitis, psoriasis, and others. The mediators of chronic itch are T helper Th2 cytokines like IL-4, IL13, IL31, and keratinocyte-generated thymic stromal lymphopoietin (TSLP).[20] IL-4, IL31, and TSLP mediate itch by acting on various intracellular JAK receptors. Dipulimab is the only biological therapy approved for prurigo nodularis, and it acts on the IL-4 α receptor. JAKi's have relatively broad targets as they act on JAK-STAT pathways, which are end-point targets for various itch-mediating cytokines. In patients with atopic dermatitis, significant improvement in pruritus has been seen with topical tofacitinib, ruxolitinib, and delgocitinib.[20] In atopic dermatitis, updacatinib was found to be more effective and faster acting than dipulimab.[21] Tofacitinib, a non-selective JAKi, has shown good response in adult and pediatric prurigo nodularis.[22,23] Maintenance of results even after withdrawal of the drug has been achieved in treated cases of prurigo nodularis. Baricitinib has been compared to dipulimab and has been shown to have faster itch relief in cases of prurigo nodularis.[24]

Adverse effect of JAKi

JAKi's come with a black box warning against their use in patients above 65 and patients with pre-existing cardiovascular conditions. This black box warning came into effect after a study in 2022 that suggested that patients with rheumatoid arthritis (RA) on tofacitinib may have increased major adverse cardiac events (MACE) and venous thromboembolism (VTE). Hence, the use of JAKi's in dermatology has often been guarded. A recent meta-analysis of RCTs on the adverse reactions of JAKi's in dermatology

patients has found no increased risk of MACE or VTE in dermatological patients compared to placebo.[25] Common adverse effects of JAKi's were headache, respiratory infection, and gastrointestinal side effects such as nausea.[25] This difference could be explained by the fact that most dermatological patients are usually younger than patients of RA, which decreases their risk for MACE and VTE. Also, RA patients have an inherently higher risk of MACE as well as compared to the general population.[26] Results on baricitinib, JAK1/JAK2 inhibitor, across dermatology and rheumatology specialties have concluded that rate of adverse effect is linked to the underlying risks inherent in the treatment population.[27] Hence, side effects of JAKi's could be different in different patient populations.

With tofacitinib, the adverse effects are reactivation of systemic and cutaneous infections such as herpes zoster, herpes simplex, and latent tuberculosis infection (LTBI). Hence, it is recommended that all patients who undergo therapy with tofacitinib be evaluated for LTBI. LTBI screening can be done with the Mantoux test and interferon-gamma release assay (IGRA). Isoniazid is recommended in patients with LTBI who are to be started on tofacitinib. Other common infections are upper respiratory tract infections and nasopharyngitis. Laboratory abnormalities such as raised creatinine phosphokinase (CPK) enzyme, liver function tests, and dyslipidemia have been observed. Cytopenias are not that common but can be seen. The baseline investigations for starting tofacitinib are blood counts, liver function test, CPK, creatinine, viral markers, and LTBI screening.[2] Further monitoring is done monthly, followed by three monthly.[2]

Topical JAKi's such as ruxolitinib have been associated with acne-related adverse effects with occasional worsening of acne and pruritus.[11]

Conclusion

We can safely conclude that JAKi's are there to stay with us. Apart from the indications discussed above, JAKi's have been tried in other dermatological indications like granuloma annulare, systemic lupus, sarcoid, and more. Because of the ease of prescription and easy acceptance by the patients, their prescriptions are on the rise. We need to be aware of their adverse effect profile, esp. in our part of the world where LTBI is more common. We also need to be well-versed in the monitoring of these drugs.

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