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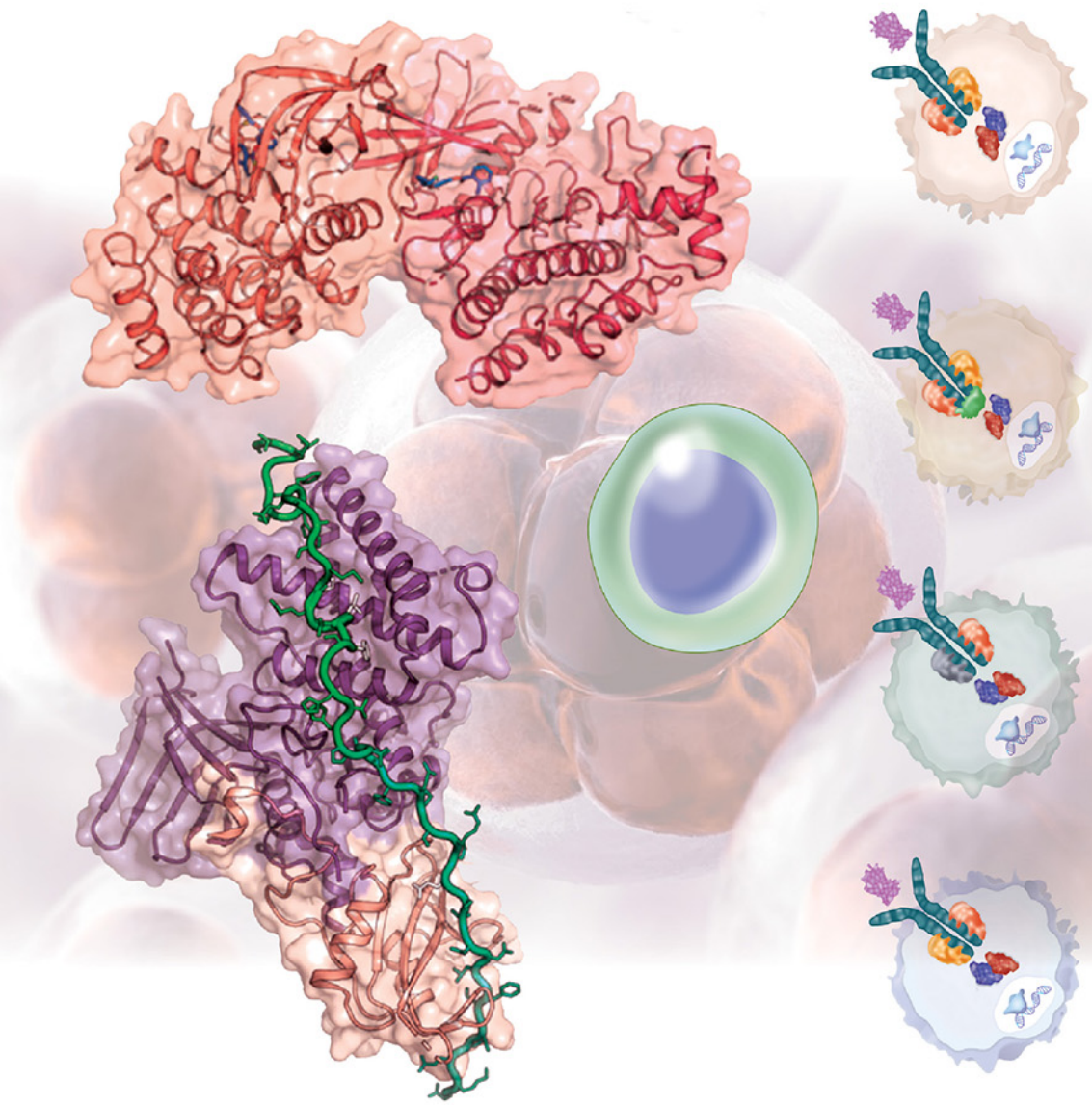
JAK Inhibitors in Dermatology



Kabir Sardana

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CHAPTER 9

JAK Inhibitors in Pruritic Disorders

Ramkumar Ramamoorthy, Kabir Sardana

"Nothing is more powerful than an idea whose time has come."
—Victor Hugo

Overview

- **Introduction**
- **Rationale of Janus Kinase inhibitors**

INTRODUCTION

Itch is a prominent and distressing symptom in many dermatological disorders. Pruritus is a cardinal feature of atopic dermatitis (AD)[1] and lichen planus (LP).[2] Around 70% of patients diagnosed with psoriasis report itch in involved and uninvolved skin as well.[2] Therefore, any medication which gives adequate relief from this uncomfortable sensation is always a welcome addition to a therapeutic armamentarium for the treatment of skin diseases in routine practice.

In this section we provide a summary of the promising results shown by Janus kinase inhibitors (JAKis) in providing itch relief in skin disorders and discuss the scope for using a JAKi in managing itch in various skin disorders in the near future.

RATIONALE OF JANUS KINASE INHIBITORS

Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is the major pathway employed by cytokines for intracellular signal transduction besides other pathways activated in various cell types.[3]

One of these signaling cascades is mediated by JAKs (also see Chapter 2). Recently, it could be shown on a molecular level that JAK1 directly activates frontal cortex neurons and thus can cause chronic itching.[4] This was revealed by knock down experiments conducted in mouse, which suggested a key role for JAK1, a ubiquitously expressed enzyme in human body in mediating itch signaling through sensory neurons, and therefore play a significant role in inducing neurogenic inflammation in skin diseases.

Several cytokines act on receptors present in sensory neurons to mediate itch[1] either directly [interleukin 31 (IL-31), thymic stromal lymphopoietin (TSLP), IL-2, and IL-17] or indirectly by sensitizing the neurons to other cytokines (IL-4 by lowering the threshold for response to histamine and IL-31). Itch is mainly transmitted through unmyelinated type C

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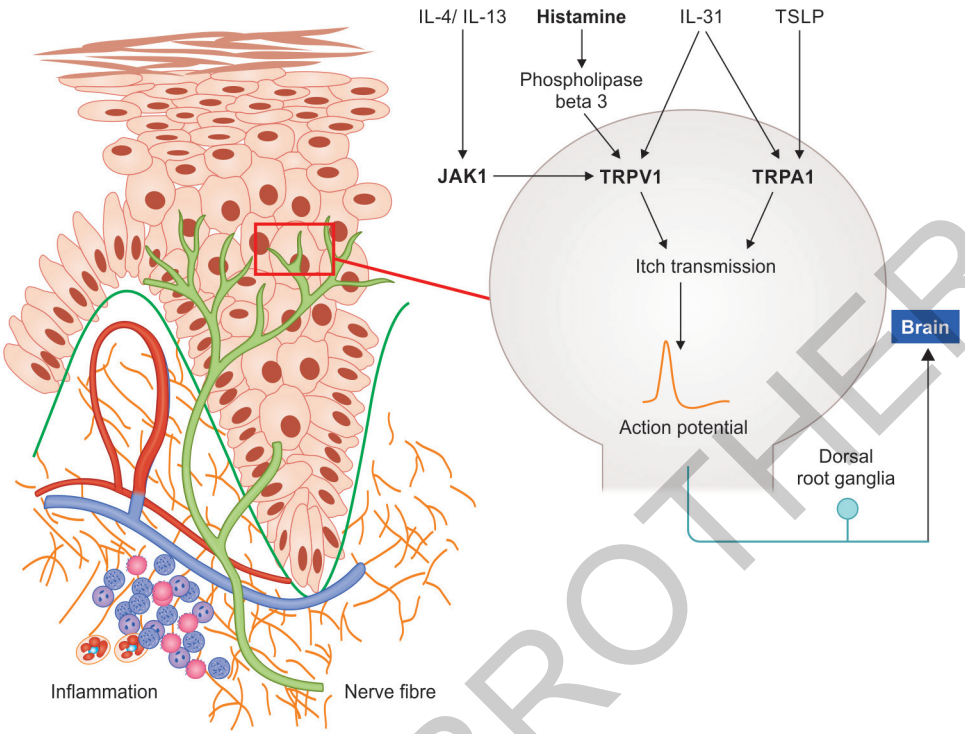

(IL: interleukin; JAK1: Janus kinase 1; TSLP: thymic stromal lymphopoietin; TRPA1: transient receptor potential ankyrin 1; TRPV1: transient receptor potential vanilloid 1)

FIG. 1: Overview of the role of JAK1 receptor and cytokines and their role in transmission of the sensation of itch.

fibers in dermoepidermal junction and epidermis by several mediators with a key role for TRPV channels [transient receptor potential vanilloid 1 and ankyrin 1 (TRPV1 and TRPA1)] in the signaling cascade (**Fig. 1**). Among the list of mediators, proteases such as tryptase released from mast cell and serine esterases from epidermis signal through protease-activated receptors (PARs), which play a major role in transmitting nonhistaminergic itch. PAR-2 receptors have been shown to activate TRPV channels through protein kinase C-dependent signaling pathway.[5] Thus, T helper 2 (Th2) immunity is a driver of chronic pruritus and these cell lines are active in AD and in other Th2-dominated inflammatory and pruritic skin disorders (**Box 1**). IL-4, IL-13, and IL-31 are not only proinflammatory mediators but are strong pruritogenic cytokines.

Atopic Dermatitis—Effect of Janus Kinase inhibitors in Itch Relief

The itch relief in AD patients on treatment with JAKis is dramatic and sustained until the end of study period in the published studies where the itch severity is documented by employing universally validated scoring systems. Rapid relief from pruritus was noted within days of instituting treatment. Earliest improvement was observed within 24 hours after intake of abrocitinib,[6] 1 week for 4 mg of baricitinib,[8] and 2 week after intake of 2 mg of baricitinib. Upadacitinib relieved itch within 2 days of the initial dose of treatment.[7] More than 4 points improvement in the Numerical Rating Scale (NRS) score [Peak Pruritus (PP)-NRS 4] was observed after 2 weeks of therapy with 30 mg upadacitinib per day and with

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BOX 1 T helper 2 (Th2)-mediated skin disorders.

- Atopic dermatitis
- Bullous pemphigoid
- Chronic pruritus of unknown origin (CPUO)
- Cutaneous helminth infestations
- Cutaneous T-cell lymphoma
- Insect bite reactions
- Prurigo nodularis
- Scabies

200 mg abrocitinib. Similar improvement was noted after 6 weeks of treatment with 4 mg of baricitinib. Overall upadacitinib 30 mg is ranked as the most efficacious medication for AD and is the most potent inhibitor JAK1 in cellular assays, which corresponds to the itch relief.[8,9]

In AD, abrocitinib[10,11] via its action on JAK1 and JAK2 can block the cytokines IL-31, TSLP via its inhibition of common gamma chain cytokines. Abrocitinib (200 mg) was found to be better in itch relief than dupilumab[12,13] due to inhibition of multiple cytokines which signal through JAK-STAT pathway. Notably, this superiority was not noted for 100 mg of abrocitinb[14] and has been explained by the less pronounced action of abrocitinib on JAK2 enzyme, which mediates signal transduction from IL-5.[15]

Similarly, 30 mg daily of upadacitinib achieved faster and superior itch control than dupilumab during 16 weeks of treatment in adults with moderate to severe AD[16] and was also superior to baricitinib and/or dupilumab.[17]

The other drugs that have been trialed in AD include baricitinib,[18] ruxolitinib (1.5%),[19] tofacitinib (1–3%),[20,21] while delgocitinib (a pan JAKi) has been used both in AD and hand eczema.[22]

While tofacitinib was developed to target JAK3, it also targets JAK1 and JAK2 and tends to work on multiple cytokines of the Th1, Th2, and Th17 family, even though it is the least potent inhibitor of interferon alpha signaling among all JAKis.[8] However, barring few case reports, published studies done on oral tofacitinib usage in AD are not available,[23,24] even though in real world settings the drug tends to work in moderate to severe AD (see Chapters 5 and 8).

Psoriasis—Itch Relief from Janus Kinase Inhibitors

Itch in psoriatic patients is attributed to the release of several mediators, such as neuropeptides, opioids, vascular endothelial growth factor, and some cytokines such as IL-2, IL-31, and IL-17A.[25] Nerve growth factor is known to upregulate the activity of transient receptor potential (TRP) channels. Oral tofacitinib 10 mg twice a day was shown to be noninferior to etanercept.[26] Also topical tofacitinib improved itch score by 4 weeks of routine use.[27] Tofacitinib gave relief from pruritus in both 10 and 20 mg daily doses. Deucravacitinib, a JAKi, which selectively inhibits pseudokinase domain of tyrosine kinase 2 (TYK2), has also been found to efficacious in psoriasis with a sustained improvement till 52 weeks. The itch control was significant for the skin and scalp lesions.[28]

Lichen Planus—Itch Relief from Janus Kinase Inhibitors

Itch in LP is not a well-studied subject. Several cytokines[29,30] released by multiple polarized T-cell subsets have been implicated including IL-31, IL-5, IL-10, IL-17, tumor necrosis factor

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alpha (TNF-α) in addition to mast cell-derived tryptase and serine protease produced by epidermis, which mediate pruritus through PARs type 2 in sensory neurons. Upregulation of TRPV1 channels has been reported in mucosal LP.[31]

Tofacitinib 10 mg/day has been found to give satisfactory results in few cases.[32] More studies are needed to explore the possibility of using topical and systemic JAKis to manage pruritus in LP patients.

Prurigo Nodularis

The itch in prurigo nodularis is mediated by Th2 signaling, resulting in high levels of expression of IL-31, IL-13, and IL-4. Other factors that are implicated include matrix metalloproteinases, insulin-like growth factors, periostin, neurotrophic factors, and CXCL2.[33,34] Upregulation of TRPV1 channels and a dysregulated Th17 axis also result in excessive expression of IL-23 and IL-17A.[33,35] In an open phase 2 trial a daily oral dose of 200 mg of abrocitinib decreased pruritus scores significantly in 80% of patients who were diagnosed with prurigo nodularis.[36] Recently, reports of sustained and dramatic reduction in lesions have been reported from India (see Chapters 8 and10).

Chronic Pruritus of Unknown Origin

Chronic pruritus of unknown origin (CPUO) is a distressing disorder, which is characterized by a lack of obvious skin changes with concomitant intense itching with a predominant finding of marked eosinophilia (> 4% or > 0.30 K/mm^3). Varied agents have been tried including antihistamines, mirtazapine [noradrenergic and specific serotonergic antidepressant (NaSSA)], and gabapentinoids (gabapentin and pregabalin) with no consistently effective treatment regimen. Published data has revealed that Th2 immune pathways and the associated cytokines (IL-4, IL-10, IL-13, and IL-33) mediate itching.[1,2] This is consistent with the concept of "immunosenescence" with loss of Th1 cell-driven protective immunity and skewing toward an allergic Th2 response.[3] Also, IL-4 receptor alpha (IL-4Rα) and JAK1 mediate sensory neuron activation, cause chronic itching (**Fig. 1**). A recent study administered tofacitinib 10 mg with a reduction in itching, which was sustained during the study duration. The rationale is that the signaling of major cytokines in CPUO is via JAK heterodimers (IL-4, JAK1/3; IL-13, JAK1/TYK2; IL-5, JAK1/2; and IL-31, JAK1/2), thus a drug that inhibits JAK1, 2, 3 seemed to be ideal for CPUO.[37]

SUMMARY

Immune responses in Th2 immunodermatoses (AD and LP) typically involve a complex interplay of multiple cytokines. JAKis target intracellular pathways shared by multiple cytokines. While JAKis do not continuously or completely inhibit cytokine signaling, they have shown impressive results in relieving itch associated with AD due to their impact on multiple cytokines. Selective JAKis are more effective and act faster than dupilumab in reducing itch severity due to AD. Topical JAKis provide itch relief within days of treatment initiation. Thus, JAK inhibition is emerging as a promising new therapeutic strategy to reduce pruritus in various skin disorders. Upcoming trials will provide more knowledge on the role of JAKis in the management of itch associated with psoriasis and LP.

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Kabir Sardana is a author of best-selling books on Dermatology on Amazon. He began writing on common diseases and then books for MBBS and MDs. His books are replete with images and artist-drawn diagrams that are made to simplify complex topics. He belongs to an Armed Forces family, settled in Dehradun and topped the UPSC interview for selection as an Assistant Professor in Dermatology after having done his medical school training at MAMC and LHMC, Delhi. He has worked in various academic posts at LHMC, CNBC, MAMC Delhi and is a recognized faculty of both Delhi University and IP University. He is the author of 300 papers with 70 original articles listed on PubMed and an H-index of 34. He presently heads the Department of Dermatology at RML hospital, New Delhi, India. His team at RMLH has been involved in original pioneering work in India on tissue cytokines, JAK, STAT, and immunological cells in varied disorders with a special interest on applied immunology which is the future of therapeutics in India.

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