JAK inhibitor: Introduction

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Abstract

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is a key regulatory signaling system for cellular proliferation, differentiation, and apoptosis. In addition, JAK signaling pathway plays critical roles in orchestrating immune response through its interactions with the cytokine receptors and the transcriptions factors. Several key cytokines use JAK-STAT signaling proteins to transduce intra-cellular signals which are involved in the pathogenesis of autoimmune and inflammatory diseases such as in psoriatic disease (psoriasis, psoriatic arthritis), atopic dermatitis, alopecia areata, vitiligo, rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, Sjogren's syndrome, and other autoimmune diseases. In recent years, understandings of the molecular mechanisms of JAK-STAT pathway in the inflammatory proliferative cascades of autoimmune diseases has led to the development of JAK inhibitors and has opened a new dimension for the treatment of systemic and cutaneous inflammatory diseases. In this symposium we have provided a broad perspective on the use of Janus kinase inhibitors in cutaneous autoimmune diseases.

Autoimmune diseases are associated with chronic, persistent inflammation of various organs because of an altered kinetic response of the immune system. In these immune-mediated inflammatory conditions cytokines or chemokines, the well-known mediators of inflammation play a critical role by activating the Janus kinase–signal transducers and activators of transcription cell signaling proteins (JAK–STAT). These signaling proteins are a group of intracellular kinase molecules. Cytokines regulate cellular functions and the cell signaling system through a variety of cell surface receptors. Cytokines along with their extracellular domains of the receptors induce conformational changes at the intracellular domain, which leads to activation that is phosphorylation of the intracellular kinase enzymes, which triggers the signal transduction events and leads to gene transcription. The Janus kinases (JAK) are a family of intracellular tyrosine kinases that regulate an inflammatory response because of their association with the signaling process of multiple cytokines.[1,2] The Janus kinase family is comprised of four members: JAK1, JAK2, JAK3 and TYK2.[1,2] JAK-1/2/3 and Tyk2 are recruited and activated by multiple cytokines as mentioned below, which influences several possible functions of T cells that are required for immune-mediated inflammatory diseases:

- IL-2: A growth factor for T cell, activates JAK-1, 2 and 3
- IL4: Promotes Th2 cell differentiation/proliferation, activates JAK-1,3
- IL-5: A regulatory cytokine associated with Th2-induced inflammation, activates JAK2
- IL9: A growth factor for T cells and also induce pannus formation, activates JAK-1,3
- IL-12: An inducing factor for Th1 differentiation, activates JAK2, TYK2
- IL-22: An inflammatory cytokine for psoriasis, PsA and AS, activates JAK 1, TYK2
- IL-23: An inducing factor for Th17 differentiation/growth and have a critical role in psoriatic disease, activates JAK2, TYK2
- IFN-γ: A Th1 pro-inflammatory cytokine, possible role in RA and psoriatic disease, activates JAK-1,2

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This is only a brief description of the Janus kinase family in respect to immune mediated dermatological diseases. IL-4 and IL-5, because of their regulatory role in Th2 cells, are important in atopic dermatitis.

With the broader understanding of Janus kinases on the potentiation of pro-inflammatory signals, a new field in clinical immunology has emerged to evaluate the role of Janus kinases in the pathogenesis of autoimmune diseases and its opportunities for its therapeutic application.[1–5] Janus kinase inhibitors (JAKi) have provided a new dimension for treatment of autoimmune diseases. Janus kinase Inhibitors are novel, orally active drugs developed to target various cytokines and growth factors which are involved in the pathogenesis of several immune-mediated diseases. In contrast to biologic disease-modifying anti-rheumatic drugs (bDMARDs), Janus kinase inhibitors are targeted to inhibit specific intracellular cell signaling molecules, making them targeted synthetic DMARDs (tsDMARDs). As most of the Janus kinase inhibitors are approved for the diseases managed by rheumatologists and dermatologists, it is essential for them,to have an updated knowledge about the functional significance of the Janus kinase–signal transducers and activators of transcription cell signaling proteins kinase cascades in cutaneous and systemic inflammatory diseases of autoimmune origin; and possible uses of topical and oral synthetic Janus kinase–signal transducers and activators inhibitors.[3–7] In addition to the first-generation Janus kinase inhibitors, several new-generation Janus kinase inhibitors are currently being evaluated with the goals to have higher potency and less adverse effects as compared to their predecessors.[3,4] The emergence of tsDMARDs represents a new phase in targeted therapy of immune-mediated diseases owing to the ability of these agents to simultaneously block multiple signaling pathways.

The upcoming series of articles highlights the origin, mechanism of action and role of these novel Janus kinase inhibitors in various immune-mediated diseases. The learning objectives are:

(i) To discuss the functional significance of the Janus kinase–signal transducers and activators cascades in the inflammatory-proliferative processes of autoimmune diseases and their cellular or molecular mechanisms
(ii) To discuss progress in development of oral synthetic Janus kinase inhibitors (JAKi) and their therapeutic efficacies in systemic and cutaneous autoimmune diseases.
(iii) To discuss the risks, benefits and the adverse effects of Janus kinase inhibitors

To achieve these objectives, in this issue the first article "JAK-STAT inhibitors in Immune mediated diseases—An Overview" provides (i) a general update on Janus kinase–signal transducers and activators kinase signaling system, (ii) principles and logistics of Janus kinase inhibition and Janus kinase inhibitors (iii) a summarised section about the risks, benefits and adverse effects of Janus kinase inhibitors. We also have another article focused on the scope and practice of Janus kinase inhibitors in dermatologic diseases. Subsequent articles are on the following diseases which are often co-managed by dermatologists: atopic dermatitis, alopecia areata, psoriatic arthritis and spondyloarthritis. Each section of this article has detailed information about the use of Janus kinase inhibitors in these conditions, results of the drug trials and risks / benefits of the specific Janus kinase inhibitors used for these conditions.

Take home message: Therapeutic efficacy of Janus kinase inhibitors is now well established in the treatment of an array of autoimmune and inflammatory diseases. The USFDA has approved several Janus kinase inhibitors for the following inflammatory diseases: atopic dermatitis, psoriasis, alopecia areata, psoriatic arthritis (PsA), ankylosing spondylitis, rheumatoid arthritis and inflammatory bowel disease. In addition, trials are going on with enthusiasm in conditions such as vitiligo, lupus, hidradenitis suppurativa and many others. Treatment of autoimmune inflammatory disease is constantly evolving as more molecular targets are identified. Oral route of administration, rapid onset of action and efficacy of Janus kinase inhibitors in bDMARD non-responders definitely represent progress and provide new hope for management of severe and unresponsive patients suffering from these diseases. It is obvious that Janus kinase inhibitors like other medications have certain limitations with respect to adverse effects, and as these medicines are relatively new in our practice they need to be used appropriately and judiciously as per the guidelines discussed. Janus kinase inhibitors have brought another paradigm shift in respect to therapy for autoimmune diseases. In the coming 10 years, this new field of knowledge is going to unfold and hopefully lead to broader use of Janus kinase inhibitors in an array of autoimmune and inflammatory diseases.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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