Editorial

JAK Inhibitors: Exploring a new era in Dermatology

The spectrum of diseases nomenclature in dermatology are expanding very fast and newer treatment options are emerging and thus putting dermatologists in dilemmas especially in choosing an appropriate treatment option. While for a long period the morphology of diseased skin was prominent for disease classification and therapeutic procedures, now the advanced tools are available for deeper analysis of molecular processes and immunological pattern analysis responsible for the pathophysiological alterations. These advances changed our therapeutic vision in dermatology remarkably. It seems that dermatology is going to be dominated by novel targeted therapeutics. The scope of use for Janus kinase inhibitors, also known as (jakinibs) in dermatology is constantly evolving and expanding. JAK inhibitors are a type of medication that functions by inhibiting the activity of one or more of the Janus kinase family of enzymes (JAK1, JAK2, JAK3, TYK2), thereby interfering with the JAK-STAT signaling pathway. The Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathwayis utilized by cytokines including interleukins, interferon (IFNs), and other molecules totransmit signals from the cell membrane to the nucleus.[1]

Their mechanism of action reveals that cytokines play key roles in controlling cell growth and the immune response. Many cytokines function by binding to and activating type I and type IIcytokine receptors. These receptors in turn rely on the Janus kinase family of enzymes for signal transduction. Thus, Janus kinases block cytokine signaling. In sporadic autoimmune and auto inflammatory conditions, a variety of disease-causing cytokines rely on JAK-STAT signaling in order to elicit their pathogenic effect. Together these observations have led to the development of JAK inhibitors for the treatment of human disease.These inhibitors have therapeutic applications in the treatment of cancer and inflammatory diseases. These agents have revolutionized treatments for a heterogeneous group of disorders, such as myeloproliferative neoplasms, inflammatory bowel disease, and multiple immune-driven dermatological diseases.[2]

To date, JAK inhibitors have shown efficacy in the treatment of dermatologic conditions such as atopic dermatitis (AD), alopecia areata (AA), psoriasis, and vitiligo, among others. Both new oral and topical JAK inhibitors are being developed and studied. Smaller case series and case reports suggest that the usefulness of JAK inhibitors may be even broader than these early clinical studies suggest.[2]

In atopic dermatitis, experimental studies have proven the efficacy of tofacitinib and oclacitinib in inhibiting the IL-4 and IL-13 dependent Th2 differentiation which seems to be the main pathogenesis involved in AD. Both topical and oral tofacitinib were proven to be effective in improving the skin barrier.[1,2] The pathogenesis of alopecia areata (AA) involves hair follicle attack by aut-reactive CD8 T cells. In AA,JAK-STAT dependent cytokines including IFN-γ and IL-15 drive proliferation andactivation of auto-reactive T cells, suggesting that JAK inhibition might be an effectivetreatment. Both systemic and topical JAK inhibitors (tofacitinib and ruxolitinib) promoted hair regrowth in multiple open-label clinical trial and case reports. Tofacitinib causes hair regrowth in 64% of patients of AA, alopecia universalis (AU) and alopecia totalis (AT) with >50% improvement in SALT score in 32%-58% cases in only 3 months of therapy.[3] Baricitinib demonstrated an average of 80% hair regrowth within 36 weeks and only JAK inhibitor which got FDA approvalfor AA.[4] Topical and oral ruxolitinib is also widely studied and found to be effective. However, hair growth durability following discontinuation of treatment is a concern for AA.

To date, in dermatology, psoriasis has been the most heavily studied indication for JAK inhibitors. JAK-STAT-dependent cytokines IL-12 and IL-23 are fundamental mediators of psoriasis. Tofacitinib is the most widely studied and only JAK inhibitors that completed phase III psoriasis clinical programme. It is suggested that the PASI 75 response to tofacitinib at 12 weeks is 40% and 64% in the 5mg twice daily and 10mg twice daily groups, respectively. The FDA is yet to approve tofacitinib for psoriasis. Currently, oral tofacitinib is approved by FDA for the treatment of psoriatic arthritis (PsA), RA, and ulcerative colitis.

Baricitinib has proven efficacious in moderate to severe plaque psoriasis in clinical trials. The Topical ruxolitinib formulation showed promising results in multiple trials. Selective JAK1, JAK3 and TYK2 Inhibitors are being studied in multiple trials for psoriasis; however, their clinical development in psoriasis has been abandoned, mostly due to their efficacy-safety ratio.[5-6] Vitiligo is mediated by targeted destruction of melanocytes by CD8 T cells, with IFN-γplaying a central role in disease pathogenesis. IFN-γ signaling utilizes the JAK-STAT pathway, and therefore vitiligo may be susceptible to treatment with JAK inhibitors.Treatment of patients with generalized vitiligo with tofacitinib resulted in nearcomplete regimentation of affected areas of the face, forearms, and hands over 5 months;however, depigmentation recurred after discontinuing tofacitinib. Ruxolitinib for 20 weeks demonstrated significant facial repigmentation.[1,7] While not commercially available, the use of topical JAK inhibitors has been explored inAD, psoriasis, AA, and vitiligo. JAK inhibitors have shown promise in multiple other dermatologic diseases including dermatomyositis, chronic actinic dermatitis, erythema multiforme, hypereosinophilic syndrome, hidradenitissuppurativa,cutaneous graft-versus-host disease, lichen planus and lupus.[1,2,7] Not only in dermatology, in COVID-19 cases, a number of case-control or observational studies with baricitinib have also been reported that the addition of baricitinib as to standard-of-care therapy has been associated with improvement in clinical signs and symptoms, respiratory functions and mortality.[8]

JAK inhibitors have been established to be efficacious including in circumstances in which biologics have failed and with a few exceptions they also appear to be as safe as biologics. Like biologics, a common side-effect of jakinibs is infections, including serious and opportunistic infections and immunosuppression. The rate of infections is similar to biologics with the exception of herpes zoster, which is more common with jakinibs; therefore, when possible, immunizations should be performed prior to initiating therapy. Therapy is also associated with elevated cholesterol. Their possible involvement in increasing the risk of cardiovascular disease, venous thromboembolic event (VTE) and malignancy is raised and FDA has given a black box warning. However, the mechanism for the reported adverse events is not understood properly and it is currently not known whether JAK specificity alters the safety profile. Therefore, these side effects lack supporting evidence.[9-10]

In Bangladesh, JAK inhibitors have been predominantly used in rheumatological diseases. However, over the last few years, they are being practised in dermatological diseases and are found to be effective, particularly in alopecia areata and vitiligo. Its use in psoriasis is not still widely prasticed. More clinical trials need to be conducted on JAK inhibitors' efficacy in this part of the world. It will help clinicians to identify the potential advantages and disadvantages of jakinibs and quantify the risk-benefit ratio in terms of cost-effectiveness. As we have done in the past and will do in the future, the optimal treatment strategy will have to be tailored based on individual patient risk factors and preferences in a shared-decision making process. We hope, JAK inhibitors will be more utilized in dermatology and other disciplines which have the potential to drastically change the therapeutic landscape for inflammatory dermatoses and hold immense promise for patients and dermatologists in near future.

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