

JAK Inhibitors (Topical)

Janus kinase (JAK) inhibitors represent a class of disease-modifying antirheumatic drugs (DMARDs) that modulate the immune system by interfering with specific signaling pathways. These drugs, originally approved for conditions such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA), have expanded to include new indications for skin conditions. Since 2022, the U.S. Food and Drug Administration (FDA) has approved JAK inhibitors for treating atopic dermatitis, alopecia areata, and vitiligo, further broadening their therapeutic potential.

Mechanism of Action

JAK inhibitors are small molecule drugs that target and block the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, a critical signaling mechanism involved in the regulation of immune responses and inflammation. Cytokines, which are immune system proteins, typically bind to receptors that activate JAK enzymes, leading to the phosphorylation of STAT proteins. This cascade ultimately promotes gene expression and the activation of inflammatory processes. By inhibiting JAK enzymes, JAK inhibitors block this cascade, thus reducing the production of pro-inflammatory cytokines and alleviating immune-mediated tissue damage. This mechanism helps control chronic inflammation in various autoimmune and inflammatory diseases.

Clinical Applications

JAK inhibitors can be administered topically or orally. Topical JAK inhibitors, in particular, provide a localized treatment option for skin conditions, offering rapid relief of symptoms such as itching and inflammation. These drugs are especially useful for treating conditions where skin involvement is significant, and they minimize the systemic effects typically seen with oral medications.

- **Atopic Dermatitis:** Topical JAK inhibitors such as *Ruxolitinib* (Opzelura) have been approved for the treatment of mild to moderate atopic dermatitis, providing a targeted approach to control inflammation and pruritus. Studies have demonstrated that topical JAK inhibitors are effective in improving symptoms with minimal systemic absorption.
- **Vitiligo:** *Ruxolitinib* has also been approved for the topical treatment of non-segmental vitiligo, a disorder characterized by depigmented skin patches. By inhibiting the JAK-STAT pathway, ruxolitinib has been shown to promote repigmentation in patients with this condition, offering a promising therapeutic option for this challenging dermatological disorder.

- **Chronic Hand Dermatitis:** In Japan, *Delgocitinib* (Corectim) has been approved for the treatment of chronic hand dermatitis, offering an effective solution for patients with persistent dermatitis affecting the hands. This approval further highlights the role of topical JAK inhibitors in managing chronic inflammatory conditions.

Approved Topical JAK Inhibitors and Their Indications

Disease	Approved Topical JAK Inhibitors
Atopic Dermatitis	<i>Ruxolitinib, Delgocitinib</i>
Vitiligo	<i>Ruxolitinib</i>
Chronic Hand Dermatitis	<i>Delgocitinib</i>

Side Effects and Safety Profile

Topical JAK inhibitors have a generally favorable safety profile, primarily due to their localized action. Unlike systemic JAK inhibitors, which can impact multiple cytokine signaling pathways throughout the body, topical formulations are designed to minimize systemic absorption, thereby reducing the risk of widespread immune suppression and systemic side effects. However, excessive use of topical treatments can lead to increased absorption, potentially resulting in adverse effects.

- **Local Reactions:** Common side effects associated with topical JAK inhibitors include local reactions at the application site. These may include burning, itching, and irritation. In some cases, infection at the application site has been reported, though this is less common compared to systemic therapies.
- **Systemic Effects:** Systemic side effects are rare when topical JAK inhibitors are used correctly. However, if used excessively or on large body surfaces, there may be an increased risk of systemic absorption. This could lead to side effects such as an increased susceptibility to infections, which is a concern associated with systemic JAK inhibitors. Therefore, proper application is crucial to minimizing these risks.

Common Adverse Effects

- **Local Reactions:** Burning, itching, or irritation at the site of application.
- **Systemic Risks:** Rare systemic effects, particularly with excessive application, include infections or an increased risk of immune suppression.

Conclusion

Topical JAK inhibitors represent an important advancement in the management of various dermatologic and inflammatory conditions, such as atopic dermatitis, vitiligo, and chronic hand dermatitis. These drugs provide a targeted treatment approach, allowing for the direct application of medication to the affected areas while minimizing the risk of systemic side effects. As the understanding of JAK inhibitors continues to evolve, these treatments are expected to play a growing role in managing immune-mediated diseases with significant skin involvement.

References

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