OASIS DERMATOLOGY GROUP

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JAK Inhibitors (Oral)

Janus kinase (JAK) inhibitors are a class of disease-modifying antirheumatic drugs (DMARDs) that have transformed the treatment landscape for a variety of immune-mediated conditions. Originally approved for conditions such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA), JAK inhibitors have expanded to treat other diseases, including atopic dermatitis, alopecia areata, and vitiligo.

Mechanism of Action

JAK inhibitors exert their therapeutic effects by disrupting the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. This pathway is activated by cytokines, which are proteins that regulate immune system functions, including inflammation. By inhibiting JAK enzymes, these drugs block the downstream activation of STAT proteins, thereby reducing the production of pro-inflammatory cytokines and immune responses. This mechanism is akin to turning off a valve to stop the flow of water in a pipe, thus reducing the inflammatory cascade that contributes to various autoimmune and inflammatory disorders.

Clinical Uses

JAK inhibitors have proven effective in treating a range of immune-mediated diseases, especially those involving chronic inflammation.

- ***Rheumatoid Arthritis (RA)***: The initial approval of JAK inhibitors was for the treatment of RA. Drugs like *Xeljanz* (tofacitinib) and *Olumiant* (baricitinib) are now commonly used when traditional DMARDs are insufficient, offering rapid symptom relief and disease modification.
- ***Psoriatic Arthritis (PsA)***: Similar to RA, JAK inhibitors such as *Xeljanz* and *Rinvoq* (upadacitinib) are approved for PsA, providing relief for joint pain and skin lesions associated with the disease.
- ***Atopic Dermatitis***: In 2022, the U.S. Food and Drug Administration (FDA) approved the use of JAK inhibitors for the treatment of moderate to severe atopic dermatitis, with drugs such as *Cibinqo* (abrocitinib) and *Rinvoq* showing efficacy in reducing inflammation and pruritus.
- ***Alopecia Areata***: The FDA also approved *Olumiant* (baricitinib) for the treatment of alopecia areata, a condition that causes patchy hair loss. Studies have demonstrated significant hair regrowth in patients treated with JAK inhibitors, making them a promising option for individuals with this autoimmune disease.
- ***Vitiligo***: The role of JAK inhibitors in the treatment of vitiligo, a condition characterized by depigmentation of the skin, is also gaining attention. *Jakafi* (ruxolitinib) has shown promise

in repigmenting skin in clinical trials, offering a potential treatment for this dermatologic disorder.

- ***Other Conditions***: In addition to the aforementioned indications, JAK inhibitors are also FDA-approved for conditions like myelofibrosis, polycythemia vera, and certain forms of inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease.

Common JAK Inhibitors and Their Indications:

- ***Xeljanz (Tofacitinib):*** Approved for RA, PsA, polyarticular juvenile idiopathic arthritis, and ulcerative colitis; under investigation for atopic dermatitis and vitiligo.
- ***Olumiant (Baricitinib)***: Approved for RA, moderate to severe alopecia areata, and severe COVID-19 requiring respiratory support.
- ***Rinvoq (Upadacitinib) and Cibinqo (Abrocitinib):*** Approved for atopic dermatitis; Rinvoq also approved for PsA, IBD, and ankylosing spondylitis.
- ***Jakafi (Ruxolitinib):*** Approved for myelofibrosis, polycythemia vera, and vitiligo.

Contraindications and Safety Considerations

JAK inhibitors are contraindicated in patients who have severe liver disease, as their metabolism may be impaired, leading to elevated drug levels. Furthermore, because JAK inhibitors suppress the immune system, they are not recommended for concurrent use with other biologic agents or immunosuppressants, as this could increase the risk of serious infections. They are also contraindicated during pregnancy and breastfeeding due to potential fetal harm and excretion in breast milk.

Adverse Effects

The broad immunosuppressive effects of JAK inhibitors result in several potential adverse effects. The most concerning are the increased risks of serious infections, including bacterial, viral (e.g., herpes zoster), fungal, and mycobacterial infections. Screening for tuberculosis (TB) is recommended before initiating treatment. Other common adverse effects include:

- *Infections*: Nasopharyngitis, upper respiratory infections, urinary tract infections.
- *Gastrointestinal*: Nausea, diarrhea.
- *Neurological*: Headache.
- *Hematological*: Cytopenias (e.g., anemia, neutropenia), especially with selective JAK inhibitors.
- *Metabolic*: Hyperlipidemia, particularly with long-term use.
- *Cardiovascular*: Increased risk of serious cardiac events and venous thromboembolism (VTE).
- *Oncological*: Potential association with malignancies, although the causal relationship remains unclear.
- *Dermatological*: Rapid relapse of dermatologic conditions after discontinuation, particularly for those used in conditions like atopic dermatitis or alopecia areata.

Conclusion

JAK inhibitors represent a groundbreaking class of medications that have revolutionized the treatment of autoimmune and inflammatory diseases. Their ability to target specific immune pathways offers significant therapeutic benefits, especially in diseases like rheumatoid arthritis, psoriatic arthritis, and atopic dermatitis. However, their broad immunosuppressive effects necessitate careful monitoring for infections and other serious side effects. Ongoing research continues to explore additional indications, such as vitiligo and alopecia areata, underscoring the expanding role of JAK inhibitors in modern medicine.

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