JAK INHIBITORS (ORAL)

http://www.aocd.org

Janus kinase (JAK) inhibitors are a class of disease-modifying antirheumatic drugs (DMARDs) that modulate the immune system by targeting specific signaling pathways. Initially approved for conditions like rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, their use has expanded. In 2022, the FDA approved JAK inhibitors for treating atopic dermatitis, alopecia areata, and vitiligo.

Mechanism of Action

JAK inhibitors are small molecules that disrupt the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathways. These pathways are crucial for transmitting signals from cytokines, proteins that play a key role in the immune response. By blocking JAK-STAT signaling, JAK inhibitors effectively reduce inflammation and immune-mediated damage, much like shutting off a valve to control water flow in a hose.

Uses

Due to their small molecular size, JAK inhibitors can be administered both topically and orally, in contrast to biologic agents that require injection. They offer rapid relief of symptoms such as itching and inflammation in various conditions.

Common JAK Inhibitors and Their Uses:

- **Xeljaz (tofacitinib):**
  - Initially approved for rheumatoid arthritis in 2012, and later for psoriatic arthritis, ulcerative colitis, polyarticular juvenile idiopathic arthritis, and active ankylosing spondylitis.
  - Off-label uses include treatment of psoriasis.
  - Under investigation for atopic dermatitis and vitiligo.
- **Olumiant (baricitinib):**
  - Approved for moderate to severely active rheumatoid arthritis when DMARDs are ineffective.
  - Also approved for hospitalized adults with COVID-19 requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
  - Also, Alopecia Areata in adults 18 years and older
- **Rinvoq (upadacitinib) and Cibinqo (abrocitinib):**
  - Approved in 2022 for the treatment of moderate to severe atopic dermatitis in adults and children over 12.
  - Also approved for moderate to severely active inflammatory bowel disease, particularly in cases unresponsive to anti-TNF drugs.

FDA Approved Oral JAK Inhibitors by Disease

Disease	Approved Oral JAK Inhibitors
Acute or Chronic Graft vs Host Disease	Jakafi (ruxolitinib)
Alopecia Areata	Litfulo (ritlecitinib) Olumiant (baricitinib)
Ankylosing Spondylitis	Rinvoq (upadacitinib) Xeljanz (tofacitinib)
Atopic Dermatitis	Cibinqo (abrocitinib) Jakafi (ruxolitinib) Rinvoq (upadacitinib)

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Crohn's Disease	Rinvoq (upadacitinib)
Myelofibrosis	Inrebic (fedratinib) Jakafi (ruxolitinib) Ojjaara (momelotinib) Vonjo (pacritinib)
Non-Radiographic Axial Spondyloarthritis	Rinvoq (upadacitinib)
Plaque Psoriasis	Sotyktu (deucravacitinib)
Polyarticular Course Juvenile Idiopathic Arthritis	Xeljanz (tofacitinib)
Polycythemia Vera	Jakafi (ruxolitinib)
Psoriatic Arthritis	Rinvoq (upadacitinib) Xeljanz (tofacitinib)
Rheumatoid Arthritis	Olumiant (baricitinib) Rinvoq (upadacitinib) Xeljanz (tofacitinib)
Severe COVID-19 in hospitalized adults required breathing support	Olumiant (baricitinib)
Ulcerative Colitis	Rinvoq (upadacitinib) Xeljanz (tofacitinib)
Vitiligo	Jakafi (ruxolitinib)

Contraindications

JAK inhibitors should not be used concurrently with other biologic or immunosuppressive agents due to the risk of excessive immunosuppression. They are contraindicated in patients with severe liver disease. Because JAK inhibitors cross the placenta and are excreted in breast milk, they should be avoided during pregnancy and breastfeeding.

Side Effects

JAK inhibitors can interfere with the signal transduction of multiple cytokine receptors, leading to broad alterations in immune responses. This non-selective targeting increases the risk of serious infections, including bacterial, fungal, mycobacterial, and viral infections. For this reason, screening for tuberculosis (TB) is recommended before starting treatment. Reactivation of herpes viruses is also common, making zoster vaccination advisable prior to initiating therapy.

Common Adverse Effects:

- Infections: Nasopharyngitis, upper respiratory infections, urinary tract infections.
- Gastrointestinal: Nausea, diarrhea.
- Neurological: Headache.
- Hematological: Cytopenias, particularly with selective JAK inhibitors.
- Metabolic: Hyperlipidemia, especially with long-term use.
- Cardiovascular: Increased risk of serious cardiac events and venous thromboembolism (blood clots).
- Oncological: Potential association with malignancy, though this is not fully understood.
- Dermatological: Rapid relapse of dermatologic disease after discontinuation of a JAK inhibitor is common.

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