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Adverse Reactions and Management Principles of JAK Inhibitors in Rheumatoid Arthritis

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Abstract: ***Janus kinase (JAK) inhibitors act on JAK/STAT signaling and thereby reduce cytokine-driven inflammation and disease activity in rheumatoid arthritis (RA). Their wider use has also brought greater attention to safety issues, notably infection, hematologic abnormalities, cardiovascular events, malignancy, and gastrointestinal reactions. This review describes their mechanisms and clinical use, summarizes common adverse reactions, and discusses management through pretreatment risk evaluation, clinical and laboratory follow-up, dose modification, and targeted intervention. It is intended to inform a safer and more individualized use of JAK inhibitors in RA.***

Keywords: Janus kinase inhibitors, Rheumatoid arthritis, Adverse reactions, Safety, Risk management**.**

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that can cause marked pain and loss of function. Janus kinase (JAK) inhibitors have become an important targeted option for RA and have shown favorable efficacy in recent years. At the same time, treatment may be complicated by infection, hematologic abnormalities, cardiovascular events, and other adverse reactions. Familiarity with these problems and their management is therefore important to patient safety and treatment effectiveness. This article provides a systematic overview of adverse reactions reported during JAK inhibitor therapy in RA and the corresponding management principles, with the aim of supporting clinical use and a balanced assessment of benefit and risk.

2. Mechanisms of Action of JAK Inhibitors in Rheumatoid Arthritis

Janus kinases (JAKs) are non-receptor tyrosine kinases located on the intracellular side of cytokine receptors, where they relay receptor-mediated signals. The family consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Signaling through the JAK–STAT pathway contributes to cell proliferation, differentiation, apoptosis, and other fundamental biological processes, and dysregulation of this pathway is associated with many immune-mediated and inflammatory diseases [1–2]. JAK inhibitors bind selectively to the ATP-binding sites of these kinases, reducing JAK/STAT signaling, abnormal inflammatory activity, and excessive immune activation, with a consequent decrease in pro-inflammatory cytokine production. In RA, their effects can be considered in the following aspects.

2.1 Blockade of Cytokine Production and Signal Transduction

JAK inhibitors occupy the ATP-binding sites of JAKs and thereby reduce kinase activity and JAK–STAT pathway activation. As a result, the production of tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-17 (IL-17), and other pro-inflammatory cytokines is limited, together with downstream signal transmission, which helps relieve joint inflammation [3].

2.2 Inhibition of Aberrant Immune Cell Activation and Differentiation

The JAK/STAT pathway, with STAT3 as a key component, is required for Th17-cell differentiation and induction of retinoic acid receptor-related orphan receptor γt (RORγt). Its inhibition restrains abnormal Th17 differentiation and lowers IL-17 secretion, reducing the pro-inflammatory and bone-destructive activity attributed to these cells in RA [4]. Effects on this pathway may also alter the activation of other immune-cell populations and, in turn, help correct immune imbalance.

2.3 Inhibition of Synovial Hyperplasia and Promotion of Apoptosis

Within the rheumatoid synovium, cytokines such as IL-6 stimulate synovial cells through JAK/STAT signaling and promote both proliferation and inflammation. Blocking this signaling suppresses synovial-cell activation and removes part of its anti-apoptotic support, allowing pathologically expanded synovial cells to undergo apoptosis. The resulting reduction in invasive synovial growth may slow structural joint damage [5].

2.4 Reduction in the Activity of Joint-Destructive Enzymes

TNF-α and IL-17 act synergistically to raise matrix metalloproteinase (MMP) levels, which accelerates the breakdown of cartilage and bone. JAK inhibition reduces the production and combined action of these cytokines; MMP activity is consequently lowered, and injury to synovial cells, chondrocytes, and bone tissue is reduced, contributing to protection of the joint [3].

3. Clinical Application of JAK Inhibitors in the Treatment of RA

Five JAK inhibitors are currently approved for the clinical treatment of RA: tofacitinib, baricitinib, upadacitinib,

peficitinib, and filgotinib. Of these, filgotinib has not been approved for RA in China.

3.1 Tofacitinib

Tofacitinib is a pan-JAK inhibitor that blocks JAK1, JAK2, and JAK3, with weaker activity against TYK2. In 2012, it became the first JAK inhibitor approved by the US Food and Drug Administration (FDA), and approval in China followed in 2017. It is used in patients with RA who respond inadequately to or cannot tolerate methotrexate (MTX), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), or biologic agents such as tumor necrosis factor (TNF) inhibitors [1]. In the prospective study by Haraoui et al. [6], 504 patients with RA were followed for up to 3 years during tofacitinib treatment, with improvements in the Clinical Disease Activity Index (CDAI) and several other measures of disease activity. Its efficacy and safety have also been evaluated across multiple clinical studies.

3.2 Baricitinib

Baricitinib is a selective, reversible inhibitor of JAK1 and JAK2, although it also has some inhibitory activity against JAK3 and TYK2. The drug was first approved in Japan, followed by the European Union in 2017 and China in 2019. It is indicated for adults with moderately to severely active RA who have responded inadequately to or cannot tolerate one or more disease-modifying antirheumatic drugs (DMARDs). Caporali et al. [7] reported that 2- and 4-mg doses of baricitinib were effective in achieving and maintaining low disease activity, defined as a Simplified Disease Activity Index (SDAI) score of ≤11, for as long as 6.5 years, with generally good tolerability.

3.3 Upadacitinib

Upadacitinib is a newer, highly selective JAK inhibitor with preferential activity against JAK1 rather than JAK2, JAK3, or TYK2. The US FDA approved the drug in August 2019, and it received approval in China in February 2022. It is indicated for adults with moderately to severely active RA who have had an inadequate response to or are intolerant of one or more TNF inhibitors. Clinical studies have reported remission rates of up to 90% after 6 months of treatment, with improved physical functioning in more than 70% of patients [8].

3.4 Peficitinib

Peficitinib is a pan-JAK inhibitor active against JAK1, JAK2, JAK3, and TYK2, with relatively greater selectivity for JAK3. It was approved in Japan in March 2019 and in China in August 2024 for RA. The drug is indicated for patients with moderately to severely active RA who have responded inadequately to conventional disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX). Clinical studies have shown sustained efficacy for up to 6 years and good tolerability among Asian patients with RA [9]. At doses of 100 or 150 mg once daily, peficitinib has produced efficacy outcomes comparable or superior to those of tofacitinib 5 mg twice daily and baricitinib 2 or 4 mg once daily [10].

3.5 Filgotinib

Filgotinib is a highly selective JAK inhibitor that primarily targets JAK1. It was first approved in the European Union and Japan in September 2020 but remains unapproved in China. The drug is indicated for patients with moderately to severely active RA who have responded inadequately to conventional treatment, including therapy intended to prevent structural joint damage. In patients with active RA, Kavanaugh et al. [11] found that filgotinib at 100 or 200 mg once daily was effective and well tolerated both as monotherapy and in combination with other treatment.

3.6 Other JAK Inhibitors

JAK inhibitors still being investigated for RA include SHR0302 (Ivarmactinib), LNK01001, WXFL10203614, KL130008, CS12192, and TLL-018 (Table 1). By contrast, development of decernotinib, AC430, R348, CT1578 (SB1578/ONX0805), and itacitinib in RA has been discontinued because of adverse reactions or changes in development strategy.

Table 1: JAK inhibitors currently under clinical investigation for the treatment of RA

Drug	Company	Target	Indications	Development stage
SHR0302 (Ivarmactinib)	Ruishi Biopharmaceutical Co., Ltd./ Jiangsu Hengrui Pharmaceuticals Co., Ltd.	JAK1	Alopecia areata; rheumatoid arthritis; ankylosing spondylitis; atopic dermatitis; axial spondyloarthritis; ulcerative colitis; psoriatic arthritis; and mild, moderate, or severe atopic dermatitis	Marketing application submitted
LNK01001 (Zemprocitinib)	Lynk Pharmaceuticals (Hangzhou) Co., Ltd.	JAK1	Moderate atopic dermatitis; ankylosing spondylitis; and rheumatoid arthritis	Phase III
WXFL10203614	Wuxi Fuxin Pharmaceutical Research and Development Co., Ltd.	JAK1	Rheumatoid arthritis; atopic dermatitis; and moderately to severely active ulcerative colitis	Phase III
KL130008	Kelun Biotech Biopharmaceutical Co., Ltd.	JAK1/JAK2	Alopecia areata and rheumatoid arthritis	Phase II
CS12192	Shenzhen Chipscreen Biosciences Co., Ltd.	JAK1/JAK3	Alopecia areata; atopic dermatitis; inflammatory bowel disease; multiple sclerosis; rheumatoid arthritis; and systemic lupus erythematosus	Phase I
TLL-018 (Girocitinib)	Hangzhou Highlightll Pharmaceutical Co., Ltd.	JAK1/TYK2	Chronic urticaria; rheumatoid arthritis; plaque psoriasis; psoriasis; atopic dermatitis; and systemic lupus erythematosus	Phase III

4. Common Adverse Reactions and Events Associated with JAK Inhibitors

4.1 Risk of Infection

JAK inhibitor treatment is associated with a greater risk of infection, particularly in patients who are also receiving immunosuppressive therapy. Bacterial infections are reported most often, while viral infections—especially herpes zoster and herpes simplex virus infection—also occur more frequently than in control groups. Patients with RA have been reported to face a 1.5- to 2-fold higher risk of herpes zoster than the general population [12]. Clinicians should therefore remain alert to infection during JAK inhibitor therapy and, where appropriate, consider preventive measures such as varicella-zoster vaccination.

4.2 Hematologic Abnormalities

Leukopenia is among the more common hematologic adverse reactions and may further increase susceptibility to infection. White blood cell counts should therefore be monitored closely during treatment, with adjustment of therapy when needed. Neutropenia has been reported with all JAK inhibitors [18], whereas thrombocytopenia has been observed with all agents except baricitinib [13]. Platelet counts should consequently be checked at regular intervals, and management should be tailored to the patient's clinical status.

4.3 Cardiovascular Events

JAK inhibitor therapy has also been linked to cardiovascular events. In trials with at least 1 year of follow-up, Maqsood et al. reported a significantly higher risk of venous thromboembolism with JAK inhibitors than with placebo or approved biologic or targeted comparators [14]. Despite their clinical efficacy, these potential cardiovascular risks require careful attention. Risk factors should be assessed before treatment, followed by a comprehensive cardiovascular evaluation and appropriate preventive measures.

4.4 Malignancy

Compared with the general population, patients with RA have a higher baseline risk of malignancy. A 2022 analysis of the World Health Organization pharmacovigilance database detected disproportionality signals linking tofacitinib and baricitinib with melanoma and non-melanoma skin cancer (NMSC), suggesting a possible increase in skin cancer risk during JAK inhibitor use [15–16]. In the ORAL Surveillance study, malignancy occurred at approximately twice the rate among patients receiving tofacitinib compared with those receiving TNF inhibitors. Lung cancer was the most common malignancy, particularly in patients older than 65 years who had a history of smoking or pulmonary disease [17]. Accordingly, clinicians should explain the possible malignancy risk before treatment and consider further measures when clinically warranted.

4.5 Gastrointestinal Reactions

Nausea, diarrhea, abdominal pain, and other gastrointestinal reactions may occur during JAK inhibitor therapy. In nine randomized controlled trials (RCTs), gastrointestinal perforation was reported at an incidence of 0.04 per 100 patient-years [18]. Attention to new gastrointestinal symptoms during follow-up is therefore needed to allow early recognition and treatment of relevant adverse events.

4.6 Other Adverse Reactions

Adverse reactions have also been reported in the hepatobiliary and nervous systems, as well as in the skin and subcutaneous tissues [19]. Table 2 summarizes the adverse reactions described for the five JAK inhibitors.

Table 2: Adverse reactions associated with five JAK inhibitors

Drug	Infections	Hematologic abnormalities	Cardiovascular events	Malignancies	Gastrointestinal reactions	Other adverse reactions
Tofacitinib	Herpes zoster; pulmonary tuberculosis; urinary tract infection	Leukopenia; anemia; lymphopenia; thrombocytopenia	VTE; MACE; hypertension	Breast cancer; hepatocellular carcinoma; thyroid cancer; lung cancer	Diarrhea; abdominal pain; vomiting; gastritis; nausea; dyspepsia; gastrointestinal perforation	Dehydration; peripheral edema; hypokalemia; dyslipidemia; abnormal blood glucose; musculoskeletal pain; arthralgia; tendinitis; joint swelling; hepatic steatosis; abnormal liver function; headache; dizziness; paresthesia; insomnia; disorientation; rash; erythema
Baricitinib	Herpes zoster; oral herpes; urinary tract infection	Anemia; thrombocytosis; lymphopenia	VTE; MACE; hypertension	Lung cancer; lymphoma	Nausea; vomiting; abdominal pain; diarrhea; gastrointestinal perforation	Serious infection; hypersensitivity reactions; dyslipidemia; dehydration; elevated blood glucose; musculoskeletal pain; arthralgia; tendinitis; joint swelling; arthritis; elevated liver enzymes; hepatic steatosis; headache; dizziness; cerebral infarction; facial paralysis; rash; acne
Upadacitinib	Herpes zoster; pneumonia; urinary tract infection; sepsis; sinusitis	Anemia; neutropenia; lymphopenia; thrombocytopenia	VTE; MACE; hypertension; arrhythmia; angina pectoris; atrial fibrillation	Non-melanoma skin cancer; basal cell carcinoma; melanoma	Nausea; vomiting; diarrhea; abdominal pain; gastrointestinal perforation	Hypersensitivity reactions; weight gain; serious infection; dyslipidemia; elevated blood glucose; myalgia; arthralgia; increased fracture risk; elevated liver enzymes; cholecystitis; liver injury; hepatitis; headache; dizziness; paresthesia; depression; peripheral neuropathy; acne
Peficitinib	Nasopharyngitis; herpes zoster; gastroenteritis	Anemia; leukopenia; lymphopenia; thrombocytopenia	VTE; pulmonary embolism	Lung cancer	Nausea; vomiting; diarrhea; constipation; abdominal pain; decreased appetite	Dry eyes; blurred vision; hand-foot syndrome; dyslipidemia; hyperphosphatemia; arthralgia; myalgia; abnormal liver function; dizziness; headache; fatigue; rash; pruritus; dry skin
Filgotinib	Nasopharyngitis; urinary tract infection; pneumonia; bronchitis	Neutropenia; lymphopenia; thrombocytopenia	VTE; MACE; hypertension	None reported to date	Nausea; vomiting; diarrhea; abdominal pain; stomach pain	Infection; edema; hypercholesterolemia; arthralgia; myalgia; abnormal liver function; headache; dizziness; insomnia; depression; rash

Abbreviations: VTE, venous thromboembolism; MACE, major adverse cardiovascular events.

5. Management Principles for Adverse Reactions Associated with JAK Inhibitors

5.1 Preventive Measures

Before a JAK inhibitor is prescribed, the patient's medical history, previous and current medications, and family history should be reviewed for factors that may increase risk. Pretreatment counseling should make patients aware of likely adverse reactions and the steps to take if symptoms arise. Greater caution is needed in older patients and in those with comorbid disease, for whom the risk of adverse reactions may be higher.

5.2 Clinical Monitoring Parameters

Clinical follow-up is used both to judge whether treatment is working and to detect adverse reactions before they become severe. Vital signs, swollen and tender joint counts, pain scores, and functional status are among the routine measures. Changes reported by patients should be considered alongside the clinician's observations. This combined information supports timely assessment of efficacy and safety and helps determine whether the treatment regimen needs to be modified.

5.3 Laboratory Examinations

Laboratory monitoring is an important part of safety assessment during JAK inhibitor therapy. Repeated testing of liver and kidney function, blood-cell indices, and markers of infection may identify drug-related abnormalities at an early stage. A planned testing schedule therefore improves the consistency of adverse-reaction monitoring and provides practical support for clinical decisions [20].

5.4 Management of Adverse Reactions

5.4.1 Management of Infections

When infection develops during JAK inhibitor treatment, anti-infective therapy should be started promptly. The choice of antibiotic or antiviral agent depends on the type and severity of infection and the suspected pathogen. For bacterial infection, empirical antimicrobial treatment may be used when clinically indicated and then refined in light of microbiological and susceptibility results; appropriate viral infections require antiviral therapy. Taken together, these approaches can lessen the clinical impact of JAK inhibitor-associated infection and help maintain patients' quality of life [21].

5.4.2 Management of Hematologic Abnormalities

Baseline hematologic testing is required before treatment begins [20]. If an abnormal result appears during therapy, the regimen should be reassessed promptly. The response to anemia, leukopenia, or thrombocytopenia depends on its type and severity and may involve dose reduction, temporary withdrawal, or a change of treatment. Leukopenia calls for closer attention to infection and stronger preventive measures; in selected patients, hematopoietic growth factors may be used. In thrombocytopenia, drugs that increase bleeding risk should be avoided, while severe bleeding may necessitate supportive treatment, including transfusion of blood components.

5.4.3 Management of Cardiovascular Events

Cardiovascular risk needs to be evaluated before starting a JAK inhibitor. Relevant information includes personal and family history, recognized cardiovascular risk factors, and lifestyle. During treatment, blood pressure and lipid concentrations should be checked regularly, and therapy adjusted when indicated. In patients with established cardiovascular disease or a high baseline risk, measures to reduce that risk should be selected individually; statin treatment may be appropriate in some cases [22]. Advice on regular exercise and a healthy diet should form part of the same risk-management approach.

5.4.4 Management of Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions may be managed with symptomatic therapy, dietary adjustment, adequate hydration, and dose modification when needed. Patients with clinically important nausea or vomiting may receive antiemetic treatment. Adequate fluid intake and avoidance of greasy or spicy foods can help reduce gastrointestinal discomfort. Antidiarrheal drugs may be considered in severe diarrhea once infection and other serious causes have been excluded.

5.4.5 Recommendations for Medication Use

In patients with hepatic or renal impairment, dose modification or treatment discontinuation may be required. When mild-to-moderate dysfunction necessitates a dose change, the regimen should be individualized to limit organ toxicity without compromising efficacy. If severe hepatic or renal dysfunction leads to treatment withdrawal, restarting therapy should be considered only after recovery, comprehensive reassessment, and confirmation that retreatment is compatible with the prescribing information for the specific JAK inhibitor. Hepatic and renal function should be monitored closely if therapy is resumed. Recommended doses are listed in Table 3.

Table 3: Dosing recommendations for five JAK inhibitors

Drug	Recommended dosage	Efficacy and safety characteristics
Tofacitinib	5 mg twice daily	Provides an optimal balance between efficacy and safety [23]
Baricitinib	2–4 mg once daily	Efficacy: 4 mg > 2 mg; safety: 2 mg > 4 mg. For patients aged ≥65 years or those at increased risk of adverse reactions, 2 mg once daily is recommended. The dose may be increased to 4 mg once daily in patients with an inadequate therapeutic response [24]
Upadacitinib	15 mg once daily	Provides an optimal balance between efficacy and safety [25]
Peficitinib	150–200 mg once daily	The safety of 200 mg once daily has been demonstrated [26], whereas 150 mg once daily provides the optimal therapeutic effect [27]
Filgotinib	200 mg once daily	A dosage of 200 mg once daily provides the optimal pharmacodynamic profile [28]

5.4.6 Dietary Guidance

Diet can be adjusted as an additional measure to reduce adverse reactions. Patients may be advised to: (1) eat foods that provide antioxidants, vitamins, and minerals in support of immune function; (2) obtain sufficient high-quality protein for immune function and tissue repair; and (3) limit foods rich in fat and sugar, because of the possible cardiovascular risk associated with JAK inhibitors and the added cardiovascular burden of such foods.

6. Conclusion

JAK inhibitors are now an effective option for RA and other autoimmune diseases, yet their adverse-reaction profile remains an important limitation. Serious events have been reported, so prescribing decisions should take account of each patient's underlying disease, concomitant medication, genetic background, and other individual factors, followed by a management plan suited to that risk. Larger randomized controlled trials with longer follow-up are still needed to define the safety profile more fully. A national system for monitoring adverse drug reactions could also facilitate the early recognition and handling of newly emerging safety concerns. Thus, the clinical value of JAK inhibition is clear, but it must be weighed against safety through continued study and routine surveillance to provide a firmer evidence base for practice.

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