

JAK inhibitors

Oral small molecules that block intracellular Janus kinase signalling rather than an extracellular cytokine, and that all carry the same five-part boxed warning - serious infection, mortality, malignancy, major cardiovascular events and thrombosis - added after a single large safety trial of one member reshaped the labelling of the whole class.

Online guide: <https://www.medguideglobal.com/pharmacology/immunomodulators/jak-inhibitors>

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Quick revision

One Liner: Three oral drugs that block Janus kinases inside the cell rather than a cytokine outside it - and one landmark safety trial of tofacitinib, ORAL Surveillance, added a five-part boxed warning to all three labels even though only tofacitinib itself was actually studied in that trial.

1. Tofacitinib, baricitinib and upadacitinib are targeted synthetic DMARDs (tsDMARDs): oral small molecules that inhibit intracellular Janus kinases rather than binding an extracellular target the way biologic DMARDs do. [4]
2. All three carry a boxed warning covering serious infection including TB, mortality, malignancy, major adverse cardiovascular events (MACE) and thrombosis. [1][2][3]
3. That boxed warning followed the ORAL Surveillance trial, a postmarketing safety study of tofacitinib in RA patients 50 years and older with at least one cardiovascular risk factor, comparing tofacitinib against TNF blockers. [1]
4. ORAL Surveillance found higher rates of all-cause mortality (including sudden cardiovascular death), lymphoma, lung cancer, MACE and thrombosis with tofacitinib than with TNF blockers. [1]
5. Baricitinib and upadacitinib have not been studied in a comparably sized dedicated cardiovascular-safety trial, so their labels state the risk has not been adequately evaluated for those two drugs even as they carry the same boxed-warning language. [2][3]
6. Tofacitinib's higher 10 mg twice-daily / 22 mg extended-release once-daily doses are specifically not recommended for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or polyarticular juvenile idiopathic arthritis because of the elevated risk seen at that dose. [1]
7. None of the three has an absolute contraindication beyond hypersensitivity in its own label; the boxed warning works through required TB testing, cardiovascular and cancer risk assessment, and ongoing laboratory monitoring instead. [1][2][3]
8. All three require monitoring for lymphopenia, neutropenia, anaemia and dose-related lipid elevation, and all three have been linked to gastrointestinal perforation and herpes zoster reactivation. [1][2][3]

Overview

1. JAK inhibitors are the newest of the three DMARD categories - conventional synthetic, biologic and targeted synthetic - and the label "targeted synthetic" describes exactly what separates them from the other two. Like conventional DMARDs they are oral small molecules, but like biologics they act on one defined signalling system: the Janus kinase family (JAK1, JAK2, JAK3 and TYK2) that cytokine receptors use to activate STAT transcription factors inside the cell. Blocking that intracellular relay, rather than the extracellular cytokine itself, is the pharmacological idea the whole class is built on. [4]
2. The class's defining safety event was not a finding about all three drugs at once - it was a single large postmarketing trial of one of them. ORAL Surveillance enrolled rheumatoid arthritis patients aged 50 or older with at least one additional cardiovascular risk factor and compared tofacitinib against TNF blockers. It found higher rates of all-cause mortality including sudden cardiovascular death, of major adverse cardiovascular events, of thrombosis, and of malignancy - with lymphoma and, in current or past smokers, lung cancer specifically elevated - in the tofacitinib arm.

The FDA required a boxed warning covering all five findings. [1]

3. What did not happen is equally important to the evidence picture: baricitinib and upadacitinib were not the drugs studied in ORAL Surveillance. Their labels carry the same boxed-warning language as tofacitinib's, but each explicitly states that the drug has not been studied in a trial of similar size and design, so the corresponding risk has not been adequately evaluated for that specific molecule. Reading the class-wide boxed warning as three drugs having identically demonstrated risks, rather than one drug's demonstrated risk extended by regulatory caution to its relatives, would overstate what the trial evidence actually shows for baricitinib and upadacitinib. [2][3]

4. A second consequence of the same trial was dose-specific rather than drug-specific: tofacitinib's higher-dose regimens (10 mg twice daily, or the 22 mg once-daily extended-release equivalent) are explicitly not recommended for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or polyarticular juvenile idiopathic arthritis, because the elevated risk in ORAL Surveillance tracked with dose. [1]

Classification and drug examples

Intro: All three are oral JAK inhibitors, but they differ in which Janus kinases they inhibit most potently, and that selectivity is part of what each label discusses even though the boxed warning now reads almost identically across the class.

1. Name: JAK1/JAK3-leaning inhibitor

1. Note: The first oral JAK inhibitor approved for rheumatoid arthritis, and the only member actually studied in the large postmarketing cardiovascular-safety trial that reshaped the whole class's labelling.

Name: Tofacitinib

1. Xeljanz

2. Xeljanz XR

Route: Oral

Note: Higher-dose regimens are specifically not recommended for RA, PsA, AS or pcJIA because of the dose-related risk increase seen in ORAL Surveillance. [1] [1]

2. Name: JAK1/JAK2-leaning inhibitor

2. Note: Greater inhibitory potency at JAK1, JAK2 and TYK2 relative to JAK3 in enzyme assays.

Name: Baricitinib

Olumiant

Route: Oral

Note: Also approved for hospitalised COVID-19 requiring supplemental oxygen or ventilation, and for severe alopecia areata, alongside its rheumatoid arthritis indication. [2] [2]

3. Name: JAK1-selective inhibitor

3. Note: Marketed as more JAK1-selective than the earlier two members, though it shares the same boxed warning.

Name: Upadacitinib

1. Rinvoq

2. Rinvoq LQ

Route: Oral

Note: The broadest indication list of the three, extending into ulcerative colitis, Crohn's disease and giant cell arteritis alongside its rheumatic indications. [3] [3]

Mechanism of action

Summary: Cytokine receptors relevant to inflammation - including those for interleukin-6, interferons and several interleukins involved in lymphocyte signalling - rely on the intracellular Janus kinases JAK1, JAK2, JAK3 and TYK2 to phosphorylate and activate STAT transcription factors after the cytokine binds its receptor. JAK inhibitors block that phosphorylation step inside the cell, downstream of receptor binding, which is what distinguishes them mechanistically from the biologic DMARDs that intercept the cytokine or the receptor itself before signalling starts.

Target: Intracellular Janus kinases JAK1, JAK2, JAK3 and TYK2, with differing relative potency at each across the three drugs

Cidal Static: Immunomodulatory rather than cytotoxic - suppresses cytokine-driven gene transcription rather than killing a cell population

Kill Kinetics: Onset over weeks; effect requires continued dosing and is lost once the drug is stopped

1. Step: 1

1. Title: A pro-inflammatory cytokine binds its cell-surface receptor

1. Detail: Receptors for cytokines central to rheumatoid and other inflammatory disease, including several interleukins, associate with Janus kinases on their intracellular tail. [4]

2. Step: 2

2. Title: Receptor engagement activates the associated JAKs

2. Detail: Janus kinases are phosphotransferases whose enzymatic function is switched on by cytokine receptor engagement. [4]

3. Step: 3

3. Title: Activated JAKs phosphorylate STAT proteins

3. Detail: Baricitinib's label describes this step directly: the drug modulates the signalling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. [2]

4. Step: 4

4. Title: The JAK inhibitor competes at this intracellular step, not at the receptor

4. Detail: In enzyme assays baricitinib shows greater inhibitory potency at JAK1, JAK2 and TYK2 relative to JAK3, while tofacitinib and upadacitinib have their own differing relative potency across the four kinases - the shared mechanism is blockade at the phosphorylation step, not identical selectivity. [2]

5. Step: 5

5. Title: Blocked STAT activation reduces transcription of inflammatory genes

5. Detail: Without phosphorylated STATs translocating to the nucleus, transcription of the genes the cytokine signal would otherwise switch on is reduced, damping the downstream inflammatory response. [4]

Major clinical uses

1. Drug: Tofacitinib

1. Organism: Not applicable

1. Indication: Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis (adults); polyarticular course juvenile idiopathic arthritis from age 2

1. Line: generally after inadequate response to a TNF blocker

1. Note: Higher-dose regimens are specifically not recommended for RA, PsA, AS or pcJIA. [1]

2. Drug: Baricitinib

2. Organism: Not applicable

2. Indication: Rheumatoid arthritis with inadequate response to TNF blockers; hospitalised COVID-19 requiring supplemental oxygen or mechanical ventilation; severe alopecia areata

2. Line: reserved/second-line for RA

2. Note: Its indication list spans rheumatology, infectious disease and dermatology, unusually broadly for this class. [2]

3. Drug: Upadacitinib

3. Organism: Not applicable

3. Indication: Rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, non-radiographic axial spondyloarthritis, polyarticular juvenile idiopathic arthritis, giant cell arteritis

3. Line: option after inadequate response to one or more TNF blockers, indication-dependent

3. Note: The broadest FDA indication list of the three JAK inhibitors covered here. [3]

4. Drug: All three as a class

- 4. Organism: Not applicable
- 4. Indication: Moderately to severely active rheumatoid arthritis
- 4. Line: generally after inadequate response to methotrexate or a TNF blocker
- 4. Note: None is typically positioned as a first-choice agent ahead of a conventional DMARD trial. [4]

Pharmacokinetics

- 1. Drug: Tofacitinib
 - 1. Route: Oral, immediate-release or extended-release
 - 1. Absorption: Well absorbed orally
 - 1. Csf Penetration: See prescribing reference
 - 1. Metabolism: Hepatic, via CYP3A4 with a lesser CYP2C19 contribution
 - 1. Elimination: Hepatic and renal
 - 1. Dose Adjust: Renal and hepatic impairment; concomitant strong CYP3A4 inhibitors or inducers; avoid the higher-dose regimen in RA/PsA/AS/pcJIA [1]
 - 2. Drug: Baricitinib
 - 2. Route: Oral
 - 2. Absorption: Well absorbed orally
 - 2. Csf Penetration: See prescribing reference
 - 2. Metabolism: Limited hepatic metabolism
 - 2. Elimination: Primarily renal
 - 2. Dose Adjust: Renal impairment is the principal dose-adjustment driver for this member of the class [2]
 - 3. Drug: Upadacitinib
 - 3. Route: Oral, extended-release tablet or oral solution
 - 3. Absorption: Well absorbed orally
 - 3. Csf Penetration: See prescribing reference
 - 3. Metabolism: Hepatic, primarily via CYP3A4
 - 3. Elimination: Hepatic and renal
 - 3. Dose Adjust: Concomitant strong CYP3A4 inhibitors or inducers; hepatic impairment [3]
1. This page gives no dose regimens by design. Dose selection, including which tofacitinib regimen is appropriate for which indication, depends on diagnosis, prior therapy, renal and hepatic function, and concomitant drugs, and belongs in a current prescribing reference used by the treating clinician.
2. Unlike the biologic DMARDs, all three JAK inhibitors are small molecules with real cytochrome P450 interaction potential - tofacitinib and upadacitinib both depend substantially on CYP3A4 - which is the pharmacokinetic property that most differentiates this class from the injectable biologics. [1][3]
3. Baricitinib's elimination is predominantly renal rather than hepatic, which is why renal function is the main pharmacokinetic variable driving its dose adjustment, in contrast to the hepatic-metabolism-driven adjustments for tofacitinib and upadacitinib. [2]

Adverse effects

- 1. Effect: Lipid elevation
 - 1. Detail: Dose-related increases in total cholesterol, LDL and HDL are described for all three drugs; tofacitinib's label recommends assessing lipids 4 to 8 weeks after starting, and baricitinib's around 12 weeks. [1][2][3]
- 2. Effect: Upper respiratory and other infections
 - 2. Detail: Increased infection rates are described across the class, consistent with the broader immunomodulatory mechanism. [1][2][3]
- 3. Effect: Herpes zoster reactivation
 - 3. Detail: Viral reactivation, including herpes zoster, has been reported in clinical studies of baricitinib and upadacitinib,

and is a recognised risk with tofacitinib as well. [2][3]

1. Effect: Serious infection, including tuberculosis

1. Detail: All three carry increased risk of serious bacterial, fungal, viral and opportunistic infection, including TB; most affected patients on upadacitinib were also taking concomitant immunosuppressants such as methotrexate or corticosteroids.

1. Action: Latent TB is tested for and treated before starting, and treatment is interrupted if a serious infection develops until it is controlled. [1][2][3]

2. Effect: Mortality, including sudden cardiovascular death

2. Detail: ORAL Surveillance found a higher rate of all-cause mortality with tofacitinib compared with TNF blockers in RA patients 50 years or older with a cardiovascular risk factor; the finding drove the same boxed-warning language onto baricitinib and upadacitinib even though they were not the drugs studied in that trial.

2. Action: This is disclosed and weighed by the treating clinician against disease severity and the patient's own cardiovascular risk profile; it is not a reason for a patient to alter their own treatment without medical advice. [1][2][3]

3. Effect: Malignancy, including lymphoma and lung cancer

3. Detail: A higher rate of lymphomas was observed with tofacitinib versus TNF blockers, and a higher rate of lung cancers in current or past smokers specifically.

3. Action: Smoking status and cancer history are part of the risk discussion the treating clinician has before starting or continuing a JAK inhibitor. [1]

4. Effect: Major adverse cardiovascular events

4. Detail: A higher rate of MACE, defined as cardiovascular death, myocardial infarction and stroke, was observed with tofacitinib versus TNF blockers in ORAL Surveillance.

4. Action: Cardiovascular risk factors are assessed before starting and monitored during treatment. [1]

5. Effect: Thrombosis, including pulmonary embolism, DVT and arterial thrombosis

5. Detail: Reported across the class, with many adverse events serious and some resulting in death; an earlier interim analysis of the same postmarketing trial programme first identified an increased risk of pulmonary embolism and death specifically in patients on the higher, 10 mg twice-daily tofacitinib dose, which is part of why that higher-dose regimen is now restricted to specific indications rather than used broadly.

5. Action: New symptoms of DVT or PE - leg swelling, chest pain, breathlessness - are an urgent reason to seek medical attention rather than to wait. [1][2]

6. Effect: Gastrointestinal perforation

6. Detail: Reported across the class, particularly in patients on concomitant NSAIDs.

6. Action: New abdominal symptoms during treatment are evaluated promptly by the treating clinician. [1][2][3]

7. Effect: Cytopenias

7. Detail: Neutropenia (ANC below 1000 cells/mm³), lymphopenia (ALC below 500 cells/mm³) and anaemia (haemoglobin below 8 g/dL) are monitored thresholds across all three drugs.

7. Action: Laboratory monitoring at defined intervals is part of routine care with this class, and dose interruption criteria are set out in each product's own prescribing information. [1][2][3]

1. Drug: Tofacitinib

1. Effect: The only member of this class with an explicit dose-based risk stratification in its own label: the higher-dose regimens are specifically not recommended for RA, PsA, AS or pcJIA because of the elevated risk seen at that dose in ORAL Surveillance. [1]

2. Drug: Baricitinib

2. Effect: The only one of the three with an FDA indication in hospitalised COVID-19 and in severe alopecia areata, alongside rheumatoid arthritis. [2]

3. Drug: Upadacitinib

3. Effect: The broadest indication list of the three, including inflammatory bowel disease and giant cell arteritis, which is not shared by tofacitinib or baricitinib in the material reviewed here. [3]

Contraindications, precautions and interactions

1. Upadacitinib: known hypersensitivity to upadacitinib or any excipient in RINVOQ/RINVOQ LQ. [3]
2. Tofacitinib and baricitinib carry no absolute contraindications beyond hypersensitivity in their own labelling. [1][2]
1. Active infection of any kind is a reason to defer or interrupt treatment with any JAK inhibitor until it is controlled. [1][2][3]
2. Current or past smoking status is specifically relevant to the lung-cancer signal identified with tofacitinib and is part of the individualised risk discussion for any JAK inhibitor. [1]
3. A history of major cardiovascular event, malignancy or thrombosis is weighed carefully by the treating clinician before starting this class, given the boxed warning. [1][2][3]
4. Lymphopenia, neutropenia and anaemia below labelled thresholds are reasons to withhold or interrupt treatment pending clinical review. [1][2][3]
1. With: Strong CYP3A4 inhibitors or inducers
1. Effect: Alter tofacitinib and upadacitinib exposure meaningfully; dose adjustment or avoidance is directed by the prescribing information. [1][3]
2. With: Other immunosuppressants, including biologic DMARDs
2. Effect: Concomitant use with a biologic DMARD or with potent immunosuppressants such as azathioprine or ciclosporin is not recommended because of additive immunosuppression and infection risk. [4]
3. With: NSAIDs
3. Effect: Concurrent use is associated with the gastrointestinal perforation events reported with this class. [1]

Comparison tables

Title: One boxed warning, unevenly demonstrated risk

Caption: All three share the same five-part boxed warning, but only tofacitinib was the drug actually studied in the trial that produced it. Choice of agent belongs to the treating clinician.

1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: selectivity
2. Label: Relative JAK selectivity
3. Key: evidence
3. Label: ORAL Surveillance status
4. Key: distinguishing
4. Label: Distinguishing indication
1. Drug: Tofacitinib
1. Selectivity: JAK1/JAK3-leaning
1. Evidence: The drug actually studied; higher dose specifically not recommended in RA/PsA/AS/pcJIA
1. Distinguishing: First-in-class oral JAK inhibitor for RA [1]
2. Drug: Baricitinib
2. Selectivity: JAK1/JAK2/TYK2-leaning, less JAK3
2. Evidence: Not studied in a comparable trial; risk stated as not adequately evaluated for this drug
2. Distinguishing: Hospitalised COVID-19 and severe alopecia areata [2]
3. Drug: Upadacitinib
3. Selectivity: JAK1-selective
3. Evidence: No trial of comparable size conducted; its own label states the risk has not been adequately evaluated
3. Distinguishing: Broadest indication list, including IBD and giant cell arteritis [3]

High-yield exam pearls

1. Pearl: "Targeted synthetic DMARD" means oral and small-molecule like the conventional DMARDs, but single-pathway like a biologic.
1. Why: It is the defining structural idea of the class and the reason JAK inhibitors sit in their own DMARD category rather than being folded into either of the other two. [4]
2. Pearl: Only tofacitinib was the drug in ORAL Surveillance - baricitinib and upadacitinib inherited the boxed warning by regulatory extension, not by their own dedicated trial of the same size.
2. Why: Both labels explicitly state that risk has not been adequately evaluated for that specific drug, which is a genuinely different evidentiary status from tofacitinib's own findings. [2][3]
3. Pearl: Tofacitinib's boxed-warning risk was dose-related, not simply drug-related.
3. Why: The higher-dose regimens are specifically not recommended for RA, PsA, AS or pcJIA - a dosing distinction that a class-wide safety statement would miss. [1]
4. Pearl: The lung-cancer signal in ORAL Surveillance was specific to current or past smokers.
4. Why: It is a subgroup-specific finding, not a uniform risk across every tofacitinib-treated patient. [1]
5. Pearl: Baricitinib's elimination is mainly renal, unlike tofacitinib and upadacitinib's hepatic CYP3A4-driven clearance.
5. Why: This is the reason renal function, rather than hepatic function or CYP3A4 co-medications, is the main dose-adjustment driver specifically for baricitinib. [2]

Common exam traps

1. Trap: Assuming baricitinib and upadacitinib have the same trial-level evidence for MACE and mortality as tofacitinib.
1. Correction: Both labels state explicitly that they have not been studied in a trial comparable to ORAL Surveillance, so the risk has not been adequately evaluated for those two specific drugs, even though they carry the same boxed-warning wording. [2][3]
2. Trap: Treating the JAK-inhibitor boxed warning as uniform across every dose of every drug.
2. Correction: The elevated risk identified in ORAL Surveillance was dose-related for tofacitinib, which is why its higher-dose regimens are specifically not recommended for several indications rather than the drug being withdrawn outright. [1]
3. Trap: Believing JAK inhibitors are biologics because they are used in the same conditions as TNF inhibitors.
3. Correction: They are oral small molecules metabolised substantially by cytochrome P450 enzymes, with real drug-drug interaction potential that the injectable biologic DMARDs do not share. [1][3]
4. Trap: Assuming the malignancy signal in ORAL Surveillance applied equally to every cancer type.
4. Correction: The label specifies higher rates of lymphomas generally and of lung cancers specifically in current or past smokers - not an undifferentiated rise across all malignancy types. [1]

Self-test questions

1. Question: What structurally distinguishes JAK inhibitors from biologic DMARDs?
1. JAK inhibitors are injectable proteins like biologics
2. JAK inhibitors are oral small molecules that block intracellular signalling, while biologics are typically proteins that bind an extracellular target
3. JAK inhibitors have no immunosuppressive effect
4. There is no meaningful difference between the two categories
1. Explanation: JAK inhibitors are oral small molecules that block the intracellular JAK-STAT signalling relay downstream of the cytokine receptor, whereas biologic DMARDs are typically proteins acting on an extracellular target such as TNF-alpha or CD20. [4]
2. Question: Which JAK inhibitor was the drug actually studied in the ORAL Surveillance trial that produced the class's

boxed warning?

1. Baricitinib
2. Upadacitinib
3. Tofacitinib

4. All three were studied together in one arm

2. Explanation: ORAL Surveillance was a postmarketing safety trial of tofacitinib specifically, comparing it against TNF blockers in RA patients 50 years or older with a cardiovascular risk factor; baricitinib and upadacitinib were not the drugs studied. [1]

3. Question: What do the baricitinib and upadacitinib labels say about their own MACE and mortality risk relative to tofacitinib's trial findings?

1. That the risk is proven to be identical to tofacitinib's
2. That these two drugs have not been studied in a trial of comparable size, so the risk has not been adequately evaluated for them specifically

3. That these two drugs are proven safer than tofacitinib

4. That the boxed warning does not apply to them

3. Explanation: Both labels state plainly that they have not been studied in a trial similar to the large tofacitinib safety trial, so the corresponding risk has not been adequately evaluated for baricitinib or upadacitinib even though the same boxed-warning language appears. [2][3]

4. Question: Which of the following is a labelled restriction specific to tofacitinib rather than the whole JAK-inhibitor class?

1. A requirement for lipid monitoring

2. The higher-dose regimens are not recommended for RA, PsA, AS or pcJIA

3. A requirement for latent TB testing

4. Monitoring for neutropenia

4. Explanation: The dose-based restriction against the higher tofacitinib regimens for these specific indications is unique to tofacitinib's label, reflecting the dose-related risk pattern seen in ORAL Surveillance. [1]

5. Question: In ORAL Surveillance, the increased lung cancer rate with tofacitinib was specifically observed in which subgroup?

1. All patients regardless of smoking history

2. Current or past smokers

3. Only patients under 50

4. Only patients never exposed to a TNF blocker

5. Explanation: The label specifies a higher rate of lung cancers in current or past smokers treated with tofacitinib compared with TNF blockers, a subgroup-specific rather than a uniform finding. [1]

6. Question: Which pharmacokinetic property most differentiates baricitinib from tofacitinib and upadacitinib within this class?

1. Baricitinib is eliminated primarily by the kidney, while the other two rely mainly on hepatic CYP3A4 metabolism

2. Baricitinib is not absorbed orally

3. Baricitinib has no monitoring requirements

4. Baricitinib is a biologic protein, not a small molecule

6. Explanation: Baricitinib's elimination is predominantly renal, which is why renal function rather than CYP3A4-mediated drug interactions is its principal dose-adjustment driver, unlike tofacitinib and upadacitinib. [2]

Frequently asked questions

1. Question: Do all three JAK inhibitors carry the same proven cardiovascular and cancer risk?

1. Answer: They carry the same boxed-warning wording, but not the same evidentiary weight. Tofacitinib was the drug actually studied in ORAL Surveillance, the large trial that found the increased risks. Baricitinib and upadacitinib have

not been studied in a comparably sized dedicated trial, and their own labels say the risk has not been adequately evaluated for them specifically - the FDA extended the warning as a precaution across the class rather than confirming an identical finding for each drug. [1][2][3]

2. Question: Why is only tofacitinib's higher dose restricted, rather than the whole drug being withdrawn?

2. Answer: Because the elevated risk in ORAL Surveillance tracked with dose. The label response was to specifically not recommend the higher-dose regimens (10 mg twice daily, or the 22 mg once-daily extended-release equivalent) for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or polyarticular juvenile idiopathic arthritis, rather than to remove the lower, still-effective dose from use. [1]

3. Question: How are JAK inhibitors different from the older biologic DMARDs in day-to-day use?

3. Answer: They are oral tablets rather than injections or infusions, and their clearance depends substantially on hepatic cytochrome P450 enzymes (tofacitinib and upadacitinib) or the kidney (baricitinib), which gives them a real drug-interaction profile the injectable biologics do not have. Their monitoring - lipids, blood counts, TB and infection screening - overlaps with the biologics but adds lipid tracking specific to this class. [1][2][3]

4. Question: Is smoking relevant to the decision to use a JAK inhibitor?

4. Answer: It is specifically relevant to tofacitinib, whose ORAL Surveillance data showed a higher rate of lung cancer in current or past smokers compared with TNF blockers. Smoking history is one of the factors the treating clinician weighs before starting or continuing this class, alongside cardiovascular risk factors and malignancy history. [1]

References

[1] XELJANZ / XELJANZ XR (tofacitinib) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cf74ba2f-afc5-4baa-8594-979c889a5831>

[2] OLUMIANT (baricitinib) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=866e9f35-9035-4581-a4b1-75a621ab55cf>

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[4] Disease-Modifying Antirheumatic Drugs (DMARDs). StatPearls Publishing / NCBI Bookshelf 2025. <https://www.ncbi.nlm.nih.gov/books/NBK507863/>

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