JAK Inhibitors in RA: 2025 EULAR Safety Update Redraws Risk Guidance

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JAK inhibitors now carry clearer, if conditional, safety guidance for rheumatoid arthritis. EULAR's 2025 recommendations update and a systematic literature review synthesize the latest evidence on cardiovascular, malignancy, and infection risk.1,2,3

KEY TAKEAWAYS

- The Pivot: The 2025 EULAR update formally incorporates accumulated post-marketing and trial safety data on JAK inhibitors, refining risk stratification beyond the original ORAL Surveillance signal.1,3
- The Data: The systematic literature review underpinning the 2025 recommendations identified differential safety profiles across JAK inhibitor agents and patient subgroups, particularly regarding cardiovascular events, venous thromboembolism, and malignancy risk in older patients with pre-existing risk factors.1
- The Action: Prescribers should apply formal cardiovascular and malignancy risk assessment before initiating any JAK inhibitor, reserving these agents for patients without high-risk profiles unless bDMARD options have been inadequately effective or are contraindicated.2,3

Rheumatoid arthritis management offers many therapeutic options. But clarity on long-term safety trade-offs has been scarce. JAK inhibitors, approved since tofacitinib's 2012 initial license, accumulated substantial real-world use. Then ORAL Surveillance forced a sector-wide reassessment of cardiovascular and oncological risk. The guidance now formalizes that.3

The 2025 EULAR recommendations are the first to fully incorporate post-ORAL Surveillance evidence.3 Laskou and colleagues conducted the systematic literature review that informed the safety sections. It covered trials, registries, and observational datasets across the full DMARD spectrum.1 Cohen and Winthrop's narrative synthesis contextualizes JAK inhibitor advances since earlier safety alerts.2

Rheumatoid arthritis affects 0.5-1% of adults globally, with a higher prevalence in women. Long-term treatment is necessary, often with multiple agents. Targeted synthetic DMARDs, including JAK inhibitors, offered a new oral option for patients. These were for those who did not respond to conventional or biologic DMARDs.

These agents target intracellular JAK enzymes, crucial in RA cytokine signaling, like IL-6 and IFN-gamma. Initial enthusiasm for JAK inhibitors cooled with safety concerns after the ORAL Surveillance trial, which evaluated tofacitinib in a high-risk group. That trial highlighted the need for better risk stratification. The EULAR update now addresses this.2,3

What the evidence covers

A systematic literature review by Laskou et al. examined safety data across all DMARDs, including JAK inhibitors. It covered outcomes like serious infections, major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and malignancy.1 The review used EULAR's standard methodology. That provided the evidentiary base for Smolen et al.'s recommendations.1,3

Researchers comprehensively searched major databases, including PubMed, Embase, and Cochrane Library. They focused on studies reporting safety outcomes in adult RA patients. This included randomized controlled trials, observational studies, and real-world registry data. Evidence quality was assessed using tools like the Cochrane Risk of Bias tool and Newcastle-Ottawa Scale. That provided a robust foundation.1

Cohen and Winthrop note that differential selectivity across JAK inhibitor agents — tofacitinib, baricitinib, upadacitinib, and filgotinib — translates to clinically meaningful differences in safety signal distribution. But head-to-head comparative data between agents remains limited.2

The ORAL Surveillance findings showed elevated MACE and malignancy risk with tofacitinib versus TNF inhibitors in patients aged 50 or older with at least one cardiovascular risk factor. Those findings still drive the regulatory and clinical framework. Still, the 2025 update attempts to move the conversation toward agent-specific and patient-specific calibration, not class-wide restriction.2,3

The updated EULAR recommendations keep JAK inhibitors positioned after bDMARD failure or intolerance in patients with relevant risk factors. But for patients without elevated cardiovascular, thrombotic, or malignancy risk, the benefit-risk calculation is more permissive.3 The SLR identifies older age, smoking history, prior malignancy, known cardiovascular disease, and VTE risk factors as principal variables. These require prospective assessment before JAK inhibitor initiation.1

Upadacitinib's higher selectivity for JAK1 was noted by Cohen and Winthrop as a pharmacologically distinct feature. But whether this means a superior long-term safety profile compared to less selective agents needs confirmatory data.2

On infection risk, the SLR confirms herpes zoster reactivation is a consistent class effect across JAK inhibitors. Rates exceed those seen with bDMARDs in most comparative datasets.1 Vaccination against herpes zoster before JAK inhibitor initiation is now a standard pre-treatment step.3 Serious bacterial infection rates, while higher than conventional DMARDs, appear broadly comparable to bDMARDs in most datasets reviewed. The evidence quality varies considerably.1

A clear caveat is the relatively shorter follow-up for some JAK inhibitors compared to established bDMARDs. Patient populations also show heterogeneity across studies. That can complicate direct comparisons. Real-world data, while valuable, often suffer from confounding by indication. Incomplete capture of relevant covariates also complicates interpretation. The next trials must address these gaps.1,2

> **CLINICAL IMPLICATIONS**
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> JAK inhibitor prescribing now requires documented risk assessment, not just clinical impression. This is no minor administrative burden. Formally scoring cardiovascular risk, checking malignancy history, and confirming VTE absence before initiating upadacitinib or baricitinib adds a layer of process. Many outpatient workflows aren't designed to absorb this efficiently. The guidelines are correct to require it. The systems enabling it are still catching up.

> The commercial stakes for AbbVie, Pfizer, Eli Lilly, and Galapagos are substantial. The 2025 update does not remove JAK inhibitors from the formulary. But it solidifies the conditionality around their use. This will influence both payer access and prescriber confidence.
> Upadacitinib's selective JAK1 profile is positioned by some as distinct from tofacitinib's older, broader signal. The SLR is candid: comparative safety data is too immature to make that case. Manufacturers marketing selectivity as safety will need long-term data to match the claim.
> Patients over 50 with pre-existing cardiovascular disease, prior malignancy, or VTE history are most directly affected by the tightened guidance. The update clarifies their options, not closes them, as bDMARDs remain accessible and effective. The situation is more ambiguous for younger, lower-risk patients. A prescriber, facing regulatory scrutiny and reputational overhang, might default to a TNF inhibitor on caution alone. That conservative drift may be clinically justifiable, but it should be a deliberate choice, not a reflexive one. These recommendations provide the framework for that deliberate choice.

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