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IN BRIEF

New Warnings for Janus Kinase Inhibitors

The FDA has required updates to the boxed warnings in the labeling of the Janus kinase (JAK) inhibitors tofacitinib *(Xeljanz, Xeljanz XR)*, baricitinib *(Olumiant)*, and upadacitinib *(Rinvoq)* describing increased risks of major adverse cardiovascular events, malignancy, thrombosis, and death with their use.[1] The new warnings were prompted by the results of a postmarketing safety trial with tofacitinib and were added to the labels of baricitinib and upadacitinib based on the presumption of a class effect. The tofacitinib package insert had contained a boxed warning about an increased risk of thrombosis and mortality with a dosage of 10 mg twice daily since 2019,[2] but the new warnings are not limited by dose.

In a randomized, double-blind trial (ORAL Surveillance), 4362 patients ≥50 years old with moderate to severe rheumatoid arthritis and at least one cardiovascular risk factor received tofacitinib 5 or 10 mg twice daily or a tumor necrosis factor (TNF) inhibitor (adalimumab 40 mg once every 2 weeks or etanercept 50 mg once weekly). Patients taking tofacitinib 10 mg twice daily were transitioned into the 5-mg group after an interim analysis showed elevated risks of pulmonary thromboembolism and death with the higher dosage.[2,3]

After a median follow-up of 4 years, tofacitinib (both dosage groups assessed together) failed to meet the prespecified criteria for noninferiority (upper bound of 95% CI <1.80) compared to the TNF inhibitors for the coprimary endpoints of major adverse cardiovascular events (0.98 vs 0.73 cases per 100 patient-years; HR 1.33 [95% CI 0.91-1.94]) and malignancy excluding nonmelanoma skin cancer (1.13 vs 0.77 cases per 100 patient-years; HR 1.48 [95% CI 1.04-2.09]). Differences in rates of malignancy, particularly lung cancer, between the tofacitinib and TNF inhibitor groups were higher among current and past smokers. Cases of thrombosis and all-cause mortality were also numerically greater with tofacitinib than with a TNF inhibitor.[1,3]

Tofacitinib, baricitinib, and upadacitinib are FDA-approved for treatment of rheumatoid arthritis; tofacitinib is also indicated for treatment of psoriatic arthritis, ulcerative colitis, and polyarticular juvenile idiopathic arthritis. They should not be used for these indications unless TNF inhibitors are ineffective or cannot be tolerated. Clinicians should consider the risks associated with JAK inhibitors when deciding whether to initiate or continue their use, particularly in current or past smokers and patients with other cardiovascular risk factors or malignancies (except successfully treated nonmelanoma skin cancer).[1] ■

1. FDA Drug Safety Communication. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. September 1, 2021. Available at: https://bit.ly/399nnBj. Accessed September 15, 2021.
2. In brief: Risk of pulmonary thromboembolism and death with tofacitinib (Xeljanz). Med Lett Drugs Ther 2019; 61:136.
3. NIH. Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis. Available at: https://bit.ly/3lcBCdZ. Accessed September 15, 2021.

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