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Janus Kinase Inhibitor Boxed Warning

Statement from the American College of Rheumatology
Updated: January 28, 2022

Background

JAK inhibitors [tofacitinib (Xeljanz/Xeljanz XR), baricitinib (Olumiant) and upadacitinib (Rinvoq)] are targeted synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs) widely used for treatment of Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA), with tofacitinib recently being approved for Ankylosing Spondylitis (AS) and polyarticular course Juvenile Idiopathic Arthritis (pcJIA). The 2021 ACR RA Clinical Practice Guideline recommended the addition of either a biologic or targeted synthetic DMARD such as a JAK inhibitor to methotrexate non-responders. [1] However, the guideline noted potential emerging safety signals and anticipated upcoming results of an FDA-mandated long term prospective open label non-inferiority safety clinical trial in RA patients. This study was completed recently, with two doses of tofacitinib (5 mg and 10 mg bid) compared to anti-tumor necrosis inhibitors (TNFi) (adalimumab and etanercept) with 2 co-primary endpoints of major adverse cardiac events (MACE) and malignancy. The international study was performed on 4,362 RA patients older than 50 years who had at least one additional cardiovascular risk factor.

On September 1, 2021, the FDA announced required revisions to the Boxed Warning for all JAK inhibitors approved for RA, PsA, pcJIA and AS to include information about the risks of serious heart-related events, cancer, blood clots, and death. These drugs are now approved for patients who have not responded to, or cannot tolerate, one or more TNF inhibitors. Although the trial was done in RA patients treated with tofacitinib, the FDA, citing a similar mechanism of action, broadened the change in indication to cover all JAK inhibitors across RA, PsA, pcJIA and ankylosing spondylitis (AS).[2] The data was officially published on Jan 27, 2022.[3]

Data

The published data behind this recommendation is noted below in Table 1. In summary, there was an increased risk of MACE, malignancy, thrombotic events and mortality in those on tofacitinib when compared to those treated with TNFi's. Higher risk patients were identified as smokers, men, those over 65 years of age, or those with prior cardiac events, stroke, or prior malignancy other than a successfully treated nonmelanoma skin cancer.

Table 1 Oral Surveillance: adjudicated MACE, malignancies and VTE [3]

EVENT *Hazard Ratio (HR) Tofacitinib vs TNFi (Confidence Interval)*	**Tofacitinib 5 mg BID** (N=1455)	**Tofacitinib 10 mg BID** (N=1456)	**TNFi adalimumab 40mg q 14 days -OR- etanercept 50mg q 7 days** (N=1451)
MACE *(All fatal CV events, non-fatal MI, or non-fatal CVA)*	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	Referent
Pulmonary embolism	2.93 (0.79-10.83)	8.26 (2.49-27.43)	Referent
DVT	1.54 (0.60-3.97)	2.21 (0.90-5.43)	Referent
VTE	1.66 (0.76-3.63)	3.52 (1.74-7.12)	Referent
Malignancy *(all non-melanoma cancer)*	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	Referent
Non-melanoma Skin Cancer	1.90 (1.04-3.47)	2.16 (1.19-3.92)	Referent
Death from any cause	1.49 (0.81-2.74)	2.37 (1.34-4.18)	Referent

Summary

- On 9/1/21, the FDA placed a Boxed Warning on tofacitinib, baricitinib and upadacitinib due to data demonstrating increased risk of MACE, malignancy, thrombotic events and mortality when tofacitinib was compared to TNFi in long term surveillance data.

- The ORAL surveillance study was performed on RA patients over 50 with at least one additional cardiovascular risk factor and compared tofacitinib to a TNF inhibitor (either adalimumab or etanercept). Citing a similar mechanism of action, the FDA included tofacitinib, baricitinib and upadacitinib and all associated indications in its warning.

- The FDA recently adjusted the applicable RA, PsA, pcJIA and AS indications for tofacitinib, upadacitinib and barcitinib, limiting the approved indications to those with an inadequate response or intolerance to one or more TNF inhibitors.

- The ACR recommends shared decision making between the patient and the provider regarding the risk/benefit of JAK inhibitors as a potential treatment option for patients in whom continued TNFi use is not a viable option. These data will help more clearly shape that decision.

NOTE: The ACR releases treatment guidelines for treatment of inflammatory disorders using a rigorous, thorough process that involves an exhaustive literature review, expert discussion and ultimately finalization of guidelines. The ACR guidelines (Clinical Practice Guidelines (rheumatology.org)) are updated with revisions as indicated by changes in science. Based on the newly available data, revisions may occur and will take months to be finalized; hence, this is an interim statement.

References

1. Fraenkel, Bathon, England et al. Arthritis Care & Research Vol. 73, No. 7, July 2021, pp 924–939 DOI 10.1002/acr.24596
2. 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 | FDA
3. Ytterberg, SR, Bhatt, DL, Mikuls TR et al. N Engl J Med 386: 4: 316-326 DOI: 10.1056/NEJMoa2109927

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