In This Issue

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Safety Alert: Thromboembolism with Tofacitinib

By: Alex Taylor, Pharm.D.

Background: The Janus kinase (JAK) inhibitors are a novel class of oral biological therapies that modulate immune cell function by inhibiting the JAK enzymatic pathway responsible for regulation of gene expression, intracellular activity, and hematopoiesis.[1,2] Tofacitinib (Xeljanz®, Xeljanz® XR; Pfizer, Inc.), a JAK inhibitor, gained Food and Drug Administration (FDA) approval as a second- or third-line agent in adults for the treatment of moderate to severe rheumatoid arthritis (RA) in 2012, psoriatic arthritis in 2017, and ulcerative colitis (UC) in 2018.[3,4] Other agents in the JAK inhibitor class approved for a variety of autoimmune diseases include baricitinib (Olumiant®; Lilly Pharmaceuticals), fedratinib (Inrebic®; Celgene Corporation), ruxolitinib (Jakafi®; Incyte Corporation), and upadacitinib (Rinvoq®; AbbVie, Inc.).[5-8] The JAK inhibitors have grown in popularity due to their oral route of administration; however, there have been recent reports of increased risk of thrombosis and death with these agents.[1-4, 9-11]

FAERS Reports: Post-marketing data from the FDA Adverse Event Reporting System (FAERS) for tofacitinib (immediate and extended-release) and ruxolitinib were published in 2018.[12] Reporting odds ratios (RORs) and empirical Bayesian geometric mean (EBGM) were used to determine the statistical significance of the reported versus the expected spontaneous occurrence rates for thromboembolic events associated with the use of these agents; RORs with a two-sided confidence bound >1 and EBGM one-sided confidence bound >1 were considered significant.[12,13] The reporting rates for deep vein thrombosis, pulmonary embolism, and thrombosis were not significantly higher than the expected spontaneous occurrence rates for these JAK inhibitors. However, for pulmonary

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Safety Alert: Breathing Difficulties with Gabapentinoids

By: Samantha Minnick, Pharm.D.

Background: Gabapentinoids including gabapentin (Neurontin®; Pfizer) and pregabalin (Lyrica®, Lyrica CR®; Pfizer) are a class of medications used for seizure disorders and a variety of nerve related pain conditions.[1-3] These non-opioid medications have become appealing adjunctive pain options during the opioid crisis.[4] Between 2012 and 2016 there was an increase in annual gabapentin prescriptions of 8.3 to 13.1 million and an increase in annual pregabalin prescriptions of 1.9 to 2.1 million. A physician office-based survey in 2016 noted that 14% and 19% of patient encounters involving gabapentin and pregabalin, respectively, included concomitant opioid use. With the increased prescribing of these agents there have been growing reports of breathing difficulties associated with their use, especially in those with pre-existing respiratory conditions, advanced age, or concomitant central nervous system (CNS) depressant use such as opioids, antihistamines, antipsychotics or benzodiazepines.

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thrombosis the RORs and EBGM were statistically significant as follows: 2.46 (95% Confidence Interval [CI]:1.55-3.91) and 2.46 (one-sided 95% CI:1.64) for tofacitinib, respectively, 2.48 (95% CI:0.80-1.53) and 1.25 (one-sided 95% CI: 0.7) for tofacitinib XR, respectively and 1.46 (95% CI: 0.76-2.80) and 1.56 (one-sided 95% CI:0.57) for ruxolitinib, respectively. Furthermore, FAERS data included 18 cases of pulmonary thrombosis associated with tofacitinib, nine for ruxolitinib, and three for tofacitinib XR in which these medications were classified as the "primary suspect" drug. In addition the RORs and EBGM for portal vein thrombosis with ruxolitinib were statistically significant as follows: 4.08 (95% CI:2.25-7.38) and 3.04 (one-sided 95% CI:1.79), respectively. Although the post-marketing surveillance datum suggests increased risk for certain thrombotic events with these agents, analysis of FAERS data is limited by inability to establish causal relationships, confounders, and underreporting. Therefore, post-marketing safety trials were needed to further establish the thromboembolic risk of JAK inhibitors.

Post-Marketing Studies: On February 19, 2019, Pfizer announced the FDA post-marketing requirement study A3921133 was transitioning RA patients who were receiving tofacitinib 10 mg twice daily to 5 mg twice daily.[11] This action was in response to a safety notification from the Tofacitinib Rheumatology Data Safety Monitoring Board regarding increased incidence of pulmonary embolism and overall mortality in the 10 mg treatment arm.[10,11] Study A3921133 is an ongoing, open-label study to evaluate the cardiovascular, malignant, and infectious side effects of tofacitinib 5 mg and 10 mg versus a tumor necrosis factor (TNF) inhibitor control group.[11] To meet enrollment criteria, patients were required to be ≥50 years old, have at least one cardiovascular risk factor, and be on stable doses of methotrexate. Based on the interim results of the A3921133 study reported in January 2019, there were 19 cases of pulmonary embolism and 45 cases of death out of 3884 patient-years in the tofacitinib 10 mg twice daily arm versus three cases of pulmonary embolism and 25 cases of death out of 3982 patient-years in the TNF inhibitor arm.[10]

Black Boxed Warnings: In response to the preliminary results of the A3921133 study, the FDA released a Drug Safety Communication on February 25, 2019, alerting the public to the increased risk of pulmonary embolism and death in patients with RA receiving tofacitinib 10 mg twice daily.[4] On July 26, 2019, the FDA released a follow-up notification announcing the approval of black boxed warnings for thrombosis and mortality with tofacitinib and tofacitinib XR.[10] Baricitinib and upadacitinib also have black boxed warnings for thrombosis, but not mortality.[5,8] The tofacitinib dose of 10 mg twice daily is FDA-approved only for UC to be given as induction therapy for up to 16 weeks and as maintenance therapy if there is a loss of response to the 5 mg twice daily regimen.[1-3,10]

Pharmacist Considerations: Health-care providers should follow the FDA-approved dosing recommendations for tofacitinib.[1-4,10] For UC therapy, the 10 mg twice daily maintenance dose should only be used for the shortest duration necessary to maintain remission. Tofacitinib should be avoided in patients ≥50 years of age with ≥ 1 cardiovascular risk factor. Patients should be advised to stop taking tofacitinib and seek immediate medical attention if experiencing signs and symptoms of thrombosis.

Formulary Status: For inpatients, tofacitinib is restricted to the Department of Gastroenterology for initiation of therapy in adult patients with moderate to severe UC refractory to corticosteroid therapy.[1] Continuation of home therapy is not restricted. It is non-formulary for pediatric patients.

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FAERS Reports: Between January 2012 and October 2017 there were a total of 49 cases of respiratory depression with gabapentinoid use reported to the FDA Adverse Event Reporting System (FAERS); 12 of the 49 cases resulted in death.[4] The FDA also reviewed the results of two randomized, double-blind, placebo-controlled studies in healthy individuals, three observational trials, and several animal studies. One observational trial by Weingarten and colleagues evaluated the rate of respiratory depression post-anesthesia following total joint arthroplasty with a multimodal preoperative pain protocol which included gabapentinoids and sustained-release (SR) oxycodone.[5] A total of 11,970 patients were identified between January 2008 and December 2012. Dosing regimens for gabapentin and SR oxycodone were adjusted based on age. Respiratory depression occurred in 2836 (23.7%) of patients (237 per 1000 cases). Significantly more respiratory events occurred in patients who received preoperative gabapentin (>300 mg) and SR oxycodone (>10 mg) with general anesthesia. The authors concluded that patients undergoing total knee or hip arthroplasty were at an increased risk for postoperative respiratory depression when agents with sedative potential such as gabapentin and SR oxycodone were used within a preoperative multimodal analgesia protocol with anesthesia.

Post-Marketing Data: Literature documenting respiratory failure with gabapentin was published as early as 2001.[6] A 69 year-old man with a history of chronic obstructive pulmonary disease (COPD) experienced respiratory distress following concomitant gabapentin and benzodiazepine use. Once gabapentin was discontinued the patient remained stable after discharge. Deljou and colleagues performed a retrospective case-control study from 2011-2015 to evaluate the associated risk with chronic or acute perioperative gabapentinoid use and respiratory depression within 48 hours of a surgical procedure.[7] Gabapentinoid home use was associated with an increased risk of respiratory depression; odds ratio (OR): 1.62, (95% Confidence Interval [CI]:0.63-4.17). Continuation of chronic gabapentin dosing postoperatively was associated with an increased risk of respiratory depression; OR: 6.30, 95% CI:2.38-16.66). The patients in this study chronically using a gabapentinoid were stratified into 'low' (<1800 mg gabapentin or 300 mg pregabalin daily) or 'high' (≥1800 mg gabapentin or ≥ 300 mg pregabalin daily) dose groups. A *post hoc* analysis found the associated risk for respiratory depression for each dosing regimen was as follows; low dose OR: 5.1, 95% CI:1.4-18.0, p=0.013 and high dose OR:14.1, 95% CI:2.6-76.4, p=0.002. It was noted that patients who were continued on gabapentinoid use postoperatively were re-initiated on their home dosing regimen rather than a reduced dose. The authors concluded that the use of chronic gabapentinoid medications, especially at higher doses, continued into the postoperative period was associated with an increased risk of respiratory depression.

FDA Changes: The FDA will require a warning of respiratory depression added to all prescribing information for gabapentinoids.[4] Drug manufacturers will also be required to conduct clinical trials regarding the abuse potential of these agents, especially in conjunction with opioids, with emphasis being given to evaluating the respiratory depressant effects.

Pharmacist Considerations: Health-care providers should be aware of the additive respiratory effects of gabapentinoids with other CNS depressing medications, especially in the elderly and those with underlying respiratory risk factors.[4] Patients should be educated on the signs and symptoms of respiratory depression or hypotension while using gabapentinoids. When initiating therapy the lowest effective dose should be used and titrated to the desired effect. If continuing therapy from home, confirm the correct dose has been ordered to decrease the risk of oversedation.[7] Careful monitoring for respiratory depression should be done in patients using gabapentinoids with concomitant CNS depressants, especially during the perioperative period.[4,5] If a provider is interested in discontinuing chronic gabapentinoid therapy it is important to taper the medication off over at least one week to avoid seizures or withdrawal symptoms.[1]

Formulary Status: Gabapentin and pregabalin are on both the adult and pediatric CCHS Formularies with no restrictions.[1]

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