Drug Saf (2018) 41:357–361
https://doi.org/10.1007/s40264-017-0622-2

SHORT COMMUNICATION

Analysis of Spontaneous Postmarket Case Reports Submitted to the FDA Regarding Thromboembolic Adverse Events and JAK Inhibitors

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Published online: 2 December 2017

Abstract

Introduction The Janus kinase (JAK) inhibitor baricitinib is approved in Europe and Japan for the treatment of rheumatoid arthritis. In April 2017, the US FDA expressed concern about thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]) observed in placebo-controlled clinical trials of baricitinib. The European and Japanese labels for baricitinib were recently updated to include a precaution related to potential thromboembolic events in patients at risk. Given that the FDA-approved drugs tofacitinib and ruxolitinib are in the same class, we conducted a safety review of the FDA's Adverse Event Reporting System (FAERS) to assess postmarketing reporting rates for related thromboembolic risks.

Methods Adverse event (AE) data for tofacitinib, tofacitinib extended-release (XR), and ruxolitinib were obtained from the FAERS. Reporting odds ratios (RORs) and the R package 'PhViD' to estimate the empirical Bayesian geometric mean (EBGM) were used to detect AEs with higher-than-expected reporting rates within the FAERS.

Results We did not find evidence in the FAERS for elevated reporting rates for DVT and PE across the three JAK inhibitors we analyzed. However, multiple drug–AE combinations relating to thromboembolic events had both RORs and EBGM values above 1, indicating a trend toward higher-than-expected reporting rates. For pulmonary thrombosis, the ROR values for ruxolitinib, tofacitinib, and tofacitinib XR were 1.46 (95% confidence interval [CI] 0.76–2.80), 2.46 (1.55–3.91), and 2.48 (0.80–7.71), respectively, while the EBGM values were 1.25 (0.70), 2.46 (1.64), and 1.56 (0.57), respectively. Ruxolitinib had ROR values of 4.08 (2.25–7.38) and 1.22 (0.97–1.53) for portal vein thrombosis and thrombosis, respectively. The EBGM values for the same drug–AE combinations were 3.04 (1.79) and 1.16 (0.96).

Conclusions Our safety review of postmarketing FAERS reports associated with three FDA-approved JAK inhibitors did not find elevated reporting rates for DVT and PE specifically. However, the FAERS data indicated that pulmonary thrombosis may potentially be a class-wide issue for JAK inhibitors. Portal vein thrombosis may also be a potential risk for ruxolitinib. While these FAERS data add to a growing body of evidence that JAK inhibitors may be contraindicated in patients at risk of thromboembolic events, the data need to be confirmed by future AE reporting trends, analysis of electronic health records, and/or future clinical trials.

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Key Points

Potential thromboembolic safety concerns for baricitinib, a Janus kinase (JAK) inhibitor, were recently raised by the US FDA.

The FDA has previously approved two other JAK inhibitors, tofacitinib and ruxolitinib, but has not issued any warnings regarding thromboembolic safety signals for these two medications.

A systematic review of the FDA's Adverse Event Reporting System (FAERS) found elevated reporting for both tofacitinib and ruxolitinib for certain thromboembolic adverse events, suggesting the possibility of a class-wide issue.

1 Background

Baricitinib is part of a group of compounds known as Janus kinase (JAK) inhibitors that supress the activity of one or more of the Janus kinase family of enzymes. Other prominent JAK inhibitors include two US FDA-approved drugs that are intended to treat two very different patient populations. Tofacitinib is indicated for the treatment of moderate to severe rheumatoid arthritis, while ruxolitinib is indicated for the treatment of intermediate- or high-risk myelofibrosis and polycythemia vera. Baricitinib was approved for use in patients with moderate to severe rheumatoid arthritis in Europe and Japan in February and July 2017, respectively. In April 2017, the FDA expressed concern about thromboembolic events observed during the clinical testing of baricitinib. According to the manufacturer, the reason for FDA action was "… that a new clinical study is necessary for a resubmission in order to further characterize the benefit/risk across doses, in light of the observed imbalance in thromboembolic events that occurred during the placebo-controlled period of the RA clinical program" [1]. Relatedly, the European Committee for Medicinal Products for Human Use (CHMP) recently added a precaution to the baricitinib label for patients who have risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE) [2]; the Japanese label for baricitinib includes a similar safety warning. In light of the thromboembolic safety concerns raised by the CHMP, Japanese regulators, and the FDA regarding baricitinib, we conducted a safety review of thromboembolic-related adverse events (AEs) reported to the FDA's Adverse Event Reporting System (FAERS) to assess whether similar safety signals might be associated with one or both of the FDA-approved drugs tofacitinib and ruxolitinib.

2 Methods

Spontaneous AE reports were obtained from the FAERS for tofacitinib, tofacitinib extended release (XR), and ruxolitinib, from their approval dates to 31 March 2017. Given that XR formulations of drugs can alter pharmacokinetics and other parameters, we assessed tofacitinib and tofacitinib XR separately. Cases were only included for analysis if the drug was listed as the 'primary suspect' by the person reporting the AE. Methods for data importation, normalization, and other analyses have been previously detailed by Hoffman et al. [3]. We calculated reporting odds ratios (RORs) using standard formulas [4]. ROR calculations with a two-sided lower 95% confidence bound > 1.0 were considered significant. ROR values were compared with a second statistical measure known as the empirical Bayesian geometric mean (EBGM). EBGM values were estimated using PhViD, an R package commonly used in pharmacovigilance signal detection. The one-sided 95% lower confidence bound of the EBGM (EB05) was also generated, with values > 1 considered to be significant [5]. Some individual AEs showed both ROR and EBGM results above 1.0, but without the lower bound of both measures above 1.0. We noted these as a 'trend' in the results table.

3 Results

Reported cases from the FAERS indicated that tofacitinib, tofacitinib XR, and ruxolitinib have elevated RORs and EBGMs for certain thromboembolic-related AEs (Table 1).

3.1 Pulmonary Thrombosis

The FAERS contained 18 unique cases of pulmonary thrombosis for tofacitinib, 9 cases for ruxolitinib, and 3 cases for tofacitinib XR, where the reporters identified these two medications as the 'primary suspect' drug. The ROR for pulmonary thrombosis was 2.46 (two-sided 95% confidence interval [CI] 1.55–3.91) for tofacitinib, 1.46 (0.76–2.80) for ruxolitinib, and 2.48 (0.80–7.71) for tofacitinib XR, and the EBGM for pulmonary thrombosis was 2.46 (one-sided 95% CI 1.64) for tofacitinib, 1.25 (0.70) for ruxolitinib, and 1.56 (0.57) for tofacitinib XR. Among the 18 reported cases for tofacitinib, 16 resulted in hospitalization. All of the 9 cases for ruxolitinib were reported to result in hospitalization, with two of these also suspected of causing the death of the patient. All 3 cases

for tofacitinib XR were reported to result in hospitalization. Pulmonary thrombosis is designated as an Important Medical Event (IME) Serious Event and was not listed as a potential safety risk on the labels of either tofacitinib, ruxolitinib, or tofacitinib XR at the time of this analysis. We first identified pulmonary thrombosis as a potential issue with tofacitinib on 31 December 2015 [6], and with ruxolitinib on 31 December 2016 [7].

3.2 Pulmonary Embolism

The FAERS contained 36 unique cases of PE for tofacitinib, 55 cases for ruxolitinib, and 3 cases for tofacitinib XR, where the reporters identified them as the 'primary suspect' drug. The ROR for PE was 0.33 (0.23–0.45) for tofacitinib, 0.59 (0.45–0.77) for ruxolitinib, and 0.16 (0.05–0.51) for tofacitinib XR, and the EBGM for PE was 0.37 (0.28) for tofacitinib, 0.57 (0.45) for ruxolitinib, and 0.18 (0.06) for tofacitinib XR. Among the 36 reported cases for tofacitinib, 25 resulted in hospitalization, 4 in death, and 5 as life-threatening events; of the 55 cases for ruxolitinib, 36 resulted in hospitalization, 12 in death, one in disability, and 5 as life-threatening events; and of the 3 cases for tofacitinib XR, all resulted in hospitalization. PE is designated as an IME Serious Event and was not listed as a potential safety risk on the labels of either tofacitinib, ruxolitinib, or tofacitinib XR at the time of this analysis.

3.3 Portal Vein Thrombosis

The FAERS contained 11 unique cases of portal vein thrombosis where ruxolitinib was identified by the reporter as the 'primary suspect' drug. The calculated ROR was 4.08 (2.25–7.38) and the EBGM was 3.04 (1.79). Among these 11 cases, 9 are reported as resulting in hospitalization and two in death. Portal vein thrombosis is designated as an IME Serious Event and was not a labeled safety risk for ruxolitinib at the time of this analysis. We first identified portal vein thrombosis as a potential issue with ruxolitinib on 31 December 15 [8]. In contrast, there have been no portal vein thrombosis FAERS cases regarding tofacitinib.

3.4 Deep Vein Thrombosis

The FAERS contained 18 unique cases of deep vein thrombosis for tofacitinib, 40 cases for ruxolitinib, and one case for tofacitinib XR, where the reporters identified them as the 'primary suspect' drug. The ROR for deep vein thrombosis was 0.22 (0.14–0.34) for tofacitinib, 0.57 (0.42–0.78) for ruxolitinib, and 0.07 (0.01–0.52) for tofacitinib XR. The EBGM for deep vein thrombosis was 0.24 (0.16) for tofacitinib, 0.54 (0.42) for ruxolitinib, and 0.08 (0.01) for tofacitinib XR. Among the 18 reported cases for tofacitinib, 11 resulted in hospitalization, 3 in death, one in disability, and one as a life-threatening event; of the 40 cases for ruxolitinib, 28 resulted in hospitalization, 10 in death, one in disability, and 3 as life-threatening events; and the one reported case for tofacitinib XR resulted in a non-specified serious outcome. Deep vein thrombosis is designated as an IME Serious Event and was not listed as a potential safety risk on the labels of either tofacitinib, ruxolitinib, or tofacitinib XR at the time of this analysis.

3.5 Thrombosis

The FAERS contained 43 unique cases of thrombosis for tofacitinib, 75 cases for ruxolitinib, and 5 cases for tofacitinib XR, where the reporters identified them as the 'primary suspect' drug. The ROR for thrombosis was 0.59 (0.43–0.79) for tofacitinib, 1.22 (0.97–1.53) for ruxolitinib, and 0.41 (0.17–1.00) for tofacitinib XR. The EBGM for thrombosis was 0.66 (0.51) for tofacitinib, 1.16 (0.96) for ruxolitinib, and 0.43 (0.20) for tofacitinib XR. Among the 43 reported cases for tofacitinib, 19 resulted in hospitalization, two in death, and one as a life-threatening event; of the 75 cases for ruxolitinib, 43 were reported as resulting in hospitalization, 11 in death, one in disability, and two as life-threatening events; and of the 5 cases for tofacitinib XR, 4 were reported to result in hospitalization. Thrombosis is designated as an IME Serious Event and was not listed as a potential safety risk on the labels of either tofacitinib, ruxolitinib, or tofacitinib XR at the time of this analysis.

3.6 Embolic and Thrombotic Events (Standardised Medical Dictionary for Regulatory Activities [MedDRA] Query)

The FAERS contained 494 (ROR 0.59), 326 (0.32), and 24 (0.14) unique cases listed under the Standardised MedDRA Query (SMQ) for embolic and thrombotic events where ruxolitinib, tofacitinib, and tofacitinib XR, respectively, were identified by the reporter as the 'primary suspect' drug. Overall disproportionality figures for the SMQ for embolic and thrombotic events was not above 1 for any of the three compounds (*data not shown*).

4 Discussion

A modest but growing body of evidence suggests that JAK inhibitors may not be suitable for patients at risk for thromboembolic events. Indeed, regulators in Europe and Japan have added warning labels to the labels of JAK inhibitors sold in their territories regarding thromboembolic risks. In the US, two JAK inhibitors have been FDA-approved and more are in the clinical testing stage. We

Table 1 Reporting odds ratio and empirical Bayesian geometric mean values for select thromboembolic adverse events

Drug	Adverse event	Label status	'Primary suspect' cases	ROR (95% CI[a])	EBGM (95% CI[a])
Ruxolitinib	Pulmonary thrombosis[d]	Not labeled	9	1.46 (0.76–2.80)	1.25 (0.70)
	Pulmonary embolism	Not labeled	55	0.59 (0.45–0.77)	0.57 (0.45)
	Portal vein thrombosis[c]	Not labeled	11	4.08[b] (2.25–7.38)	3.04[b] (1.79)
	Deep vein thrombosis	Not labeled	40	0.57 (0.42–0.78)	0.54 (0.42)
	Thrombosis[d]	Not labeled	75	1.22 (0.97–1.53)	1.16 (0.96)
Tofacitinib	Pulmonary thrombosis[c]	Not labeled	18	2.46[b] (1.55–3.91)	2.46[b] (1.64)
	Pulmonary embolism	Not labeled	36	0.33 (0.23–0.45)	0.37 (0.28)
	Portal vein thrombosis	Not labeled	0	–	–
	Deep vein thrombosis	Not labeled	18	0.22 (0.14–0.34)	0.24 (0.16)
	Thrombosis	Not labeled	43	0.59 (0.43–0.79)	0.66 (0.51)
Tofacitinib XR	Pulmonary thrombosis[d]	Not labeled	3	2.48 (0.80–7.71)	1.56 (0.57)
	Pulmonary embolism	Not labeled	3	0.16 (0.05–0.51)	0.18 (0.06)
	Portal vein thrombosis	Not labeled	0	–	–
	Deep vein thrombosis	Not labeled	1	0.07 (0.01–0.52)	0.08 (0.01)
	Thrombosis	Not labeled	5	0.41 (0.17–1.00)	0.43 (0.20)

CI confidence interval, *ROR* reporting odds ratio, *EBGM* empirical Bayesian geometric mean, *XR* extended release

[a]Two-sided CI for ROR; one-sided CI for EBGM

[b]ROR or EB05 lower-bound CI values > 1

[c]Both ROR and EB05 lower-bound CI values were > 1.0

[d]A trend where both ROR and EBGM were above 1.0, but neither lower-bound CI was above 1.0

assessed the FAERS, the FDA's spontaneous adverse event reporting system, to determine if there were elevated reporting trends for thromboembolic-related AEs for the JAK inhibitors currently marketed in the United States. Our review of the FAERS found elevated reporting for both tofacitinib and ruxolitinib for certain thromboembolic AEs, suggesting the possibility of a class-wide issue. Interestingly, our review did not uncover elevated reporting for two AEs (deep venous thrombosis and pulmonary embolism) previously mentioned by others as of possible concern for the drug class.

Many drugs, sometimes well after they are granted marketing approval by the FDA, develop distinct side effect profiles that were not evident during preapproval testing (examples include a fatal muscle-wasting syndrome triggered by Baycol, a cholesterol management drug [9]; life-threatening adverse cardiac events from Meridia, a weight-management drug [10]; and increased rates of both heart attacks and strokes associated with Vioxx, which was prescribed for osteoarthritis and joint pain [11]). These examples serve to underscore the fact that a drug's full safety profile is sometimes not know for many years after the completion of preclinical and clinical testing. Indeed, after approval, drugs are used in vastly more diverse populations than the relatively homogenous patients used in preapproval clinical trials. The continued monitoring of AEs that occur in a drug's postmarketing phase is therefore of great interest.

The FAERS provides data on a large volume of spontaneous reports, almost one million per year at current reporting rates [12], and can therefore be an important tool in the quest to monitor the evolving safety profile of approved medications. However, analysis of drug side effects using the FAERS has limitations. Since the FDA does not require a causal relationship to exist for an event to be reported, there is no certainty that the reported event was due to the suspected drug, the underlying disease of the patient, or some other cause. Many cases are not reported to the FAERS and the reporting rates may not be similar across the included drugs or within a given drug class. The 'primary suspect' or 'suspect' designation in the FAERS is subjective, and the influence of other drugs or factors cannot be ruled out from a given case report. Additional information from the reporter or manufacturer about a particular AE case may be available as narrative text that accompanies that case in the FAERS. These narrative texts are not included in the FAERS data provided by the FDA and were therefore not reviewed for the cases detailed here.

5 Conclusion

The FAERS data that we examined suggest that although thromboembolic-related AEs as a whole may not be a class-wide issue with JAK inhibitors, pulmonary thrombosis is a potential issue for the class, and portal vein

thrombosis may be a potential risk for ruxolitinib. The risk for any thromboembolic event has not been added to the FDA-approved label of any of the compounds within this class to date. We look forward to examining future FAERS reports, clinical trial results, and other real-world data resources such as electronic health records regarding this class of medications to determine if these potential safety signals become more robust.

Compliance with Ethical Standards

Conflict of interest Abril Verden, Mo Dimbil, Robert Kyle, and Brian Overstreet are employees and equity owners (through stock and/or stock options) of Advera Health Analytics, Inc. Keith Hoffman is a member of the Scientific Advisory Board and an equity owner (through stock and/or stock options) of Advera Health Analytics. Data from Advera Health Analytics were used in the creation of this article and its findings.

Funding No sources of funding were used to assist in the preparation of this study.

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