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ORIGINAL RESEARCH ARTICLE

Thromboembolic Safety Reporting of Tofacitinib and Baricitinib: An Analysis of the WHO VigiBase

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Abstract

Introduction The Janus kinase (JAK) inhibitors tofacitinib and baricitinib are new treatments for rheumatic diseases. Recent concerns regarding the risk of thrombosis have led to warnings by competent authorities. We therefore aimed to examine the thromboembolic safety signal for tofacitinib and baricitinib.

Methods Individual case safety reports (ICSRs) for tofacitinib and baricitinib were retrieved from the World Health Organization global database VigiBase in April 2019. Primary outcomes were deep vein thrombosis (DVT) and pulmonary thrombosis (PT) or pulmonary embolism (PE). Patient demographics were summarized and then stratified by outcome. Disproportionality analyses were conducted by estimating the reporting odds ratios (RORs) and 95% confidence intervals (CIs) worldwide, and stratified by either Europe or the US.

Results In both the tofacitinib ($n=40{,}017$) and baricitinib ($n=2138$) ICSRs, patients with reported DVT or PT/PE were older and had higher reporting of prothrombotic medications or antithrombotic treatments, suggesting a pre-existing thromboembolic risk/event. In Europe, tofacitinib was associated with increased reporting for DVT (ROR 2.37, 95% CI 1.23–4.56) and PT/PE (ROR 2.38. 95% CI 1.45–3.89). For baricitinib, a threefold increased reporting odds was observed for DVT (ROR 3.47, 95% CI 2.18–5.52) and PT/PE (ROR 3.44, 95% CI 2.43–4.88) in Europe. In the US, tofacitinib was only associated with an elevated ROR of PT (ROR 2.05, 95% CI 1.45–2.90) and no baricitinib ICSRs were reported.

Conclusion This study supports the current recommendation for cautious use of tofacitinib in patients with high thromboembolic risk. Moreover, with a similar patient profile and elevated reporting for baricitinib, a potential class effect of JAK inhibitors cannot be ruled out.

1 Introduction

In the last decade, Janus kinase (JAK) inhibitors have emerged as novel targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs). These drugs work through the inhibition of one or more of the family of JAK enzymes: JAK1, JAK2, JAK3, or TYK2 [1]. As of April 2019, two JAK inhibitors were approved for the management of rheumatoid arthritis (RA)—tofacitinib and baricitinib. Tofacitinib inhibits mainly JAK1 and JAK3, while baricitinib is a selective JAK1, JAK2 inhibitor [2]. Tofacitinib was approved by the US Food and Drug Administration (FDA) in 2012 [3] and the European Medicines Agency (EMA) in 2017 [4], and is approved as 5 and 10 mg tablets [5, 6] and extended-release tablets [3]. Conversely, baricitinib 2 and 4 mg daily was approved by the EMA in 2017 [7, 8], yet only the 2 mg daily dose was approved by the FDA in 2018 [9].

The differential approval of baricitinib between the EMA and FDA was largely due to safety concerns regarding an increased risk for thromboembolic events that appeared to be dose-related. While the EMA included a warning on venous thromboembolism in the product information [8, 10], the FDA requested additional studies to assess the safety and efficacy of the two baricitinib doses (2 and 4 mg) [11]. Following a pooled analysis of patients receiving baricitinib during clinical development (phase Ib through to phase III),

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Key Points

Thromboembolic safety concerns with the use of tofacitinib and baricitinib, both treatments for rheumatoid arthritis, need further investigation.

This study is a large, worldwide analysis of suspected adverse drug reactions reported for tofacitinib and baricitinib.

Indications of pre-existing thromboembolic risk were present in patients receiving tofacitinib or baricitinib and reporting deep vein thrombosis or pulmonary thrombosis/embolism. These particularly included elderly patients, patients with prothrombotic medication (e.g. contraceptives), or patients already under antithrombotic treatment.

The disproportionality analyses support current restrictions for the use of tofacitinib related to thromboembolic events, and expand the debate of baricitinib use, especially in Europe.

an increased risk of thrombosis was identified and this contributed to the FDA decision to restrict approval to the 2 mg daily dose and include a black-box warning [11–13].

In light of the safety concerns with baricitinib and to examine the potential for a class effect, the risk of thromboembolic events was assessed for other approved JAK inhibitors (tofacitinib, tofacitinib extended release, and ruxolitinib) in the FDA Adverse Event Reporting System (FAERS) [14]. While this study did not identify elevated reporting rates for deep vein thrombosis (DVT) or pulmonary embolism (PE) individually, it was suggested that pulmonary thrombosis (PT) could be a potential safety issue for tofacitinib, with a reporting odds ratio (ROR) of 2.46 (95% confidence interval [CI] 1.55–3.91) [14].

A recent postmarketing ongoing safety trial (study A3921133) triggered concerns of blood clots in the lungs, and death in RA patients older than 50 years of age, with at least one cardiovascular risk factor and treated with high-dose tofacitinib [15–17]. Following these findings, both the FDA and EMA recently issued new boxed warnings for tofacitinib 10 mg twice-daily doses, citing recommendations to avoid use in patients with a high risk of thrombosis (such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilization) [15–20].

Surveillance of new drugs is a necessary practice to overcome the limited safety knowledge at the beginning of their use. Thus, as both tofacitinib and baricitinib are new medications, their safety in real-world data is limited, and both regulatory bodies and clinical researchers have raised concerns about their thromboembolic risk, we sought to investigate this further. We aimed to evaluate postmarketing surveillance data on the suspected adverse drug reactions (SADRs) collected in the World Health Organization (WHO) global database of individual case safety reports (ICSRs), VigiBase. This passive drug monitoring represents a key element in early signal detection for newly marketed drugs [21]. Thus, we sought to investigate whether the safety reporting for tofacitinib, with particular focus on thromboembolic events, supports the recent safety signal. Additionally, we aimed to similarly study the thromboembolic safety reports for baricitinib, particularly in Europe where both the 2 and 4 mg doses are available.

2 Methods

2.1 Data Source

Since 1968, VigiBase [22, 23], the WHO global database of ICSRs, constitutes the key asset of the WHO Programme for International Drug Monitoring. VigiBase collects, processes, and homogenizes worldwide SADRs. These SADRs are reported as ICSRs, by healthcare professionals and patients, to pharmacovigilance centers from more than 130 countries [22]. Vigibase includes mainly post-authorization unsolicited or spontaneous reports, but, to a lesser extent, it also contains reports from clinical studies or intensive monitoring programs [22]. The ICSRs in VigiBase include details on the demographics of the patient (age, sex), reporting country, and reporter description (e.g. healthcare professional, patient). Additionally, all medications that could be potentially related to the SADR are reported at the time of the SADR, and are classified as the suspect drug, interacting drug, or comedication based on the expected causality. However, the duration or timing of each medication prior to the SADR is not accurately recorded in the databases. All reports can vary in completeness. Within the Vigibase, all potential SADRs are recorded and coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 22.1, and all medications are coded according to WHODrug.

2.2 Study Population

ICSRs including tofacitinib and baricitinib as suspect or interacting drugs were extracted on 1 April 2019 from the VigiBase database. All other ICSRs recorded in VigiBase were used as the reference group and were accessed through VigiLyze, a platform from Uppsala Monitoring Centre (UMC) enabling instant overview of the VigiBase information.

2.3 Outcomes of Interest

The primary outcomes of interest were DVT and blood clots in the lungs. DVT was identified by the MedDRA® Preferred Term (MedDRA® PT) 'deep vein thrombosis'. The ICSRs mentioning blood clots in the lungs were identified by the MedDRA® PT 'pulmonary thrombosis' and 'pulmonary embolism', and these two terms were analyzed as one single outcome (PT/PE). Thus, if an ICSR mentioned both events, it was counted as one. Subsequently, 'pulmonary thrombosis' (PT) and 'pulmonary embolism' (PE) were as well observed separately as two independent outcomes.

In a secondary analysis, we investigated other potential safety signals related to thromboembolism. These included the following MedDRA® PTs and High Level Terms (MedDRA® HLTs): 'peripheral embolism' (MedDRA® PT), 'retinal embolism and thrombosis' (MedDRA® HLT), 'ophthalmic artery thrombosis' (MedDRA® PT), 'ophthalmic vein thrombosis' (MedDRA® PT), 'renal embolism and thrombosis' (MedDRA® HLT), 'adrenal thrombosis' (MedDRA® PT), 'femoral artery embolism' (MedDRA® PT), 'spinal artery embolism' (MedDRA® PT), 'spinal artery thrombosis' (MedDRA® PT), 'subclavian artery embolism' (MedDRA® PT), 'subclavian vein thrombosis' (MedDRA® PT), 'subclavian artery thrombosis' (MedDRA® PT), 'coronary artery embolism' (MedDRA® PT), and 'coronary artery thrombosis' (MedDRA® PT). Additionally, to provide an overview of the safety profile of tofacitinib and baricitinib, the SADRs were described according to the MedDRA® System Organ Class (MedDRA® SOC).

2.4 Data Analysis

The descriptive characteristics of the ICSRs were summarized using counts and proportions or means and standard deviations (SD), as appropriate, for tofacitinib and baricitinib separately. Within each medication, ICSRs were summarized overall and stratified by the primary outcome of interest (DVT or PT/PE). The reported dose or amount (milligrams) was calculated from those ICSRs providing the amount as milligrams or as 'DF dosage form'. The dose was calculated independently of the reported frequency due to high variability and missing data. Additionally, ICSRs mentioning more than one amount were considered as a missing amount. All comedications recorded in the VigiBase data were identified and a detailed list is provided in electronic supplementary Table S1. In a sensitivity analysis, we further observed the ICSRs filtering by spontaneous reporting (unsolicited reports) for both JAK inhibitors. ICSRs with a recorded age equal to 0 months and without any other hint of transplacental administration were set to 'missing age'.

To examine signals of disproportionate reporting (SDR) of the events of interest, we calculated the ROR with corresponding 95% CIs [24], and the information component (IC) with the corresponding lower end of the 95% credibility interval (IC025) [25, 26]. These disproportionality methods aim to compare the observed versus expected reporting ratio for a specific event and a medicinal product [27]. The expected reporting ratio was calculated using the ICSRs of every other medicine in VigiBase. We conducted disproportionality analyses for the outcomes of interest and all MedDRA® SOCs, stratified by tofacitinib or baricitinib, using the VigiLyze data. Additionally, we completed a secondary analysis that stratified by reporting region to examine ICSRs originating from Europe and the US. This was done for two reasons. First, it was hypothesized that these would be the major contributors to the JAK inhibitor ICSRs. Second, this stratification would roughly match the areas covered by FDA and EMA regulations, where differential approval for baricitinib dose (2 and 4 mg) was observed. The analyses were conducted using the statistical software R [28], and plots were performed using GraphPad Prism 8 [29].

3 Results

3.1 Descriptive Analysis

We identified 42,155 ICSRs with tofacitinib or baricitinib as the suspect or interacting drug. Of these, 40,017 ICSRs were reported for tofacitinib and 2138 ICSRs for baricitinib. ICSRs were identified from 46 and 24 reporting countries for tofacitinib and baricitinib, respectively. For tofacitinib, the majority of reports were from the US (79.6%), followed by Canada (11.9%) and Europe (3.3%). Conversely, for baricitinib, 97.2% of ICSRs were from Europe, with no reports from the US or Canada. The included ICSRs were recorded from 1 June 2011 to 31 March 2019, and from 6 July 2014 to 31 March 2019, for tofacitinib and baricitinib, respectively.

The characteristics of the ICSRs are described in Table 1, stratified by the outcome of interest. The mean age was 60.5 years (SD 12.5) for tofacitinib patients and 60.8 (SD 12.6) for baricitinib patients, and the majority were female (79.2% tofacitinib and 81.4% baricitinib). In two ICSRs, age was 0 months and there was no other hint of transplacental administration, thus age was transformed to 'missing'. The majority of ICSRs stated RA as the indication for the JAK inhibitors.

When stratifying by outcome of interest, 49 tofacitinib ICSRs and 22 baricitinib ICSRs reported DVT (Table 1). These constituted 0.1% and 1.0% of the total ICSRs for tofacitinib and baricitinib, respectively. For PT/PE, we identified 114 tofacitinib ICSRs and 36 baricitinib ICSRs, which constituted 0.3% and 1.7% of the total ICSRs for tofacitinib and baricitinib, respectively. A higher frequency of elderly

Table 1 Characteristics of the individual case safety reports (ICSRs) with tofacitinib and baricitinib as suspect/interacting drugs, stratified by outcome of interest

Characteristic	Tofacitinib[a]			Baricitinib[b]		
	Total	DVT	PT/PE	Total	DVT	PT/PE
Total ICSRs	40,017 (100)	49 (100)	114 (100)	2138 (100)	22 (100)	36 (100)
Report type						
Spontaneous	37,981 (94.9)	36 (73.5)	97 (85.1)	939 (43.9)	17 (77.3)	28 (77.8)
Report from study	1751 (4.4)	13 (26.5)	17 (14.9)	1199 (56.1)	5 (22.7)	8 (22.2)
Other	285 (0.7)	–	–	–	–	–
Age, years						
Mean [SD]	60.5 [12.5]	61.2 [14.5]	61.4 [12.7]	60.8 [12.6]	65.3 [8.7]	66.4 [10.2]
0–17	98 (0.2)	–	–	–	–	–
18–49	5919 (14.8)	8 (16.3)	13 (11.4)	175 (8.2)	1 (4.6)	1 (2.8)
50–64	14,877 (37.2)	13 (26.5)	41 (36.0)	369 (17.3)	7 (31.8)	10 (27.8)
65–74	7928 (19.8)	14 (28.6)	39 (34.2)	221 (10.3)	5 (22.7)	7 (19.4)
> 75	3338 (8.3)	6 (12.2)	4 (3.5)	111 (5.2)	1 (4.6)	7 (19.4)
Unknown	7857 (19.6)	8 (16.3)	17 (14.9)	1262 (59.0)	8 (36.4)	11 (30.6)
Sex						
Female	31,705 (79.2)	33 (67.4)	85 (74.6)	1740 (81.4)	17 (77.3)	29 (80.6)
Male	6772 (16.9)	16 (32.7)	25 (21.9)	363 (17.0)	4 (18.2)	7 (19.4)
Unknown	1540 (3.9)	–	4 (3.5)	35 (1.6)	1 (4.6)	–
Date of recording in VigiBase, year						
2011	2 (0.0)	–	–	–	–	–
2012	11 (0.0)	–	–	–	–	–
2013	36 (0.1)	–	1 (0.9)	–	–	–
2014	2257 (5.6)	13 (26.5)	15 (13.2)	5 (0.2)	–	–
2015	5013 (12.5)	8 (16.3)	15 (13.2)	3 (0.1)	–	–
2016	5597 (14.0)	2 (4.1)	13 (11.4)	4 (0.2)	–	–
2017	11,259 (28.1)	5 (10.2)	26 (22.8)	92 (4.3)	4 (18.2)	3 (8.3)
2018	15,246 (38.1)	17 (34.7)	36 (31.6)	1347 (63.0)	9 (40.9)	21 (58.3)
2019	596 (1.5)	4 (8.2)	8 (7.0)	687 (32.1)	9 (40.9)	12 (33.3)
Region of reporting						
USA	31,841 (79.6)	23 (46.9)	80 (70.2)	–	–	–
Europe	1334 (3.3)	9 (18.4)	15 (13.2)	2077 (97.2)	18 (81.8)	33 (91.7)
Other	6842 (17.1)	17 (34.7)	19 (16.7)	61 (2.9)	4 (18.2)	3 (8.3)
Indication for tofacitinib/baricitinib						
Rheumatoid arthritis[c]	24,496 (61.2)	36 (73.5)	74 (64.9)	1671 (78.2)	15 (68.2)	25 (69.4)
Other	2824 (7.1)	7 (14.3)	23 (20.2)	17 (0.8)	–	4 (11.1)
Missing	12,697 (31.7)	6 (12.2)	17 (14.9)	450 (21.1)	7 (31.8)	7 (19.4)
Tofacitinib amount, mg						
5	20,377 (50.9)	21 (42.9)	56 (49.1)			
10	1431 (3.6)	13 (26.5)	17 (14.9)			
11	10,469 (26.2)	5 (10.2)	11 (9.6)			
Other	537 (1.3)	1 (2.0)	1 (0.9)			
Unknown	7203 (18.0)	9 (18.4)	29 (25.4)			
Baricitinib amount, mg						
2				268 (12.5)	5 (22.7)	4 (11.1)
4				1268 (59.3)	10 (45.5)	17 (47.2)
Other				46 (2.2)	2 (9.1)	2 (5.6)
Unknown				556 (26.0)	5 (22.7)	13 (36.1)
Number of medications per report						

Table 1 (continued)

Characteristic	Tofacitinib[a]			Baricitinib[b]		
	Total	DVT	PT/PE	Total	DVT	PT/PE
Mean [SD]	3.2 [4.0]	8.4 [6.5]	5.8 [6.6]	2.5 [2.7]	3.5 [3.7]	4.9 [5.1]
Median [IQR]	1 [1–4]	7 [2–15]	3 [1–9]	1 [1–3]	1 [1–8]	1 [1–10]
< 5 reported medications	31,704 (79.2)	20 (40.8)	69 (60.5)	1820 (85.1)	15 (68.2)	22 (61.1)
5–9 reported medications	5115 (12.8)	7 (14.3)	21 (18.4)	236 (11.0)	5 (22.7)	4 (11.1)
≥ 10 reported medications	3198 (8.0)	22 (44.9)	24 (21.1)	82 (3.8)	2 (9.1)	10 (27.8)
Comedication[d]						
Glucocorticoids	5297 (13.2)	23 (46.9)	23 (20.2)	390 (18.2)	6 (27.3)	7 (19.4)
sDMARD	10,184 (25.5)	26 (53.1)	44 (38.6)	449 (21.0)	6 (27.3)	8 (22.2)
bDMARD	3293 (8.2)	8 (16.3)	16 (14.0)	64 (3.0)	–	1 (2.8)
Contraceptives/estrogens/progestogens	551 (1.4)	6 (12.2)	18 (15.8)	13 (0.6)	–	3 (8.3)
Antidepressants	2409 (6.0)	14 (28.6)	23 (20.2)	74 (3.4)	1 (4.6)	4 (11.1)
Antithrombotic agents	1685 (4.2)	12 (24.5)	21 (18.4)	94 (4.4)	1 (4.6)	2 (5.6)
Vitamin K antagonists	269 (0.7)	2 (4.1)	5 (4.4)	18 (0.8)	–	–
Platelet aggregation inhibitors (excluding heparin)	1269 (3.2)	6 (12.2)	7 (6.1)	48 (2.3)	–	2 (5.6)
Heparins	31 (0.1)	2 (4.1)	1 (0.9)	7 (0.3)	–	–
Direct thrombin inhibitors	17 (0.0)	–	–	2 (0.1)	–	–
Direct factor Xa inhibitors	198 (0.5)	3 (6.1)	11 (9.7)	21 (1.0)	1 (4.6)	–

Data are expressed as *n* (%) unless otherwise specified

DVT deep vein thrombosis, *PT/PE* pulmonary thrombosis or pulmonary embolism, *SD* standard deviation, *IQR* interquartile range, *sDMARD* synthetic disease-modifying antirheumatic drug, *bDMARD* biologic disease-modifying antirheumatic drug, *ICSRs* individual case safety reports,

[a]ICSRs for tofacitinib identified between 1 June 2011 and 31 March 2019, from the VigiBase data extracted on 1 April 2019

[b]ICSRs for baricitinib identified between 6 July 2014 and 31 March 2019, from the VigiBase data extracted on 1 April 2019

[c]Terms used to identify rheumatoid arthritis as an indication for the JAK inhibitors are included in electronic supplementary Table S1

[d]A detailed list of drugs constituting the reported comedication is included in electronic supplementary Table S1. The reported comedication corresponds with the medication present at the time of the suspected adverse drug reaction or shortly before it, i.e. medications that could have potentially had an impact on the event and do not include medications prescribed after or as a result of the adverse event

patients (> 65 years of age) was observed in ICSRs with reported DVT or PT/PE, versus the overall ICSRs for the studied drugs (Table 1). For ICSRs with a reported DVT or PT/PE, the mean age was slightly higher than the observed among all reports, with a mean of 61.2 years and 61.4 years for tofacitinib ICSRs with DVT and PT/PE, respectively, and a mean of 65.3 years and 66.4 years for baricitinib ICSRs with DVT or PT/PE, respectively. Additionally, ICSRs with DVT or PT/PE events showed higher reporting of medications associated with an elevated thromboembolic risk (Table 1). For tofacitinib, 12.2% (DVT) and 15.8% (PT/PE) reported hormonal treatment as a comedication, compared with 1.4% of the total tofacitinib ICSRs. Similarly, higher reporting of antidepressants and antithrombotics was reported among ICSRs with a DVT or PT/PE event, when compared with the overall reporting for each drug. Similar results were obtained in the sensitivity analysis of the 37,981 and 939 spontaneous ICSRs for tofacitinib and baricitinib, respectively. Descriptive results are provided in electronic supplementary Table S2.

3.2 Disproportionality Analysis

Figure 1 provides an overview of the disproportionality analysis to identify SADRs of tofacitinib ICSRs, with a detailed overview provided in electronic supplementary Table S3. For tofacitinib, the worldwide ROR for DVT was 0.49 (95% CI 0.37–0.64), with an IC of − 1.03 (IC025 − 1.49). A similar outcome was observed in the US, but, within Europe, the observed ROR was 2.37 (95% CI 1.23–4.56), with an IC of 1.14 (IC025 0.00). For suspected PT/PE events, the tofacitinib worldwide ROR was 0.84 (95% CI 0.70–1.00), with an IC of < 0. When stratified by region, the ROR in the US was 0.52 (95% CI 0.42–0.64) and the IC was − 0.94 (IC025 − 1.30). In contrast, the European ROR was 2.38 (95% CI 1.45–3.89), with an IC of 1.18 (IC025 0.34). Notably, within Europe, no PT SADRs were reported for tofacitinib, thus the overall estimate was attributable to the 16 cases of PE. In contrast, when examined individually in the US, a discrepancy between the disproportionality measured for PE

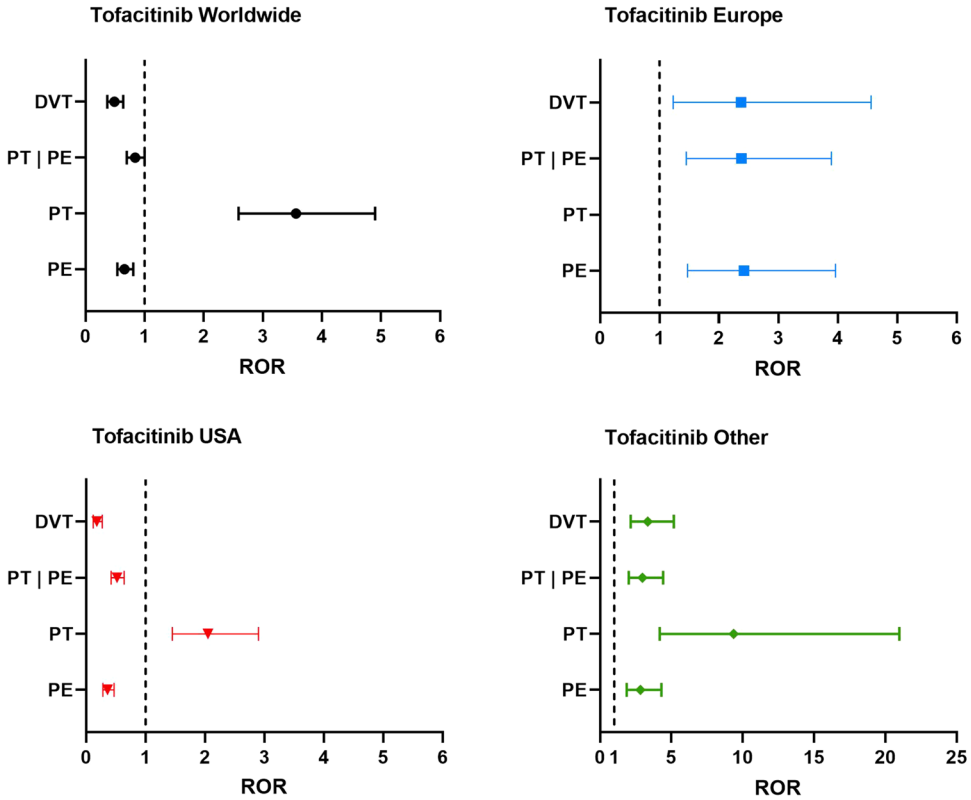

Fig. 1 Disproportionality analysis of suspected thromboembolic events for tofacitinib compared with all other medications in the WHO VigiBase data. Outcomes of DVT or PT and/or PE were defined according to the Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms version 22.1. Vertical bars on the ROR point estimate indicate the 95% confidence intervals. *ROR* reporting odds ratio, *DVT* deep vein thrombosis, *PT* pulmonary thrombosis, *PE* pulmonary embolism

(ROR 0.36, 95% CI 0.28–0.47) and PT (ROR 2.05, 95% CI 1.45–2.90) was observed.

The disproportionality analysis of baricitinib ICSRs is provided in Fig. 2 and electronic supplementary Table S4. The baricitinib worldwide ROR for DVT was 4.82 (95% CI 3.17–7.34) and the IC was 2.14 (IC025 1.43). The SDR was as well-elevated when considering only reports from Europe, with a ROR of 3.47 (95% CI 2.18–5.52) and IC of 1.69 (IC025 0.90). The disproportionality of PT/PE worldwide resulted in a ROR of 5.60 (95% CI 4.02–7.78) and IC of 2.38 (IC025 1.82), and in Europe, a ROR of 3.44 (95% CI 2.43–4.88) and IC of 1.71 (IC025 1.12). Every PT/PE event for baricitinib corresponded only with PE. No ICSRs for baricitinib were reported from the US.

Results from the secondary analysis examining other thromboembolic events are provided in electronic supplementary Tables S3 and S4. These secondary outcomes were infrequently reported for the studied drugs, as well as for all other drugs in the database.

The complete safety profile of tofacitinib and baricitinib SADRs is provided in electronic supplementary Figs. S1 and S2, respectively. For both tofacitinib and baricitinib, the MedDRA® SOC outcome 'infections and infestations' was associated with an elevated disproportionality of reporting.

4 Discussion

4.1 Discussion of Study Findings

This real-world study identified that patients with a reported DVT or PT/PE as an SADR generally had risk factors associated with thromboembolic outcomes, such as older age and higher reporting of contraceptives, antidepressants, and antithrombotic agents, which could indicate a pre-existing thromboembolic risk or event. Additionally, a safety signal was identified for DVT and PT/PE for baricitinib in Europe. For tofacitinib, we observed a discrepancy between the US and Europe. Among European reports, we identified elevated reporting of DVT and PT/PE, similar to baricitinib. However, in the US, which accounted for the majority of ICSRs, tofacitinib was associated with a lower reporting for DVT and PE but an increased reporting for PT SADRs. Overall, the results of this study support the concerns regarding the use of tofacitinib in patients at risk of thromboembolism, and, despite current regulatory discussions focusing on tofacitinib and limited existing real-world evidence for baricitinib, we cannot rule out a potential class effect due to the observed disproportionality in baricitinib ICSRs.

Our results on tofacitinib are in line with the results of Verden et al., using the US FAERS data to examine tofacitinib and ruxolitinib safety [14]. In the US FAERS data, PT showed an elevated reporting of disproportionality,

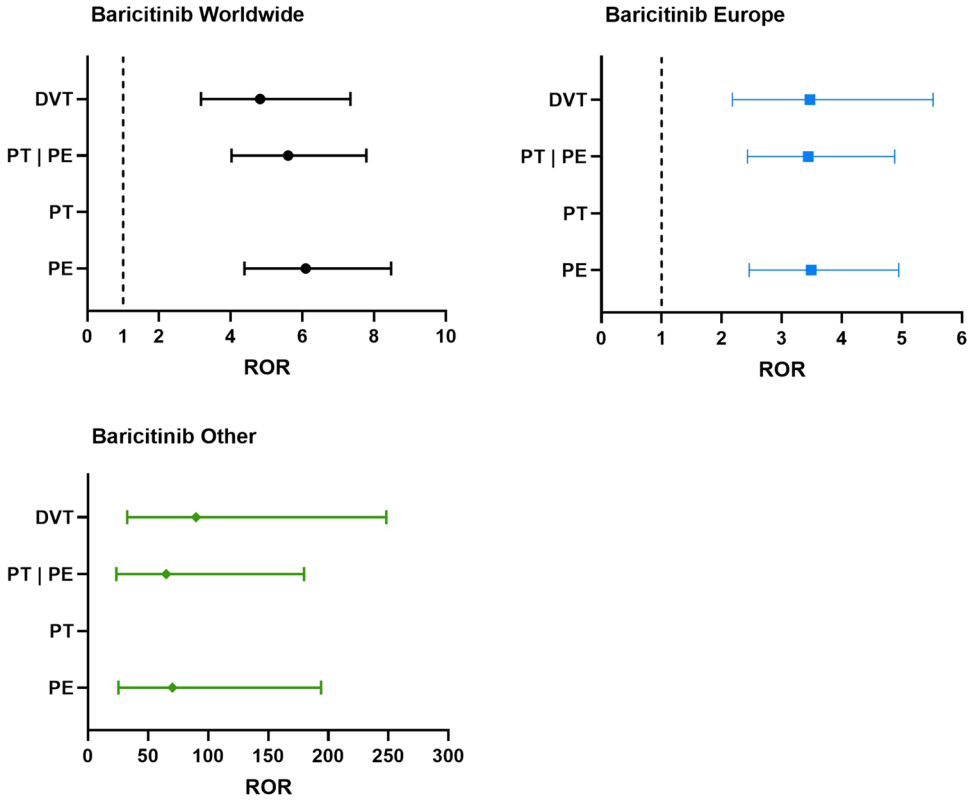

Fig. 2 Disproportionality analysis of suspected thromboembolic events for baricitinib compared with all other medications in the WHO VigiBase data. Outcomes of DVT or PT and/or PE were defined according to the Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms version 22.1. Vertical bars on the ROR point estimate indicate the 95% confidence intervals. *ROR* reporting odds ratio, *DVT* deep vein thrombosis, *PT* pulmonary thrombosis, *PE* pulmonary embolism

with a ROR of 2.46, which was similar to the ROR of 2.05 observed in our study. However, in our analysis, we identified differential reporting when comparing Europe with the US. In our WHO data, the majority of DVT and PT/PE suspected outcomes for tofacitinib were reported from the US, and the disproportionality estimates from the US for tofacitinib in our study were similar to those found in the FAERS study. Conversely, in Europe, our results identified an increased ROR for DVT and PT/PE for tofacitinib. Due to the differential reporting between countries and outcomes, we believe that earlier safety signal detection using pharmacovigilance data would have been difficult for tofacitinib, particularly as the majority of ICSRs were reported from the US. However, the differential reporting by region warrants further exploration.

The descriptive analysis of the tofacitinib users reporting DVT and/or PT/PE as SADRs may reflect a subpopulation at an elevated risk for thromboembolic events, and is in line with recent communications by the EMA and FDA [15–17, 19, 20]. Tofacitinib users reporting DVT and/or PT/PE exhibited risk factors of thrombosis, such as a slightly elevated mean age and a higher frequency of treatment with sex hormones and antithrombotics. The comedications reported in the WHO VigiBase are those that are taken at, or before, the time of the reported SADR. Thus, the elevated reporting of coadministered antithrombotics may suggest a patient population at high risk of thrombosis or even with a past thrombotic event. While these findings could suggest that patients with high thromboembolic risk may have developed DVT or PT/PE independently of tofacitinib, we cannot rule out that the administration of tofacitinib within this population was an additive risk factor. Thus, we would support the recent EMA and FDA communications to use tofacitinib with great caution in these high-risk populations.

Restricted use of tofacitinib in high-risk patient groups is also supported by safety concerns from the ongoing postmarketing safety trial (study A3921133), in which RA patients (> 50 years of age) who were already at high risk for venous thromboembolism were treated with high-dose tofacitinib or a tumor necrosis factor (TNF)-α inhibitor [17]. At the interim analysis of this study, 19 cases (from 3884 patient-years) under tofacitinib treatment experienced a PE, compared with 3 (from 3982 patient-years) receiving a TNF inhibitor [17]. Similarly, Desai et al. identified that the number of events for venous thromboembolism was higher among tofacitinib users when compared with TNF inhibitors [30]. Conversely, a recent observational study, with limited power, reported similar incident rates of thromboembolic events for tofacitinib and biologic disease-modifying antirheumatic drugs (bDMARDs) [31]. Moreover, two recent

meta-analyses of clinical trials did not show an increased thromboembolic risk with tofacitinib [32, 33]. However, meta-analyses are limited by the intrinsic limitations of the included studies. While clinical trials are the gold standard for drug efficacy, they are limited by their ability to study rare adverse events (such as thromboembolic events), and their representativeness. Observational studies can address these restraints, but the availability of these studies for tofacitinib and cardiovascular events is limited, as identified by Sepriano and colleagues in a recent review [34], where only a single observational study was included [30].

Cumulatively, our results add to the growing body of literature and the recent communication from the EMA [16, 20], which suggest tofacitinib, particularly at higher doses, should be avoided in patients at high thromboembolic risk (e.g. > 65 years of age, history of cardiovascular disease, or treated with hormone replacement therapy).

To the best of our knowledge, this is the first real-world study on the safety profile of baricitinib. While the total number of ICSRs was considerably higher for tofacitinib, likely due to the longer approval time, the reporting of DVT and PT/PE SADRs was relatively higher for baricitinib. Similar to tofacitinib, we observed that ICSRs with a DVT or PT/PE were older, suggesting a high-risk profile; however, the absolute numbers were low, making broad conclusions challenging. Nevertheless, the disproportionality analyses of baricitinib ICSRs suggested higher than expected reporting for both DVT and PE at the European and worldwide level. There were no reports of any SADRs for baricitinib originating from the US, which is likely due to the limited observation time in the US for baricitinib (approved in June 2018 [9] and data extraction in April 2019). Notably, in contrast to the EMA, the FDA did not approve the 4 mg dose of baricitinib due to unclear additional benefit versus the 2 mg dose, and also due to concerns of a dose effect in the safety profile, particularly for thromboembolism [11, 13]. Similarly, Health Canada only approved baricitinib 2 mg in August 2018, also citing dose-related safety concerns and concluding that there was an inferiority of the safety–harm profile for the 4 mg dose [35].

Thus, while we believe that the observed elevated reporting of DVT and PE SADRs for baricitinib should be taken with a high level of caution, as the premarket labeled concerns for DVT and PE [8, 10, 12] could have resulted in increased reporting of these drug-event combinations in Europe, further research is required. Moreover, in light of the results from the recent meta-analysis, which suggest that the occurrence of thromboembolic events appears to be higher with a 4 mg dose of baricitinib than a 2 mg dose [32], the recent communication regarding a dose–response effect for tofacitinib, and the FDA decision to limit approval to the 2 mg formulation, we believe the use of baricitinib 4 mg should also be re-examined in Europe. In our data, we identified that the most commonly reported amount for baricitinib was 4 mg. Unfortunately, pharmacovigilance data are not suited to explore the dose–response in more detail, and we were hindered by missing data.

Further research on the dose–response is of high interest as there remains debate on whether thromboembolic safety may be a class effect. This is largely centred on the lack of a clear mechanism of action. In an exploratory analysis to examine the mechanism of action, we included other thromboembolic events that could share a common mechanism. However, we did not identify an increase in reporting for either tofacitinib or baricitinib on these rare thromboembolic events. The lack of reporting of other thromboembolic-related outcomes (e.g. peripheral embolism) may suggest that the high reporting rate for baricitinib and DVT or PT/PE SADRs could have been triggered by previously reported and labeled safety concerns [10]. However, we identified that these secondary outcomes were poorly reported overall in the WHO VigiBase and therefore we cannot draw robust conclusions as a result of their absence in tofacitinib or baricitinib ICSRs. Nonetheless, our results identified elevated reporting of both DVT and PT/PE for tofacitinib and baricitinib in Europe, and therefore a shared mechanism in the sense of a class effect cannot be ruled out by our data. This finding is important, particularly regarding the monitoring of new JAK inhibitors currently in the pipeline, as well as the recent FDA- and EMA-approved upadacitinib (FDA-approved in August 2019 [36]; EMA-approved in December 2019 [37]).

4.2 Strengths and Limitations

A key element in pharmacovigilance, or safety surveillance of authorized drugs, is the collection and investigation of SADRs. The WHO VigiBase is the broadest pharmacovigilance database to study SADRs, as countries from all around the world submit data in an effort to join forces towards safeguarding patients' safety. Data are collected as ICSRs, which are mainly post-authorization unsolicited or spontaneous reports [22]. Therefore, this study contributes to the cumulative knowledge about the safety of JAK inhibitors using the biggest and one of most appropriate global databases for SADRs or ICSRs. Additionally, this database enables stratification by country of reporting, which resulted in a key asset for the analysis of our results. Due to the different authorization dates and prescription trends among countries, we consider that stratifying by country and individually observing the major contributors to the tofacitinib and baricitinib ICSRs provides a more informative result.

While VigiBase data are well-suited for studying safety reports, we are aware of the limitations that are intrinsic to the use of pharmacovigilance data. First, we acknowledge that causality cannot be determined, and RORs should not

be interpreted as a measure of risk but rather as an indicator of a safety signal. The information within VigiBase comes from a variety of sources, and the likelihood that an SADR is causally drug-related is not the same in all cases [38]. While we used RORs and ICs are measures to detect disproportionate reporting, we highlight that there are no universally established thresholds for identifying a clinically relevant signal. For the purpose of this study, we considered an outcome to have a higher than expected reporting if the ROR was > 1 and the 95% CI did not encompass 1, and/or the IC025 was > 0. However, as stated, while high reporting may suggest that the association between the event and the medicinal product is worth further investigation [27], we recognize that it is not a measure of causality and should not be inferred as such. Rather, these results, supported by the current clinical warning by the EMA and FDA for tofacitinib [15–20], and the thromboembolic concerns during the clinical development of baricitinib [11–13], indicate a potential safety signal, which should be followed-up in a well-designed cohort study with an active comparator group.

Along this line, we recognize that patients with RA, the most dominant indication for tofacitinib and baricitinib, have an elevated baseline risk for venous thromboembolism [39]. While future studies should examine the risk of thrombosis within RA patients, and using a suitable active comparator drug, we believe the results of this study should not be discounted on this basis. Within spontaneous reporting, events that are commonly associated with an underlying disease are unlikely to be categorized as SADRs, unless occurring following a new medication. Thus, it would be expected that health professionals treating RA patients would be aware of the associated risk, and therefore only report these events as SADRs when there is reasoning to suspect it as an adverse effect of the treatment; for example, if the event is in close temporal relationship to the start, or dose increase, of the treatment. While we were unable to identify an active comparator group, or stratify by disease, due to limitations with the data, we applied a traditional pharmacovigilance approach, whereby all other reports in the WHO serve as the comparison. Thus, our comparator group is not a 'health control' group. Rather, within our comparator group, we captured all non-tofacitinib and non-baricitinib medications, and may therefore include patient groups at similar, lower, or elevated thromboembolic risk.

Finally, reporting biases and confounding may be present [22]. Spontaneous reporting could be affected by changes in policy [40], reporter type [41], communications, prior knowledge about the product, and severity of the event, and may unevenly affect each medicinal product and each event. In this line, the preclinical-related concerns and existing label of potential risk [10] could have influenced the high reporting of thromboembolic events for baricitinib. Statistical adjustment to confounding factors is limited in pharmacovigilance data due to underrecording of comedications and indications. Moreover, certain risk factors for thromboembolic events, such as obesity, smoking status, or immobilization are not recorded in the database.

5 Conclusions

Results from this real-world pharmacovigilance analysis add to the ongoing clinical debate regarding the safety profile of tofacitinib and baricitinib. Patients with a DVT or PT/PE were older and more frequently reported use of prothrombotic medications (e.g. contraceptives) or existing clinically relevant risk factors of thromboembolism (e.g. treatment with antithrombotic agents). While, in Europe, tofacitinib was associated with an elevated reporting of DVT and PE, only increased reporting of PT was observed in the US. Similar elevated reporting for baricitinib was observed in Europe, however baricitinib reports from the US were not available at the time of data extraction.

To date, the real-world evidence regarding the safety of JAK inhibitors is lacking. While we acknowledge the inherent limitations of pharmacovigilance data, the results of this study suggest that the thromboembolic safety of JAK inhibitors requires ongoing real-world assessment to determine if a class- and dose-relationship exist.

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Compliance with Ethical Standards

Conflicts of Interest Stefan Weiler is a member of the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties. Enriqueta Vallejo-Yagüe, Raphael Micheroli and Andrea M. Burden have no conflicts of interest to declare. While the authors used data from VigiBase, the WHO global database of ICSRs, as a source of information, the conclusions do not represent the opinion of the UMC or the WHO.

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