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ORIGINAL RESEARCH

Post-Marketing Safety Surveillance of Tofacitinib over 9 Years in Patients with Psoriatic Arthritis and Rheumatoid Arthritis

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ABSTRACT

Introduction: The safety of tofacitinib in psoriatic arthritis (PsA) and rheumatoid arthritis (RA) has been demonstrated in clinical studies of ≤ 4 and 9.5 years, respectively. Post-marketing surveillance (PMS) data for tofacitinib from spontaneous and voluntary adverse event (AE) reports have been published for RA, but not PsA. To inform the real-world safety profile of tofacitinib in PsA, we evaluated AE reports submitted to the Pfizer safety database (including RA data for context).

Methods: Endpoints included AEs, serious AEs (SAEs), AEs of special interest (AESIs; serious infections, herpes zoster, cardiovascular events, malignancies, venous thromboembolism), and fatal cases. Exposure was estimated using IQVIA global commercial sales data. Number, frequency, and reporting rates (RRs; number of events/100 patient-years' [PY] exposure) were summarized by indication and formulation (immediate release [IR] 5 or 10 mg twice daily], modified release [MR] 11 mg once daily, or all tofacitinib). The data-collection period differed by indication (PsA: 14 December 2017 [US

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approval, IR/MR] to 6 November 2021; RA: 6 November 2012 [US approval, IR] to 6 November 2021; MR approval, 24 February 2016).
Results: A total of 73,525 case reports were reviewed (PsA = 5394/RA = 68,131), with 20,706/439,370 PY (PsA/RA) of exposure. More AEs were reported for IR versus MR (IR/MR: PsA = 8349/7602; RA = 137,476/82,153). RRs for AEs (IR/MR: PsA = 59.6/113.4; RA = 44.0/64.8) and SAEs (PsA = 8.1/13.6; RA = 8.0/9.5) were higher with MR versus IR. AE RRs (RA) in the first 4 years after IR approval were 95.9 (IR; 49,439 PY) and 147.0 (MR; 2000 PY). Frequency of SAEs, AESIs, and fatal cases was mostly similar across formulations and indications. The most frequently-reported AE Preferred Terms (PsA/RA) included drug ineffective (20.0%/17.8%), pain (9.7%/10.6%), condition aggravated (9.9%/10.5%), headache (8.8%/7.9%) and, for PsA, off-label use (10.5%/3.4%).
Conclusions: Tofacitinib PMS safety data from submitted AE reports were consistent between PsA and RA, and aligned with its known safety profile. Exposure data (lower MR versus IR; estimation from commercial sales data), reporting bias, reporter identity, and regional differences in formulation use limit interpretation.

Keywords: Post-marketing surveillance; Psoriatic arthritis; Rheumatoid arthritis; Safety; Tofacitinib

Key Summary Points

Why carry out this study?

Reports of the real-world safety profile of tofacitinib in psoriatic arthritis (PsA) are limited, although the safety of tofacitinib in patients with PsA and rheumatoid arthritis (RA) has been demonstrated in clinical studies of up to 4 and 9.5 years, respectively.

To date, post-marketing surveillance (PMS) safety data for tofacitinib from spontaneous and voluntary adverse event (AE) reports have been published for RA, but not for PsA.

This analysis informs the real-world safety profile of tofacitinib in PsA using AE reports submitted to the Pfizer safety database, with RA data included for context.

What was learned from the study?

The data collected in this PMS study were aligned with the established safety profile of tofacitinib, and were consistent between PsA and RA.

While these results should be interpreted in the context of the limitations of PMS studies and spontaneous AE reporting, these data provide insight to the clinician regarding expected real-world safety outcomes in patients with PsA treated with tofacitinib.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease (CID), manifesting as skin and nail lesions, peripheral arthritis, inflammation of entheseal insertion points, swollen digits, and spondylitis [1], which is estimated to affect 133 patients per 100,000 population worldwide [2]. Patients with PsA have an increased risk of comorbid cardiovascular disease, obesity, type 2 diabetes, hypertension, metabolic syndrome, malignancy, and infection, and poor health-related quality of life compared to the general population [1, 3]. Rheumatoid arthritis (RA) is a CID associated with joint pain, damage, and long-term disability [4], which has higher prevalence than PsA (estimated at 460 per 100,000 population worldwide [5]). Patients with RA have an elevated risk of cardiovascular morbidity and mortality, malignancy, and infection compared with the general population [6, 7]. PsA has been associated with a generally

lower comorbidity burden than RA, including lower rates of thyroid disease, malignancy, infection, and venous thromboembolism (VTE) [8–11]. Risk of cardiovascular disease is generally described as lower in PsA than in RA, although cardiometabolic risks such as obesity and type 2 diabetes are more frequently observed in PsA [12–14].

International treatment guidelines for PsA and RA recommend initial therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate [15–19]. In patients without sufficient clinical response to csDMARD treatment, advanced therapies are recommended, such as biologic DMARDs (bDMARDs, e.g., tumor necrosis factor inhibitors [TNFi]) or, in certain scenarios, targeted synthetic DMARDs (tsDMARDs, e.g., Janus kinase [JAK] inhibitors). Studies of patients receiving bDMARDs for RA or PsA have reported reductions in risk of cardiovascular disease, possibly owing to control of systemic inflammation [6, 13], similar rates of malignancies [20], and increased risk of infection [6, 21, 22], compared with patient populations not receiving bDMARDs.

Tofacitinib is an oral JAK inhibitor for the treatment of PsA and RA. Tofacitinib is approved for PsA and RA as a 5-mg immediate release (IR) tablet taken twice daily (BID), with other formulations available in some countries: 10 mg BID IR (for RA in Russia, Switzerland [until 2020], and Botswana) and 11 mg once daily (QD) modified release (MR). In PsA, the efficacy and safety of tofacitinib 5 and 10 mg BID have been demonstrated in phase 3 trials in combination with csDMARDs in patients with an inadequate response to TNFi [23] or csDMARDs (with or without prior TNFi treatment) [24, 25], and in a long-term extension (LTE) study with up to 48 months of observation [26]. In RA, the efficacy and safety of tofacitinib 5 and 10 mg BID administered as monotherapy or in combination with csDMARDs, mainly methotrexate, in patients with moderately to severely active RA, have been demonstrated in phase 3 [27–33], phase 3b/4 [34, 35], and LTE studies with up to 114 months of observation [36–38]. The safety profile of tofacitinib in clinical studies has been found to be comparable across PsA and RA [39]. The efficacy and safety profile of the MR formulation have also been characterized in two phase 3 and 3b/4 studies in RA [40, 41].

In the course of the tofacitinib clinical development program, increases in serum lipid levels and malignancies were observed [42–44], which prompted a head-to-head, FDA-mandated post-authorization safety study of tofacitinib and TNFi. ORAL Surveillance was a randomized, open-label study conducted from March 2014 to July 2020, which enrolled patients with RA $\geq$ 50 years of age with $\geq$ 1 additional cardiovascular risk factor [35]. In this event-driven study, non-inferiority criteria were not met in the comparison of tofacitinib (combined 5-mg BID and 10-mg BID doses) versus TNFi for the co-primary endpoints of adjudicated major adverse cardiovascular events (MACE) and adjudicated malignancies excluding nonmelanoma skin cancer (NMSC) [35]. Following communication of the ad hoc ORAL Surveillance safety analyses in 2019 and the final readout in 2021, there has been continuing interest in monitoring the safety of tofacitinib in real-world use in RA, including in patients with cardiovascular risk factors [45–47]. While comparable data for other indications including PsA are lacking, the results of ORAL Surveillance have led to revisions of regulatory labeling across all approved indications for JAK inhibitors, and have been considered in the development of treatment guidelines for RA, PsA, and axial spondyloarthritis [16, 19, 48].

Post-marketing surveillance (PMS) monitors drug safety in real-world use following market release, and complements data from clinical trials. Types of PMS include spontaneous/voluntary reporting of adverse events (AEs), post-marketing observational studies, and active surveillance. PMS data using spontaneous/voluntary AE reports have been previously published for tofacitinib in RA (including data up to November 2015) [49] and in ulcerative colitis (UC) [50], although no similar report exists for PsA, and reports of real-world safety of tofacitinib in PsA are limited [51]. The aim of this analysis was to inform the global real-world safety profile of tofacitinib in PsA, while providing context with data for RA, using

spontaneous AE reports submitted to the Pfizer safety database.

METHODS

Study Design

This was a retrospective analysis of worldwide PMS data collected from the Pfizer safety database from 14 December 2017 to 6 November 2021 (for PsA) and from 6 November 2012 to 6 November 2021 (for RA). The 5-mg BID (IR) and 11-mg QD (MR) doses were approved for PsA in the US on 14 December 2017 (in combination with nonbiologic DMARDs) and in the EU on 25 June 2018 and 20 August 2021, respectively (in combination with methotrexate). The 5-mg BID dose was first approved for RA in the US on 6 November 2012, followed by the 11-mg QD dose on 24 February 2016. In the EU, the 5-mg BID and 11-mg QD doses were approved for RA on 22 March 2017 and 16 December 2019, respectively. Spontaneous and voluntary reports of AEs occurring during or after exposure to tofacitinib were collected from patients, healthcare professionals (HCPs), regulatory authorities, post-marketing trials, non-interventional studies, solicited reports from patient support programs and market research programs, and reports extracted from the literature.

The spontaneously reported PMS AE data reported in this analysis were not collected as part of a clinical study and were non-interventional; therefore, no ethics approval was required. All data were reported in aggregate form in summary reports; no individual case-level data were evaluated or reported.

Cumulative Exposure

Cumulative exposure to tofacitinib for PsA or RA was calculated from a combination of audited unit sales from IQVIA's Multinational Integrated Data Analysis System (commercial sales) database and prescription data from IQVIA's Prescriber Insights database (https://www.iqvia.com/). Data were available from 61 countries and one region (Central America, which was available as aggregated data). The average daily dose (AVDOS) of tofacitinib was used to convert unit sales into patient-days (cumulative days of therapy) and further divided by 365.25 (days in a year) to obtain patient-years (PY) of exposure. PY for tofacitinib IR were calculated using the AVDOS of 2 units and the combined sales of tofacitinib 5 mg BID and 10 mg BID. PY for tofacitinib MR were calculated using the AVDOS of 1 unit for 11 mg QD tofacitinib sales, then adding the individual PY to generate a cumulative exposure number for tofacitinib during the relevant timeframe. Cumulative exposure data from 6 November 2012 to the third quarter of 2021 were available from IQVIA and were reported by quarter; cumulative exposure was extrapolated to the end of the reporting period (e.g., 6 November 2021) using the average cumulative exposure from the respective previous three quarters. PY of exposure by indication, sex, and age were derived through prescription share obtained from IQVIA's Prescriber Insights database, and applying the factor to the overall PY calculation obtained from the commercial sales database. International Classification of Diseases 10th revision (ICD-10) codes were used to define the indications, as follows: 'L405 Arthropathic psoriasis' for PsA and 'M06 Other Rheumatoid Arthritis' and 'M05 Seropositive Rheumatoid Arthritis' for RA.

Data Analysis

AE reports in patients with PsA or RA received by the Pfizer safety database were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0, and summarized by type and frequency according to System Organ Class (SOC) and Preferred Term (PT). Data were summarized by indication (PsA/RA) and tofacitinib formulation (IR, MR, or all tofacitinib [sum of IR + MR]). Case reports for which the tofacitinib formulation was not reported were excluded from the 'all tofacitinib' group, as no cumulative exposure data were available, and they are therefore reported separately.

Patient sex, age, indication, geographical origin, and reporter identity (HCP [e.g., physician, pharmacist, other HCP] or non-HCP [consumer, lawyer, other non-HCP]) were collected and summarized. Each case could report one or more AEs. Cases were categorized by outcome (fatal, recovered, recovering, unknown, etc.). AEs (types, most frequent AEs occurring in $\geq$ 2% of patients, serious AEs [SAEs], and AEs of special interest [AESIs]) were summarized by number, frequency, and reporting rate (RR; number of events per 100 PY of estimated exposure). SAEs were defined as AEs resulting in death, hospitalization, or prolongation of hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect; or considered to be life-threatening or an important medical event. AESIs included serious infections (including Coronavirus disease 2019 [COVID-19]), herpes zoster (HZ), cardiovascular events, NMSC, VTE, and malignancies excluding NMSC (search criteria, defined using MedDRA version 24.1, are detailed in the Supplementary Methods).

Sensitivity analyses evaluated AEs received during the following time intervals, to evaluate temporal trends in AE reporting: 2015–2017 (RA only), 2017–2019, and 2019–2021. To avoid double reporting of the same AE across multiple time intervals, case reports and their associated AEs were categorized by time interval according to the date when the case report was first received. Therefore, additional AEs reported subsequently under existing case reports may have actually occurred in later time intervals. AE reports were also evaluated during the first 4 years post-approval for RA (6 November 2012 to 6 November 2016), to align with the duration of available post-approval PsA data, and in subgroups by sex (male versus female) and age ($\geq$ 65 versus < 65 years).

RESULTS

Patient Characteristics

In total, 73,525 case reports were reviewed, comprising 5394 for PsA and 68,131 for RA. Of these, 368 (6.8%) and 4239 (6.2%), respectively, did not report a tofacitinib formulation and were excluded. In PsA, the number of case reports received for the IR versus MR formulations was similar, whereas in RA, the number of case reports received was higher for IR than for MR (Table 1). PY of exposure were higher for the IR than for the MR formulation for both indications. For both indications and formulations, AE reports were more commonly submitted for females, patients < 65 years of age, and patients from North America (Table 1). Similar trends in demographics were observed for the reports with no tofacitinib formulation specified (Table S1). Most reports originated from North America (almost all for MR), and the proportion of reports originating from Europe and the rest of the world was higher with IR than with MR (Table 1).

Approximately half of all reports were submitted by HCPs, with the remainder submitted by non-HCPs such as consumers (Table 2). A small percentage of reports included multiple indications (19.4% with PsA and 4.6% with RA) (Table 2). For PsA, the most reported co-indications were RA (46.5% of those with multiple indications), psoriasis (17.5%), and ankylosing spondylitis (3.7%). The most reported co-indications for RA were PsA (15.8% of those with multiple indications), osteoarthritis (10.1%), and arthritis (8.8%).

AEs

For both PsA and RA, a higher number of AEs were reported for tofacitinib IR (PsA, n = 8349; RA, n = 137,476) versus MR (PsA, n = 7602; RA, n = 82,153) (Table 3). For both indications, RRs for total AEs and SAEs were higher with the MR versus IR formulation, although frequency of SAEs (percentage of AEs reported as serious) was similar. No clear trends across formulations were observed in frequency or RR of AESIs and fatal cases (Table 3). Results for reports with no tofacitinib formulation specified are shown in Table S2. Over the full duration of data collection, a higher RR for total AEs was observed in PsA than in RA (Table 3). In the sensitivity analysis evaluating only the first 4 years post-approval, AE RRs were higher for RA (Table S3)

Table 1 Overall patient characteristics by tofacitinib formulation among patients with PsA and RA

	Tofacitinib IR		Tofacitinib MR		All tofacitinib	
	N	% of case reports	*N*	% of case reports	*N*	% of case reports
PsA						
Case reports	2601		2425		5026	
Sex						
Male	710	27.3	677	27.9	1387	27.6
Female	1850	71.1	1732	71.4	3582	71.3
Not reported	41	1.6	16	0.7	57	1.1
Age						
Median (SD) [range], years	56.0 (12.85) [8.0–90.0]		56.0 (12.48) [0.50–88.0]		Not available	
< 65 years	1885	72.5	1866	76.9	3751	74.6
≥ 65 years	575	22.1	525	21.6	1100	21.9
Not reported	141	5.4	34	1.4	175	3.5
Geographical region						
North America[a]	1783	68.6	2352	97.0	4135	82.3
Europe[b]	421	16.2	13	0.5	434	8.6
Rest of the world[c]	397	15.3	60	2.5	457	9.1
RA						
Case reports	39,744		24,148		63,892	
Sex						
Male	6685	16.8	4156	17.2	10,841	17.0
Female	32,425	81.6	19,864	82.3	52,289	81.8
Not reported	634	1.6	128	0.5	762	1.2
Age						
Median (SD) [range], years	61.0 (12.63) [0.25–98.0]		60.0 (12.33) [0.50–97.0]		Not available	
< 65 years	23,175	58.3	16,030	66.4	39,205	61.4
≥ 65 years	14,631	36.8	7633	31.6	22,264	34.8
Not reported	1938	4.9	485	2.0	2423	3.8
Geographical region						
North America[a]	28,730	72.3	22,468	93.0	51,198	80.1

Table 1 continued

	Tofacitinib IR		Tofacitinib MR		All tofacitinib	
	N	% of case reports	*N*	% of case reports	*N*	% of case reports
Europe[b]	1903	4.8	19	0.1	1922	3.0
Rest of the world[c]	9111	22.9	1661	6.9	10,772	16.9

IR immediate release, *MR* modified release, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation

[a]Includes case reports from Canada, Puerto Rico, and the US

[b]Includes case reports from Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the UK

[c]Includes case reports from Argentina, Australia, Brazil, Chile, China, Colombia, Ecuador, Egypt, Hong Kong, India, Japan, Korea, Kuwait, Lebanon, Malaysia, Mexico, Morocco, New Zealand, Peru, Philippines, Saudi Arabia, Singapore, South Africa, Thailand, Tunisia, and the United Arab Emirates

than in the 4-year data for PsA (Table 3) for both formulations, and higher for MR versus IR in both indications. There was limited exposure to the MR formulation in the first 4 years for RA (November 2012 to November 2016) as it was approved in February 2016 (2000 PY, versus 49,439 PY for IR).

When case reports were evaluated by 2-year time intervals, the number of case reports, AEs, and PY of exposure increased over time for both indications (Table 4). For PsA, RRs of AEs, SAEs, AESIs, and fatal cases were similar across the two time intervals examined, as were the frequencies of SAEs, AESIs, and fatal cases. For RA, RRs of AEs, SAEs, most AESIs, and fatal cases were highest in the first time interval (November 2015 to November 2017) and lower thereafter; frequencies of SAEs, AESIs, and fatal cases were comparable across time intervals (Table 4).

In patients with PsA, the most frequently reported PTs overall were drug ineffective, off-label use, condition aggravated, pain, and headache (Fig. 1). In patients with RA, the most frequently reported PTs overall were drug ineffective, pain, condition aggravated, and headache (Fig. 2). For both PsA and RA, the most frequently reported PTs were similar across IR and MR formulations (Figs. 1, 2). Results for reports with no formulation specified are shown in Fig. S1.

Across PsA and RA, RRs for AEs were higher for female patients than for male patients, although RRs for SAEs, AESIs, and fatal cases were generally consistent (Table 5). Similarly, in both PsA and RA, RRs for AEs were higher in patients < 65 years of age than in patients ≥ 65 years of age, with RRs for SAEs, AESIs, and fatal cases remaining comparable across the age categories.

AESIs

Across indications and formulations, the most reported AESI was serious infection, followed by HZ (Table 3). Within the AESI category of serious infections, the most reported PTs were pneumonia, lower respiratory tract infection, and COVID-19 or COVID-19 pneumonia (Table 6). The frequency and RR for COVID-19 infections in PsA were 0.92% and 0.71, respectively, with 10.2% (15/147) of these infections being reported as serious. Frequency and RR for COVID-19 infections in RA were 0.58% and 0.29, respectively, with 39.1% (494/1263) of these infections reported as serious. The most

Table 2 Top co-indications and reporter identities by formulation among patients with PsA and RA

	Tofacitinib IR		Tofacitinib MR		All tofacitinib	
	N	% of case reports	*N*	% of case reports	*N*	% of case reports
PsA						
Case reports	2601		2425		5026	
Indications reported (most common indications reported)[a]						
PsA	2265	87.1	1790	73.8	4055	80.7
Multiple[b]	337	13.0	636	26.2	973	19.4
Unknown	13	0.5	15	0.6	28	0.6
RA	4	0.2	4	0.2	8	0.2
Psoriasis	1	0.0	0	0.0	1	0.0
Alopecia universalis	1	0.0	N/A	N/A	N/A	N/A
AE reporter identity						
HCP[c]	1294	49.8	1844	76.0	3138	62.4
Non-HCP[d]	1307	50.2	581	24.0	1888	37.6
RA						
Case reports	39,744		24,148		63,892	
Indications reported (most common indications reported)[a]						
RA	38,372	96.6	22,616	93.7	60,988	95.5
Multiple[e]	1382	3.5	1542	6.4	2924	4.6
Unknown	106	0.3	88	0.4	194	0.3
Arthritis	2	0.0	3	0.0	5	0.0
PsA	3	0.0	1	0.0	4	0.0
Juvenile idiopathic arthritis	N/A	N/A	1	0.0	1	0.0
UC	1	0.0	N/A	N/A	1	0.0
AE reporter identity						
HCP[c]	16,354	41.2	15,456	64.0	31,810	49.8
Non-HCP[d]	23,390	58.9	8692	36.0	32,082	50.2

Percentages are based on the total number of case reports by formulation. *N/A* indicates that the indication was not included in the most common indications reported for the respective formulation.

AE adverse event, *HCP* healthcare provider, *IR* immediate release, *MR* modified release, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

[a]Case reports could contribute to multiple indications and indications could change over time; therefore, the indications listed do not add up to 100%

[b]Within the multiple indication category, the most common co-indications (as a proportion of the co-indication in which case reports were described) were RA (46.5%), psoriasis (17.5%), and ankylosing spondylitis (3.7%)

[c]HCP includes physicians, pharmacists, and 'other HCPs'

[d]Non-HCP includes consumers, lawyers, and other non-HCPs

[e]Within the multiple indication category, the most common co-indications were PsA (15.8%), osteoarthritis (10.1%), and arthritis (8.8%)

Table 3 Safety outcomes by tofacitinib formulation among patients with PsA and RA

PsA	Tofacitinib IR 14,000 PY			Tofacitinib MR 6706 PY			All tofacitinib 20,706 PY		
	N	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]
Case reports	2601			2425			5026		
AEs	8349		59.64	7602		113.36	15,951		77.04
SAEs	1136	13.61	8.11	912	12.00	13.60	2048	12.84	9.89
AESIs[c]									
Serious infections	239	2.86	1.71	200	2.63	2.98	439	2.75	2.12
HZ (serious and nonserious)	49	0.59	0.35	35	0.46	0.52	84	0.53	0.41
Cardiovascular events[d]	44	0.53	0.31	25	0.33	0.37	69	0.43	0.33
Malignancies (excluding NMSC)	30	0.36	0.21	27	0.36	0.40	57	0.36	0.28
NMSC	4	0.05	0.03	7	0.09	0.10	11	0.07	0.05
VTE[e]	27	0.32	0.19	12	0.16	0.18	39	0.24	0.19
Fatal cases	22	0.85[f]	0.16	19	0.78[f]	0.28	41	0.82[f]	0.20
RA	**Tofacitinib IR 312,632 PY**			**Tofacitinib MR 126,738 PY**			**All tofacitinib 439,370 PY**		
	N	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]
Case reports	39,744			24,148			63,892		
AEs	137,476		43.97	82,153		64.82	219,629		49.99
SAEs	24,966	18.16	7.99	11,978	14.58	9.45	36,944	16.82	8.41
AESIs[c]									
Serious infections	4944	3.60	1.58	2467	3.00	1.95	7411	3.37	1.69
HZ (serious and nonserious)	1194	0.87	0.38	529	0.64	0.42	1723	0.78	0.39
Cardiovascular events[d]	773	0.56	0.25	413	0.50	0.33	1186	0.54	0.27
Malignancies (excluding NMSC)	941	0.68	0.30	429	0.52	0.34	1370	0.62	0.31
NMSC	193	0.14	0.06	109	0.13	0.09	302	0.14	0.07
VTE[e]	318	0.23	0.10	150	0.18	0.12	468	0.21	0.11
Fatal cases	839	2.11[f]	0.27	279	1.16[f]	0.22	1118	1.75[f]	0.25

All cases reported at least one AE. Some cases reported > 1 AE; therefore, the number of AEs exceeds the number of cases
AE adverse event, *AESI* adverse event of special interest, *HZ* herpes zoster, *IR* immediate release, *MedDRA* Medical Dictionary for Regulatory Activities, *MR* modified release, *NMSC* nonmelanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *PY* patient-years, *RA* rheumatoid arthritis, *RR* reporting rate, *SAE* serious adverse event, *VTE* venous thromboembolism

[a]Percentages are based on total AEs by formulation except where otherwise indicated

[b]Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases)

[c]Search criteria for AESI categories are described in the Supplementary Methods

[d]Includes the following Standardised MedDRA Queries: central nervous system vascular disorders, myocardial infarction and associated terms, ischemic heart disease and associated terms; and the following PTs: cardiac death, cardiac failure congestive, sudden cardiac death, and pulmonary embolism

[e]Pulmonary embolism events are captured in the cardiovascular events and VTE categories

[f]Percentages based on total case reports by formulation

Table 4 Summary of safety outcomes across time intervals among patients with PsA and RA (all tofacitinib)

Time interval	PsA						RA								
	December 2017 –November 2019 7276 PY			December 2019 –November 2021 13,430 PY			November 2015 –November 2017 60,035 PY			December 2017 –November 2019 135,013 PY			December 2019 –November 2021 215,155 PY		
	N	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]
Case reports	1515			3351			15,938			18,371			22,725		
AEs	4977		68.40	10,280		76.55	59,714		99.47	61,282		45.39	72,453		33.67
SAEs	646	12.98	8.88	1276	12.41	9.50	10,388	17.40	17.30	10,098	16.48	7.48	11,001	15.18	5.11
AESIs[c]															
Serious infections	158	3.17	2.17	272	2.65	2.03	2241	3.75	3.73	2191	3.58	1.62	2023	2.79	0.94
HZ (serious and nonserious)	28	0.56	0.38	51	0.50	0.38	482	0.81	0.80	577	0.94	0.43	498	0.69	0.23
Cardiovascular events[d]	20	0.40	0.27	44	0.43	0.33	289	0.48	0.48	385	0.63	0.29	371	0.51	0.17
Malignancies (excluding NMSC)	19	0.38	0.26	33	0.32	0.25	377	0.63	0.63	424	0.69	0.31	463	0.64	0.22
NMSC	2	0.04	0.03	8	0.08	0.06	81	0.14	0.13	89	0.15	0.07	95	0.13	0.04
VTE[e]	8	0.16	0.11	30	0.29	0.22	58	0.10	0.10	165	0.27	0.12	209	0.29	0.10
Fatal cases	12	0.79[f]	0.16	22	0.66[f]	0.16	335	2.10[f]	0.56	359	1.95[f]	0.27	335	1.47[f]	0.16

Case reports and their associated AEs were categorized by time interval according to the date when the case report was first received. Therefore, additional AEs reported subsequently under existing case reports may have actually occurred in later time intervals. Regulatory approval for tofacitinib was attained in December 2017 for PsA and November 2012 for RA. RR for AEs, SAEs, fatal cases, and SAEs by SOC from 2012 to 2015 have been reported previously for RA [49]

AE adverse event, *AESI* adverse event of special interest, *HZ* herpes zoster, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* nonmelanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *PY* patient-years, *RA* rheumatoid arthritis, *RR* reporting rate, *SAE* serious adverse event, *SOC* System Organ Class, *VTE* venous thromboembolism

[a]Percentages are based on total AEs by formulation except where otherwise indicated

[b]Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases)

[c]Search criteria for AESI categories are described in the Supplementary Methods

[d]Includes the following Standardised MedDRA Queries: central nervous system vascular disorders, myocardial infarction and associated terms, ischemic heart disease and associated terms; and the following PTs: cardiac death, cardiac failure congestive, sudden cardiac death, and pulmonary embolism

[e]Pulmonary embolism events are captured in the cardiovascular events and VTE categories

[f]Percentages based on total case reports by formulation

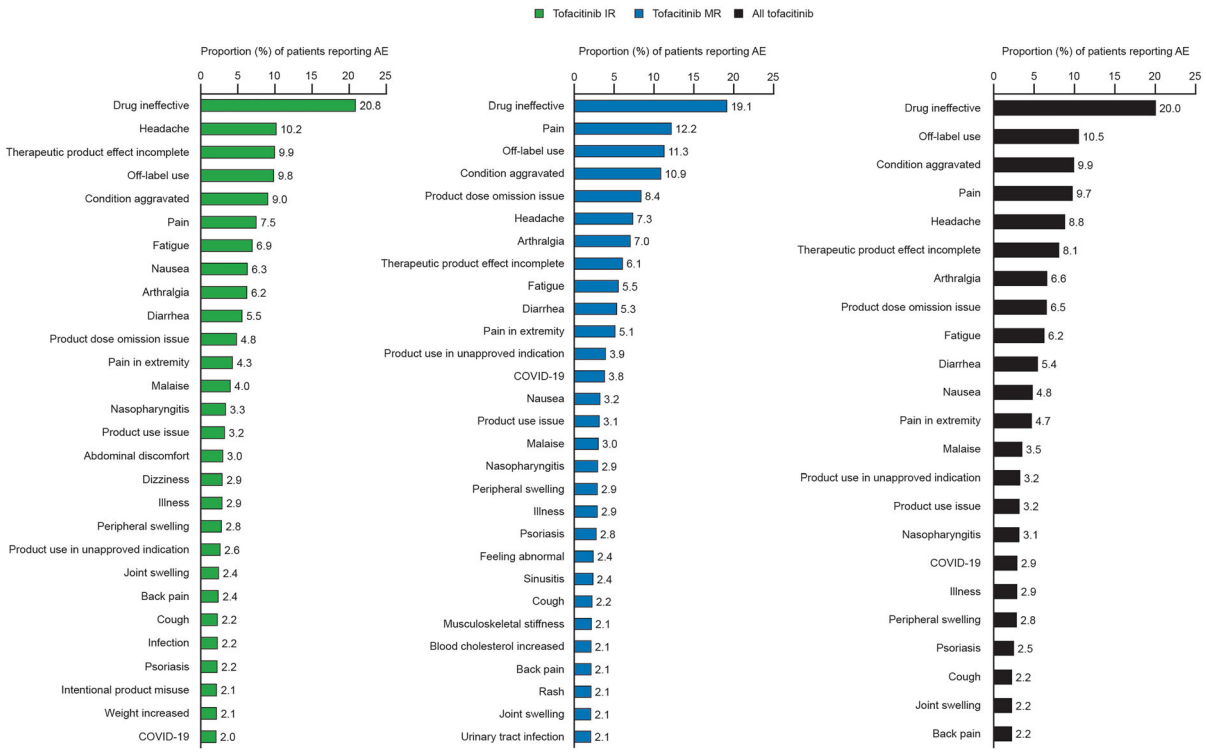

Fig. 1 Most frequent AEs occurring in ≥ 2% of patients with PsA (by PT). Percentages were calculated from the total case reports per formulation. *AE* adverse event, *COVID-19* Coronavirus disease 2019, *IR* immediate release, *MR* modified release, *PsA* psoriatic arthritis, *PT* Preferred Term

reported PTs in the HZ AESI category were HZ, ophthalmic HZ, and HZ disseminated (Table 6). Of the total HZ AEs reported, 10.2% (IR) and 8.6% (MR) for PsA and 24.1% (IR) and 9.8% (MR) for RA were considered serious. The most reported PT meeting cardiovascular event AESI criteria was cerebrovascular accident, followed by myocardial infarction and pulmonary embolism (Table 6). Excluding the nonspecific PT of neoplasm malignant, breast cancer or breast cancer female was the most reported PT meeting AESI criteria for malignancies excluding NMSC, followed by lung neoplasm malignant and colon cancer (Table 6). The most reported NMSC PT was skin cancer, followed by basal cell carcinoma and squamous cell carcinoma (Table 6). The majority of VTEs reported were pulmonary embolism, followed by deep vein thrombosis and pulmonary thrombosis (Table 6).

DISCUSSION

In this analysis, post-marketing safety of tofacitinib in PsA and RA ascertained from AE reports submitted to the Pfizer safety database was aligned with the known safety profile of tofacitinib. This analysis, with 4 years of data, is the first PMS report for tofacitinib in PsA, and extends the RA PMS data across a longer timeframe (9 years) than previously published data. Trends in reporting of overall AEs, including types and seriousness, were comparable across the PsA and RA indications. PMS data for AESIs and the most commonly reported AEs provide complementary information to the safety results of previous clinical and observational trials.

Prior post-marketing data in RA [49] and UC [50] generally showed safety reporting trends similar to those of the present study. For example, the most frequently reported AEs (by PT) were mostly consistent with those reported

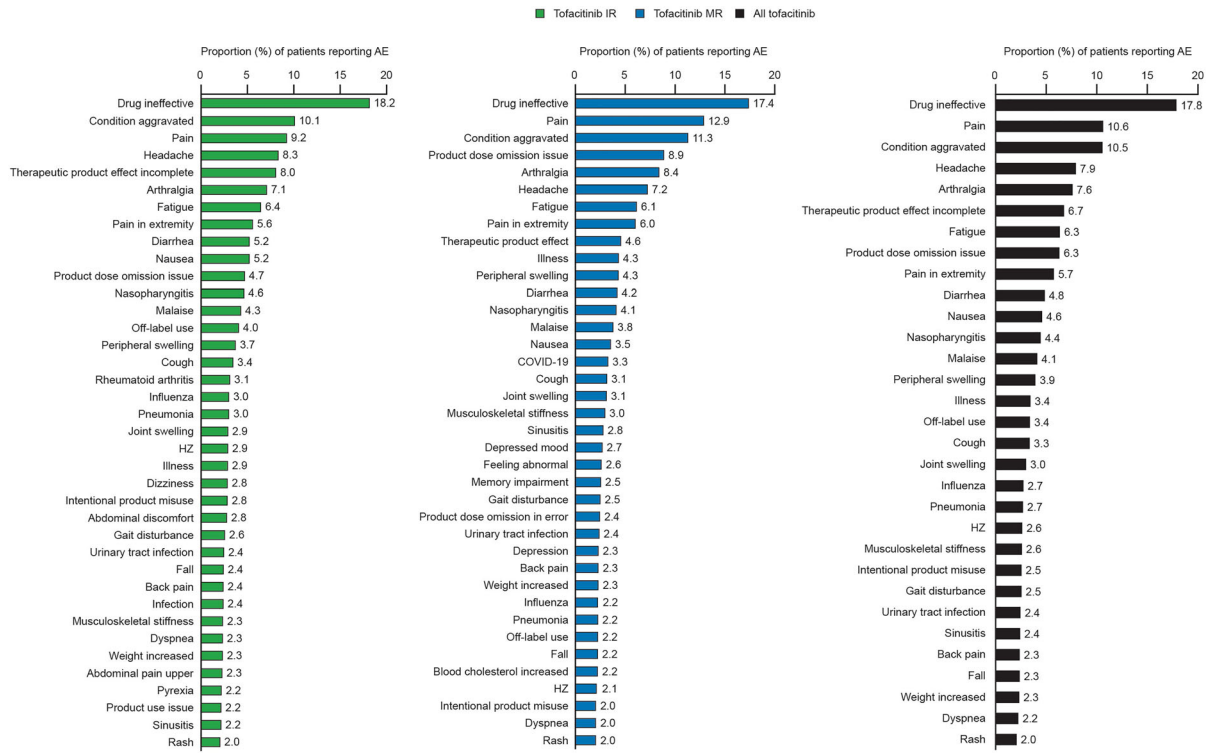

Fig. 2 Most frequent AEs occurring in ≥ 2% of patients with RA (by PT). Percentages were calculated from the total case reports per formulation. *AE* adverse event, *COVID-19* Coronavirus disease 2019, *HZ* herpes zoster, *IR* immediate release, *MR* modified release, *PT* Preferred Term, *RA* rheumatoid arthritis

in the earlier RA PMS study and the UC PMS study. In all three studies, drug ineffective, condition aggravated, headache, diarrhea, and fatigue were among the top ten most frequently reported AEs. In contrast to these findings for the PMS reports, data from the tofacitinib clinical development program found that nasopharyngitis and upper respiratory tract infections were the most common AEs experienced by patients receiving tofacitinib for PsA or RA [39]. These differences may relate to methodology; in clinical trials, all potential AEs are captured in a tightly controlled setting (including nonsevere respiratory illnesses), whereas for spontaneous reporting, AEs that are suspected to be treatment-related may be prioritized.

In this analysis, off-label use was coded as an AE in line with its inclusion as a MedDRA PT. Off-label use was the second most frequently reported AE for PsA, which might be attributable to use as monotherapy (tofacitinib is approved for PsA in combination with methotrexate or nonbiologic DMARDs, depending on the country). A recent analysis of US claims data found that 62.6% of patients treated with tofacitinib for PsA were receiving monotherapy [52]. Alternatively, off-label use may represent utilization of a higher dose, such as 10 mg BID, which is not approved for PsA, and is approved for RA in Russia and Botswana (and formerly Switzerland, until 2020).

Our study provides important insight into the safety profile of tofacitinib in PsA, which was similar overall to the safety profile in RA. Higher RRs for AEs were observed for PsA than for RA in the present study over the full period of data collection, which covered 9 years for RA and 4 years for PsA. However, when restricting the analysis to the first 4 years post-approval for each indication, to align the duration of data collection, the RRs were higher for RA versus PsA. RRs are typically highest in the first 2 years post-approval (a phenomenon referred to as the

Table 5 Safety outcomes by sex and age < 65 and ≥ 65 years among patients with PsA and RA (all tofacitinib)

PsA	Age < 65 years 13,453 PY			Age ≥ 65 years 7253 PY			Female sex 14,331 PY			Male sex 6375 PY		
	N	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]
Case reports	3299			965			3468			1338		
AEs	10,198		75.80	3505		48.32	11,455		79.93	3770		59.14
SAEs	1130	11.08	8.40	555	15.83	7.65	1402	12.24	9.78	530	14.06	8.31
AESIs[c]												
Serious infections	284	2.78	2.11	114	3.25	1.57	312	2.72	2.18	113	3.00	1.77
HZ (serious and nonserious)	46	0.45	0.34	25	0.71	0.34	59	0.52	0.41	21	0.56	0.33
Cardiovascular events[d]	31	0.30	0.23	23	0.66	0.32	38	0.33	0.27	27	0.72	0.42
Malignancies (excluding NMSC)	32	0.31	0.24	19	0.54	0.26	38	0.33	0.27	17	0.45	0.27
NMSC	6	0.06	0.04	5	0.14	0.07	10	0.09	0.07	1	0.03	0.02
VTE[e]	21	0.21	0.16	11	0.31	0.15	22	0.19	0.15	16	0.42	0.25
Fatal cases	10	0.30[f]	0.07	26	2.69[f]	0.36	24	0.69[f]	0.17	14	1.05[f]	0.22
RA	**Age < 65 years 247,644 PY**			**Age ≥ 65 years 191,726 PY**			**Female sex 336,013 PY**			**Male sex 103,357 PY**		
	N	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]	*N*	%[a]	RR[b]
Case reports	42,923			22,076			49,300			10,757		
AEs	142,559		57.57	80,419		41.94	176,244		52.45	33,014		31.94
SAEs	20,472	14.36	8.27	17,104	21.27	8.92	29,088	16.50	8.66	6292	19.06	6.09
AESIs[c]												
Serious infections	4326	3.03	1.75	3238	4.03	1.69	5904	3.35	1.76	1253	3.80	1.21
HZ (serious and nonserious)	1013	0.71	0.41	769	0.96	0.40	1389	0.79	0.41	229	0.69	0.22
Cardiovascular events[d]	519	0.36	0.21	655	0.81	0.34	831	0.47	0.25	303	0.92	0.29
Malignancies (excluding NMSC)	615	0.43	0.25	791	0.98	0.41	979	0.56	0.29	331	1.00	0.32
NMSC	117	0.08	0.05	181	0.23	0.09	211	0.12	0.06	78	0.24	0.08
VTE[e]	222	0.16	0.09	222	0.28	0.12	332	0.19	0.10	117	0.35	0.11
Fatal cases	312	0.73[f]	0.13	825	3.74[f]	0.43	744	1.51[f]	0.22	332	3.09[f]	0.32

Table 5 continued

AE adverse event, *AESI* adverse event of special interest, *HZ* herpes zoster, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* nonmelanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *PY* patient-years, *RA* rheumatoid arthritis, *RR* reporting rate, *SAE* serious adverse event, *VTE* venous thromboembolism

[a]Percentages are based on total AEs by formulation except where otherwise indicated

[b]Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases)

[c]Search criteria for AESI categories are described in the Supplementary Methods

[d]Includes the following Standardised MedDRA Queries: central nervous system vascular disorders, myocardial infarction and associated terms, ischemic heart disease and associated terms; and the following PTs: cardiac death, cardiac failure congestive, sudden cardiac death, and pulmonary embolism

[e]Pulmonary embolism events are captured in the cardiovascular events and VTE categories

[f]Percentages based on total case reports by formulation

Weber effect) [53], so these results were not unexpected, given that tofacitinib was approved for RA before PsA, and had a novel mechanism of action at the time of its first approval. Also, RA has been associated with a generally higher comorbidity burden than PsA [8], which may increase patients' likelihood of experiencing AEs [54]. In pooled analyses of the tofacitinib clinical development program, incidence rates of SAEs and AEs leading to discontinuation were higher in RA than in PsA, while rates of AESIs were generally comparable, with the exception of numerically lower rates of serious infections and HZ in PsA versus RA [39]. These differences were suggested to relate to patient characteristics including older age and higher corticosteroid use in the RA cohort versus the PsA cohort [39]. In these PMS data, we did not observe noticeable differences in frequency or RR of AESIs between PsA and RA. Previous registry studies have found higher exposure-adjusted incidence rates and/or risk ratios of infections [9], MACE [13, 14], malignancies [10], and VTE [11] in RA versus PsA. In this analysis, the most frequent AEs reported by PT were similar between PsA and RA, with the exception of differences in off-label use, as discussed above. To our knowledge, no other PMS data are available comparing rates of AESIs in PsA versus RA.

Overall, the AESIs observed in this study were aligned with those observed in other PMS studies of bDMARDs in PsA and RA [55–59], but differences in geographical regions, patient and disease characteristics, and data-collection methodology make it difficult to compare AE rates across studies. In previous real-world safety studies, rates of AESIs were generally comparable between tofacitinib and bDMARDs in overall populations of patients with RA, with the exception of HZ, which occurred more frequently with tofacitinib than with bDMARDs [45, 46, 60]. No comparable large studies have been published in PsA, but an analysis comparing tofacitinib clinical data with US Truven MarketScan registry data for bDMARDs (with patient exclusion criteria similar to those of the tofacitinib clinical trials applied) showed generally similar incidence rates for most AESIs in PsA, except for rates of HZ which, as expected, were higher in the tofacitinib clinical data than in the bDMARD observational data [61]. In patients with RA and elevated cardiovascular risk, differences in AESI rates between tofacitinib and bDMARDs have been noted in the ORAL Surveillance and STAR-RA studies [35, 45, 46].

A trend towards higher reporting of AEs and SAEs with the MR formulation than with the IR formulation was observed across indications, although RRs for AESIs and fatal cases were similar. There are several factors that might explain the higher volume of reports, and resulting RR, for MR relative to IR. Notably, SAEs occurred with similar frequency (in terms of percentage) between the MR and IR

Table 6 Most reported PTs for AESI categories[a] by tofacitinib formulation among patients with PsA and RA

N	PsA		RA	
	Tofacitinib IR	Tofacitinib MR	Tofacitinib IR	Tofacitinib MR
Serious infections				
Pneumonia (SAE)	43	29	1183	549
Lower respiratory tract infection (SAE)	30	6	354	52
COVID-19 or COVID-19 pneumonia (SAE)	15	30	196	298
COVID-19 (serious and non-serious)[b]	54	93	451	812
HZ[c]				
HZ	47	32	1143	512
Ophthalmic HZ	0	2	28	12
HZ disseminated	0	0	6	2
Cardiovascular events[d]				
Cerebrovascular accident	7	3	187	117
Myocardial infarction	8	8	178	95
Pulmonary embolism	16	6	137	66
Malignancies (excluding NMSC)[e]				
Breast cancer or breast cancer female	4	4	97	48
Lung neoplasm malignant	1	1	72	44
Colon cancer	0	2	35	12
NMSC				
Skin cancer	2	2	90	62
Basal cell carcinoma	1	2	38	18
Squamous cell carcinoma	1	2	20	13
VTE[f]				
Pulmonary embolism	16	6	137	66
Deep vein thrombosis	5	5	88	44
Pulmonary thrombosis	2	1	50	31

AESI adverse event of special interest, *COVID-19* Coronavirus disease 2019, *HZ* herpes zoster, *IR* immediate release, *MedDRA* Medical Dictionary for Regulatory Activities, *MR* modified release, *NMSC* nonmelanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *SAE* serious adverse event, *VTE* venous thromboembolism

[a]Data represent event counts for the top three PTs reported in each AESI category. Search criteria for AESI categories are described in the Supplementary Methods

[b]Includes the following PTs: asymptomatic COVID, COVID-19, COVID-19 pneumonia. The following MedDRA terms were excluded as they could apply to non-COVID-19 coronavirus: coronavirus infection, coronavirus pneumonia

[c]Total serious HZ (PTs: HZ, HZ cutaneous disseminated, HZ disseminated, HZ infection neurological, HZ meningitis, HZ meningoencephalitis, HZ oticus, HZ reactivation, ophthalmic HZ): RA tofacitinib IR $n = 170$; RA tofacitinib MR $n = 52$; PsA tofacitinib IR $n = 5$; PsA tofacitinib MR $n = 3$

[d]Includes the following Standardised MedDRA Queries: central nervous system vascular disorders, myocardial infarction and associated terms, ischemic heart disease and associated terms; and the following PTs: cardiac death, cardiac failure congestive, sudden cardiac death, and pulmonary embolism

[e]Excluding the nonspecific PT of 'neoplasm malignant'

[f]Pulmonary embolism events are captured in the cardiovascular events and VTE categories

formulations, possibly indicating that the difference could be due to reporting trends rather than a reflection of differing safety profiles. The total exposure time for the MR formulation was lower than for the IR formulation, which may have impacted the resulting RR. Almost all of the case reports received for the MR formulation originated from North America, potentially indicating a regional trend in reporting frequency. The MR formulation was first approved in North America, and the US contributes the highest number of AE reports globally to large Individual Case Safety Reports databases such as VigiBase and the FDA Event Reporting System (FAERS) [62, 63]. In addition, specialists may be more likely than general practitioners to report AEs [64], and the US has a higher density of rheumatologists than other countries with large populations [65]. Furthermore, the MR QD formulation might be preferred by patients receiving multiple treatments per day, who may have comorbidities and may potentially experience a greater number of AEs [54]. Notably, approximately twice as many patients receiving the MR formulation reported multiple indications as those receiving the IR formulation. In a randomized clinical trial setting, the safety profile of the IR and MR formulations was comparable [40]. The two formulations have been shown to have equivalent pharmacokinetic profiles based on areas under the curve [66], and similar effectiveness in the real-world CorEvitas (formerly Corrona) RA Registry [67].

External factors such as regulatory safety alerts, or changes to the approval status of a drug, have been shown to lead to increases in AE reporting [68], which is termed notoriety bias [69]. In 2019, an ad hoc safety analysis of the ORAL Surveillance study revealed increases in rates of pulmonary embolism with tofacitinib 10 mg BID versus TNFi, and all-cause mortality with tofacitinib 10 mg BID versus tofacitinib 5 mg BID and TNFi. Additionally, in the final results, non-inferiority was not shown for the combined tofacitinib doses (5 and 10 mg BID) versus TNFi for the co-primary endpoints of MACE and malignancy excluding NMSC [35]. After the results of ORAL Surveillance, signal detection studies of JAK inhibitors using FAERS and VigiBase have revealed increased reporting odds ratios for VTE or thromboembolic events [70, 71]. In another analysis of VigiBase directly comparing JAK inhibitors and TNFi, no increased reporting odds ratio was found for MACE, although an increased risk of VTE was observed [47]. In our analysis of PMS data collected from the Pfizer safety database, an increase in event reporting over time was not consistently observed across AEs, which might suggest that differences in reporter identity or training can influence post-marketing data collection.

There was a higher proportion of reports received for females than for males; this trend is expected for RA, given the epidemiological rates of disease prevalence (approximately 2–5 times higher in females than males, depending on age [72]); however, this was unexpected for PsA (approximately 1:1 female:male ratio [2]), suggesting a bias for reporting AEs in females compared with males. It is not surprising that a higher RR is observed in female patients versus male patients, given the higher volume of reports for females. It will be important to further explore whether these trends are based on a higher likelihood of the attending HCP, or the consumer, reporting an event occurring in a female, or if the rate of AEs occurring is truly higher in females. When considering SAEs, AESIs, and fatal cases, the RRs were similar between sexes. Higher RRs were also observed in patients < 65 versus ≥ 65 years of age. In this case, it is possible that AEs in patients ≥ 65 years of age are more likely to be attributed to older age than to the treatment and are therefore less likely to be reported. Alternatively, these trends in RRs could point to differences in clinical care between subgroups. In the VigiBase analysis of MACE and VTE comparing JAK inhibitors and TNFi, age and sex did not significantly influence RRs [47].

Limitations of this analysis include the potential for reporting bias (e.g., favoring female and/or younger patients), varied reporter identity/training (e.g., consumer versus physician; specialists may be more likely to report than general practitioners), and exposure estimation from commercial sales data (covering only 61 countries and one region, with indication-share derived from even fewer countries

[*n* = 18] where prescription data were available). When interpreting the AE data, the use of mixed data sources should be noted; the RRs in this analysis were calculated using the estimated exposure data, while the number and frequency (percentage) are solely based on data from case reports. Also, more data were available for RA than for PsA, and for IR than for MR tofacitinib, which should be considered when interpreting differences across indications and formulations. Furthermore, causality of AEs, considering tofacitinib compared with other concomitant medications, was not robustly collected. Most patients would have received concomitant methotrexate or other csDMARDs per regulatory labeling, so the role of these medications in contributing to AE risk cannot be ruled out. Other limitations of PMS data in general include under-reporting of nonserious AEs, difficulty identifying events with low frequency, and difficulty quantifying risks (owing to the lack of a reliable denominator) [73].

CONCLUSIONS

This PMS study using data ascertained from submitted AE reports found that safety findings for overall AEs and AESIs with tofacitinib were consistent between PsA and RA, and were aligned with the known safety profile of tofacitinib. Frequencies of SAEs, AESIs, and fatal cases (as a proportion of total AEs or total cases) were similar between tofacitinib formulations, while RRs were higher with the MR formulation versus the IR formulation. This difference in RRs may relate to differences in cumulative exposure, regional reporting trends, or different patient populations. Potential trends in reporting by sex and age require further assessment, with higher RRs observed in females than in males, and in younger than in older patients. While these results should be interpreted in the context of the limitations of PMS studies and spontaneous AE reporting, this study provides important insight into the global real-world safety profile of tofacitinib, reported here for the first time in PsA.

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Compliance with Ethics Guidelines. The spontaneously reported PMS AE data in this analysis were not collected as part of a clinical study and were non-interventional; therefore, no ethics approval was required. All data were reported in aggregate form in summary reports; no individual case-level data were evaluated or reported.

Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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