



REVIEW

Update on the Safety Profile of Tofacitinib in Rheumatoid Arthritis from Clinical Trials to Real-World Studies: A Narrative Review

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Received: October 13, 2020 / Accepted: November 11, 2020 / Published online: November 27, 2020
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ABSTRACT

Tofacitinib is approved for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who do not respond adequately or are intolerant to one or more disease-modifying anti-rheumatic drugs. The tofacitinib RA clinical development program included randomized controlled trials of 6–24-month duration and long-term extension studies with > 7061 patients and 22,875 patient-years of exposure. To date, there are no data from other randomized studies in patients with cardiovascular risk factors comparing the long-term safety of a JAK inhibitor versus an anti-TNF. Real-world studies are necessary to complete the body of evidence supporting the effectiveness and safety of a therapeutic agent. In the case of tofacitinib, real-world data derive from health insurance claims databases, registries (US Corrona Registry, Swiss Registry, and

others), national pharmacovigilance programs, and hospital databases (case series). The present article provides complete and up-to-date information on the safety profile of tofacitinib in RA, from clinical trials to real-world studies. Tofacitinib has demonstrated a consistent safety profile during up to 9.5 years of experience in randomized controlled trials and long-term extension studies. Real-world evidence has not added new safety issues with respect to those found in the clinical program. In general, the safety profile of tofacitinib is consistent with that of biologic disease-modifying anti-rheumatic drugs, with an increased risk of herpes zoster that seems to be a class effect of Janus kinase inhibitors. The continuous follow-up of therapeutic agents to treat rheumatoid arthritis is needed to adequately establish the safety profile for new mechanisms of action and potential risks associated with their longer term use.

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Keywords: Clinical trial; Real-world; Rheumatoid arthritis; Safety; Tofacitinib

Key Summary Points

Why carry out this study?

Although randomized controlled trials provide reliable evidence of the efficacy and safety of therapeutic agents, real-world studies are necessary to complete the body of evidence

To provide the available information on the safety profile of tofacitinib during its clinical development program (including phase I, II, IIIB/IV, long-term extension studies and the integrated safety analyses) and to contextualize it with that found in real-world settings

What was learned from the study?

Tofacitinib has demonstrated a consistent safety profile during up to 9.5 years of experience in randomized controlled trials and long-term extension studies

Real-world evidence has not added new safety issues with respect to those found in the clinical development program

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13214708>.

INTRODUCTION

Tofacitinib is an inhibitor of Janus kinases (JAK) [1]. It acts at the intracellular level by suppressing the phosphorylation and activation of the JAK-STAT signaling pathway, reducing the production of pro-inflammatory cytokines that regulate the immune response. Tofacitinib was approved in the USA in November 2012 and in Europe in March 2017 [1, 2]. It is indicated for

the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who did not respond adequately or are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARD), either biologic (bDMARD) or conventional ones (csDMARD). Tofacitinib can be administered in combination with methotrexate (MTX) or in monotherapy in cases of intolerance or contraindication to MTX. In 2018, tofacitinib also received approval from the European Agency of Medicines (EMA) for the treatment of active psoriatic arthritis (PsA) and moderate to severe ulcerative colitis (UC) in adults [1]. The US Food and Drug Administration (FDA) approved tofacitinib for the treatment of PsA and UC in December 2017 and May 2018, respectively. Tofacitinib is administered orally. The recommended and approved dose in Spain for RA and PsA is 5 mg twice a day (BID). Tofacitinib extended-release 11 mg tablets for the once-daily administration obtained the FDA approval for RA in February 2016 and for PsA in December 2017. EMA approval was obtained for RA in January 2020. In the case of UC, doses are 10 mg BID for induction (8 weeks) and 5 mg BID for maintenance treatment.

Data obtained during the tofacitinib RA clinical development program derive from randomized controlled trials (RCTs) of 6–24-month duration and long-term extension (LTE) studies [3–11]. For instance, the efficacy of tofacitinib and its safety profile were studied in the ORAL program, which consisted of diverse phase III RCTs using a variety of treatment schemes with tofacitinib, such as monotherapy, MTX and other DMARD combinations, comparisons with placebo or adalimumab (ADA) [5] and in different RA populations such as MTX-naïve patients or MTX- and bDMARD-insufficient responders [3–10]. A total of 4481 patients with RA (16,291 PYs of exposure) who completed previous phase I, II, or III studies with tofacitinib continued into two global LTE studies [10]. One of these studies shows the sustained efficacy and consistent safety profile of tofacitinib for > 9.5 years of treatment [12]. Integrated safety summary (ISS) data (compiling all data from phase I, II, III, IV trials and LTE studies) have additionally provided a complete

view of data across the development program for up to 9.5 years and involved > 7061 patients and 22,875 patient-years (PYs) of exposure [11]. A phase IV clinical trial, ORAL Surveillance, in a special population subgroup of > 4300 patients [> 50 years old, with at least 1 cardiovascular (CV) risk factor and followed-up for at least 3 years] was performed as an FDA requirement to study the safety profile of RA patients treated with MTX and tofacitinib 5 mg and 10 mg versus anti-TNF (clinicaltrials.gov #NCT02092467) [1]. Although RCTs provide reliable evidence of the efficacy and safety of therapeutic agents, they use patients with selective profiles. This fact limits the external validity and generalization of results to routine clinical practice [13]. Real-world studies are thus necessary to complete the body of evidence supporting the effectiveness and safety of a therapeutic agent. In the case of tofacitinib, real-world data derive from health insurance claims databases [14–21], registries (US Corrona Registry [22]; Swiss Registry and others) [23], national pharmacovigilance programs [24–26] and hospital databases (case series) [27–31]. The objective of the present manuscript is to provide the available information on the safety profile of tofacitinib during its clinical development program (including phase I, II, IIIB/IV, LTE studies and the integrated safety analyses) and to contextualize it with that found in real-world settings. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CLINICAL TRIALS VERSUS REAL-WORLD STUDIES

Data from clinical trials and real-world studies offer complementary information. Clinical trials usually compare results between well-defined homogeneous groups. They include a limited number of individuals that are followed by a limited period of time (relatively short in RCTs and longer in LTE studies). Moreover, they exclude individuals with certain levels of disease activity, active comorbidities and increased risks for toxicity [32, 33], unless specifically

designed for that purpose, such as in the Oral Surveillance trial [1]. A study to identify the proportion of RA patients in clinical practice who were eligible, according to entry criteria, for a biologic agent RCT showed that, in a real-world RA patient cohort, just 3.7% of them satisfied the eligibility criteria, demonstrating that most of patients would be excluded from RCTs [33]. By contrast, real-world studies just report information from routine clinical practice, without any selection of patients. They reflect better real practice but suffer from problems such as the lack of adequate comparators and of randomization, which can result in selection bias. Caporali and Zavaglia [34], reviewing the literature on tofacitinib in real-world settings, described the patient who initiates treatment with tofacitinib as having longer disease duration and having been exposed to longer bDMARD, compared with those initiating a bDMARD. Information from clinical practice can be influenced by the geographic location as well. Most real-world studies with tofacitinib have been conducted in the US, followed by Japan, Taiwan, Canada, Australia, and Switzerland [34–37]. Real-world studies also provide information about new safety risks that have not been detected during the clinical development program because of low frequencies or long latencies [38].

OVERALL SAFETY PROFILE

The safety profile of tofacitinib in RA has been mainly characterized in extensive RCTs, LTE studies (ORAL SEQUEL up to 9.5 years), and the phase IV Oral Surveillance trial [11]. The summary of safety results from studies in the tofacitinib clinical development program is shown in Table 1. The most frequent adverse events (AEs) reported are headache, upper respiratory tract infections, diarrhea, nasopharyngitis, hypertension, and nausea. Serious AEs (SAEs) included infections, mainly pneumonia, urinary tract infections, cellulitis, herpes zoster (HZ), appendicitis, and diverticulitis. HZ and pneumonia were the infections that most frequently led to the discontinuation of the treatment. Cohen et al. [11], in an ISS of 9.5 years of

Table 1 Summary of safety results from studies in the tofacitinib clinical development program

	References	Type of publication	Type of analysis/study	Total patients	Main findings by tofacitinib
Overall safety profile	Kivitz et al. [39]	Manuscript	Pool of phase III trials	3881	Lower IR with tofacitinib monotherapy than in combination: for SAEs (6.2–6.7 versus 10.2–13.5), discontinuation due to AEs (5.5–6.2 versus 10.8–11.0) and severe infections (1.6–1.7 versus 3.4–3.6)
	Curtis et al. [40]	Abstract	Pool of LTE studies	4934	Characteristics of patients who discontinued tofacitinib: longer disease duration at baseline, higher use of GCC, smokers/ex-smokers, and from the USA/Canada
	Wollenhaupt et al. [12]	Manuscript	LTE study (up to 9.5 years)	4481	Treatment discontinuation = 52% of patients: (24% due to AEs and 4% due to inadequate response); IR for AEs leading to discontinuation = 6.8
	Cohen et al. [11]	Manuscript	ISS data (up to 9.5 years)	7061	Treatment discontinuation due to AEs = 23.1% of patients (IR = 7.1)
	EMA [1]	SmPC	Phase IV study: ORAL surveillance Special population ≥ 50 years + ≥ 1 CVRF	4362	IR were: pulmonary embolism 0.27 (0.12–0.52), deep vein thrombosis 0.30 (0.14–0.55), mortality 0.57 (0.34–0.89), and non-fatal serious infections 3.35 (2.78–4.01) ^a

Table 1 continued

	References	Type of publication	Type of analysis/study	Total patients	Main findings by tofacitinib
Infections	Bechman et al. [48]	Manuscript	Systematic review and meta-analysis: phase II and III trials	5888	IR for serious infections = 1.97
	Strand et al. [47]	Abstract	Meta-analysis; RCTs and LTE studies	NA	IR for serious infections = 1.70 (5 mg BID) and 1.79 (10 mg BID) with tofacitinib monotherapy and were 3.44 and 3.42, respectively, when combined with methotrexate
	van Vollenhoven et al. [43]	Manuscript	Pool of phase I, II, III trials and LTE studies	7061	Tofacitinib led to an initial elevation of ALC but decreased (stabilized) in 48 months; ALC < 500 cells/mm ³ was associated with serious infections
	Winthrop et al. [45]	Letter	Pool of phase II, III, and IIIb/IV with a TNFi control/comparator arm (< 65 vs. ≥ 65 years)	2180	IR for serious infections Aged < 65 years: tofa 5 mg BID 2.35 (1.42, 3.67); tofa 10 mg BID 2.00 (0.55, 5.13); ADA 1.48 (0.60, 3.06) Aged ≥ 65 years: tofa 5 mg BID 4.55 (1.67, 9.91); tofa 10 mg BID 11.31 (3.08, 28.95); ADA 2.44 (0.3, 8.81)
Herpes zoster	Winthrop et al. [49]	Manuscript	Pool of phase I, II, III trials and LTE studies	6192	IRs for herpes zoster = 0.56 (5 mg BID tofacitinib monotherapy) versus 5.44 (10 mg BID, csDMARD and GCC)

Table 1 continued

	References	Type of publication	Type of analysis/study	Total patients	Main findings by tofacitinib
Opportunistic infections and tuberculosis	Souto et al. [54]	Manuscript	Systematic review and meta-analysis: RCTs and LTE studies	75,000 in RCTs	119 cases of active tuberculosis in LTE studies; IR of tuberculosis > 40/100,000
	Winthrop et al. [49]	Manuscript	Pool of phase II, III trials and LTE studies	5671	60 opportunistic infections; IR for tuberculosis = 0.21; concurrent treatment of isoniazid and tofacitinib was associated with no tuberculosis infection
	Chen et al. [56]	Manuscript	Basic research	–	Tofacitinib increased susceptibility to <i>Candida albicans</i> infection in BALB/c mice
Malignancies	Curtis et al. [60]	Manuscript	ISS data	5671	Malignancies in 107 patients; mainly lung cancer, breast cancer, lymphoma, and gastric cancer
	Mariette et al. [62]	Manuscript	ISS data	6194	Lymphoma occurred in 19 patients (IR = 0.10)
	Maneiro et al. [61]	Manuscript	Systematic review, meta-analysis, and network meta-analysis	–	Odds ratio for overall malignancies = 1.15; treatment with tofacitinib is not associated with an increased risk for malignancies
Interstitial lung disease	Citera et al. [65]	Abstract	ISS data	7061	Interstitial lung disease in 42 patients (0.6%); characteristics of patients associated with the event: aged \geq 65 and from Asia

Table 1 continued

	References	Type of publication	Type of analysis/study	Total patients	Main findings by tofacitinib
Cardiovascular AEs	Xie et al. [73]	Manuscript	Systematic review and meta-analysis: RCTs	11,799	Odds ratio for cardiovascular AEs = 0.63; tofacitinib is not associated with risk for cardiovascular AEs, MACEs, or VTEs
	McInnes et al. [71]	Manuscript	Phase II trial	111	Atorvastatin reduces significantly the elevated levels of total and LDL-cholesterol and triglycerides increased by tofacitinib
	Souto et al. [74]	Manuscript	Systematic review and meta-analysis: RCTs	NA	Tofacitinib is significantly associated with hypercholesterolemia (odds ratio 4.64), increased levels of HDL (2.25), and LDL (4.80) cholesterol
	Charles-Schoeman et al. [70]	Manuscript	Pool of phase III and LTE studies	4827 from LTE	IR for MACEs was 0.4 per 100 PYs). Increased HDL cholesterol level after 24 weeks of treatment
	Mease et al. [75]	Manuscript	Pool of phase I, II, and III RCTs and LTE studies	7964	IRs of venous thromboembolism and arterial thromboembolism are generally higher in patients with cardiovascular or VTE risk factors
	EMA [1]	SmPC	Phase IV study: ORAL Surveillance Special population ≥ 50 years + ≥ 1 CVRF	4362	IR for CV mortality within 28 days of the last treatment were 0.5 per 100 PYs (95% CI 0.2–0.8) for tofacitinib 10 mg, 0.2 per 100 PYs (95% CI 0.1–0.5) for tofacitinib 5 mg, and 0.2 per 100 PYs (95% CI 0.1–0.4) for TNF inhibitors

Table 1 continued

	References	Type of publication	Type of analysis/study	Total patients	Main findings by tofacitinib
Mortality	Cohen et al. [41]	Manuscript	Pool of phase II, III trials and LTE studies	4789	All-cause mortality rate = 0.3 per 100 patients-years

SLE long-term extension, *ISS* integrated safety summary, *EMA* European Medicines Agency, *SmPC* summary of product characteristics, *cDMARDs* conventional disease-modifying anti-rheumatic drugs, *IR* incidence rates, *SAEs* serious adverse events, *AEs* adverse events, *RCT* randomized controlled trials, *NA* not available, *ALC* absolute lymphocyte counts, *MACEs* major adverse cardiovascular events, *VTEs* venous thromboembolism events, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *GCC* glucocorticoids

^a For tofacitinib 5 mg

experience with tofacitinib and 7061 patients (22,875 PYs of exposure), described an incidence rate (IR) for SAEs of 9.0 [95% confidence interval, (CI): 8.6–9.4]. Wollenhaupt et al. [12], in a LTE study of up to 9.5 years of experience, showed that 52% of patients (from a total of 4481) discontinued the treatment with tofacitinib, 24% due to AEs and 4% because of inadequate response. The IR causing discontinuation was 6.8 (95% CI 6.4–7.2). Kivitz et al. [39], in a post-hoc, pooled study involving phase III studies with 3881 patients with RA and designed to compare tofacitinib in monotherapy and in combination with cDMARDs, revealed that the IR for SAEs (6.2–6.7), discontinuation due to AEs (5.5–6.2), and severe infections (1.6–1.7) was lower in monotherapy than in combination (10.2–13.5, 10.8–11.0, and 3.4–3.6, respectively). Curtis et al. [40] analyzed characteristics associated with the discontinuation of the treatment and reported that the patients who discontinued had a longer disease duration at baseline, had greater use of glucocorticoids (GCC), were smokers/ex-smokers, and came from the USA and Canada. Infections and all-cause mortality were evaluated in clinical trials in a data cut, including 4789 patients who received tofacitinib in phase II, III, and LTE studies (8460 PYs of exposure) [41]. Factors associated with an increased risk of serious infections were: age (≥ 65 years versus < 65 ; hazard ratio, HR, 2.2; 95% CI 1.6–2.9), diabetes (with versus without; HR 2.0; 95% CI 1.4–2.9), dose of GCC (≥ 7.5 mg versus < 7.5 mg of

prednisone or equivalent; HR 1.4; 95% CI 1.1–1.9), and dose of tofacitinib (10 mg versus 5 mg, BID; HR 1.4; 95% CI 1.1–1.8). In another post-hoc analysis, Curtis et al. [42] analyzed the efficacy and safety of tofacitinib in older and younger patients with RA by using data from five phase III and two LTE studies. Compared with patients aged < 65 years, the exposure to tofacitinib was lower in patients aged ≥ 65 years ($n = 475/3111$; 15.3%) in phase III studies (259 versus 1555 PYs) and LTE studies (962 versus 5072 PYs). Moreover, patients aged ≥ 65 years had a higher IR for SAEs and discontinuation due to AEs than those aged < 65 years. In the phase IV ORAL Surveillance, RA patients were ≥ 50 years old and had at least one of the following CV risk factors: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA [1]. Patients receiving tofacitinib 10 mg BID had to stop and switch to 5 mg BID because of a dose-dependent signal of venous thromboembolic events (VTE).

The safety profile of tofacitinib observed in real-world settings is in concordance with the one found during the clinical development program. The summary of safety results from studies in real-world settings using tofacitinib

for RA is shown in Table 2. Cohen et al. [24], in a 3-year post-marketing study involving data from 102,214 patients worldwide and 34,223 PYs follow-up receiving tofacitinib, reported a total of 25,417 AEs, 4352 SAEs, and 102 fatal cases. Of all AEs, 83% were considered as non-serious. No new safety signals were identified in this study compared with the previously described ones. Data from the US Corrona Registry have been presented in recent years. The IR for AEs for up to 5 years was compared among patients who started treatment with tofacitinib 5 mg BID, bDMARD, or cDMARD [22]. Propensity scores (PS)-trimmed and PS-matched were used for comparison purposes. Patients who started with tofacitinib or bDMARDs had similar IRs for major adverse CV events (MACE), serious infectious events and VTE rates. Nevertheless, the IR for HZ was higher in those starting with tofacitinib. These results are consistent with long-term clinical trial findings. Characteristics, treatment patterns and persistence in Canadian RA patients treated with tofacitinib have also been described in 4276 patients enrolled from 2014 to 2017 [36]. In this period, 1226/3678 (33.3%) discontinued, mostly from lack of efficacy (35.7%) and AEs (26.9%). Persistence was 62.7% and 49.6% after 1 and 2 years of treatment, respectively.

Infections

Serious Infections

In the final data presented for the ORAL Sequel LTE study evaluating the safety of tofacitinib 5 and 10 mg twice daily (BID) for up to 9.5 years in patients with RA, the IR for serious infections was 2.4 per 100 PYs [12]. In patients receiving tofacitinib as combination therapy, the IRs were higher with tofacitinib 10 mg BID versus 5 mg BID for all serious infections (3.0 versus 1.9, respectively). In the ISS, the IR for serious infection was 2.5 (95% CI 2.3–2.7), 2.3 (95% CI 2.1–2.5) when excluding HZ [11]. The IRs gradually reduced over time with longer exposure to tofacitinib. Pneumonia, HZ, urinary tract infection, and cellulitis were the most frequent serious infections. According to absolute lymphocyte counts (ALCs), the IRs (95%

CI) for serious infections were 7.1 (95% CI 2.6–15.5) for < 500 cells/mm³, 2.9 (95% CI 2.5–3.5) for $\geq 500 - < 1000$ cells/mm³, 2.4 (95% CI 2.1–2.7) for $\geq 1000 - < 1500$ cells/mm³, and 2.3 (95% CI 2.0–2.8) for $\geq 1500 - < 2000$ cells/mm³ [11]. Furthermore, an increased risk for serious infections in patients with ALCs < 500 cells/mm³ was confirmed [43], so ALC should be monitored at baseline and every 3 months. Lymphocyte subset counts were not strongly associated with infection events. Older and younger RA patients have shown a differential risk for serious infections. Curtis et al. [42] determined the efficacy and safety of tofacitinib in older (≥ 65 years) and younger RA patients (< 65 years) with pooled data from five phase III trials. The authors revealed an increased risk of serious infections in older patients who received tofacitinib 5 mg BID compared with younger ones. This observation was in concordance with the infection and mortality rates found by Cohen et al. [41]. In ORAL Surveillance, the IR for fatal infections within 28 days of the last treatment was 0.22 (95% CI 0.09–0.46) and 0.18 (95% CI 0.07–0.39) per 100 PYs for tofacitinib 10 and 5 mg, respectively. Regarding non-fatal serious infections, the IR was 3.51 (95% CI 2.93–4.16) and 3.35 (95% CI 2.78–4.01) per 100 PYs [1]. The mortality due to serious infections is higher in patients > 65 years old treated with tofacitinib compared with anti-TNF [44]. In these patients, the IRs for mortality with tofacitinib 5 mg (ranging between 0.98 and 2.66) and 10 mg (1.23–4.20) are higher than with anti-TNF (0.52–1.83). The IR for mortality due to infections was 0.1 patients with events/100 PYs (95% CI 0.1–0.2) with data from the ISS up to 9.5 years [11] and 0.1 (95% CI 0.0–0.1) up to 9.5 years [12]. An analysis of the clinical data set of 2180 patients to assess age-based (< 65 vs. ≥ 65 years) serious infection risk in RA patients receiving tofacitinib in phase II, III, and IIIb/IV tofacitinib studies with a TNFi control/comparator arm showed that IRs were higher in older versus younger patients for active treatments and similar among younger patients for all treatments. For older patients, versus ADA, IRs for serious infections were similar for tofacitinib 5 mg BID and numerically

Table 2 Summary of safety results from studies in real-world settings using tofacitinib for rheumatoid arthritis

	References	Type of publication	Type of study	Total patients ^a	Main findings by tofacitinib
Overall safety profile	Kremer et al. [22]	Abstract	Corrona Registry (5 years)	1544	Similar rates of MACE and serious infection events between initiating with tofacitinib and bDMARD; IR for herpes zoster higher for tofacitinib
	Cohen et al. [24]	Brief report	Post-marketing surveillance experience (3 years)	34,223 PYs	25,417 AEs, 4352 SAEs, and 102 fatal cases Of AEs, 83% were considered non-serious
	Mueller et al. [28]	Abstract	Case series: St. Gallen and-Aarau RA cohorts	144	Main reasons for discontinuation: inadequate response, gastrointestinal symptoms, and infection
	Hsieh et al. [29]	Abstract	Retrospective case series: drug-based registry	211	Incidence rate of all-cause AEs higher in tofacitinib initiators (44.9 events/100 patient-years) versus TNFi (33.1 events/100 patient-years)
	Winthrop et al. [45]	Letter	Corrona Registry	10,357	Age-/gender-standardized SIE IRs were higher in older versus younger patients, and similar between tofacitinib and bDMARD initiators for both age groups
Herpes zoster	Tamura et al. [25]	Abstract	Post-marketing surveillance experience (3 years)	3929	Herpes zoster was the most frequently reported AE by preferred term (3.7%); tuberculosis in 3 patients; IR for herpes zoster = 6.81 and for serious infection events = 5.38
	Curtis et al. [14]	Manuscript	Healthcare insurance data (5 years)	2526	Crude incidence of herpes zoster = 3.87/100 patient-years. Characteristics associated with infection: age (older), sex (female), prednisone (> 7.5 mg/day), prior infection, and higher number of hospitalizations
	Curtis et al. [15]	Manuscript	Healthcare insurance data (6 years)	8030	Incidence of herpes zoster lowest without GCC (3.4/100 patient-years with methotrexate versus 3.7 without). An increased risk associated with age (older), and sex (female)

Table 2 continued

	References	Type of publication	Type of study	Total patients ^a	Main findings by tofacitinib
Hepatitis	Chen et al. [30]	Letter	Retrospective case Series	32	Tofacitinib does not interfere with hepatitis C viral replication
	Chen et al. [31]	Letter	Retrospective case series	116	6 patients with previous hepatitis B infection were considered carriers and the remaining 75 had resolved the infections (normal levels of alanine aminotransferase)
	Serling et al. [58]	Letter	Retrospective case series	20	No hepatitis B virus reactivation in patients with resolved infection receiving tofacitinib over 3 years
Malignancies	Tamura et al. [26]	Abstract	Post-marketing surveillance experience (3 years)	3929	25 cases of malignancies within first 6 months of treatment (12 associated with the treatment); IR for malignancy = 1.25
Gastrointestinal perforation	Xie et al. [16]	Manuscript	Healthcare insurance data	4755	Incidence of lower tract gastrointestinal perforation = 1.29; predictors of risk were: age (older), diverticulitis/other gastrointestinal conditions, and prednisone (> 7.5 mg/day)
Interstitial lung disease	Xie et al. [17]	Abstract	Healthcare insurance data	1310 and 1540 PYs	IR for interstitial lung disease = 3.05
Cardiovascular AEs	Kume et al. [27]	Manuscript	Prospective case series	46	Improvement of the atherosclerosis, reduction of the disease activity, and limitation of the vascular damage
	Yun et al. [19]	Abstract	Healthcare insurance data (6 years)	2155	20 venous thrombotic events occurred in patients. IR for venous thrombotic events = 1.31
	Desai et al. [20]	Manuscript	Healthcare insurance data	2905	IR for venous thromboembolism = 0.60 and 0.34; infrequent incidence of deep vein thrombosis
DVT and PE	Verden et al. [78]	Manuscript	FDA's Adverse Event Reporting System	317	No raised rates for DVT and PE with tofacitinib

Table 2 continued

	References	Type of publication	Type of study	Total patients ^a	Main findings by tofacitinib
Mortality	Pope et al. [35]	Abstract	3-Year Canadian experience	4276	27 patients (out of 1226 of those who discontinued tofacitinib) died during tofacitinib treatment

PYs patient-years, *MACEs* major adverse cardiovascular events, *bDMARDs* biologic disease-modifying anti-rheumatic drugs, *IR* incidence rates, *AEs* adverse events, *SAEs* serious adverse events, *TNFi* tumor necrosis factor inhibitors, *NA* not available, *GCC* glucocorticoids, *DVT* deep venous thrombosis, *PE* pulmonary thromboembolism

^a Unless indicated otherwise, values are total number of patients

higher for tofacitinib 10 mg BID. HRs revealed similar serious infection risk between older and younger patients for tofacitinib 5 mg BID and ADA while the risk was significantly greater in older versus younger patients with tofacitinib 10 mg BID [45].

Moreover, Strand et al. [46, 47] in a systematic review and meta-analysis compared the IRs for serious infections among tofacitinib, baricitinib, and bDMARDs in patients with RA. Results suggested that the IR for tofacitinib in monotherapy [tofacitinib 5 mg IR 1.7 (95% CI 0.9–2.9)] and in combination with MTX IR 3.4 (95% CI 2.4–4.8) is comparable to that of baricitinib and bDMARDs in monotherapy in patients with moderate to severe RA. Bechman et al. [48], in a recent systematic review and meta-analysis involving 11 RCTs using tofacitinib and 5888 patients, reported an IR for serious infections of 2.0 (95% CI 1.4–2.7) per 100 PYs.

Data from real-world studies showed an IR for serious infections in a post-marketing worldwide surveillance of 2.6 events for 100 PY [24]. An interim analysis (3 years) of a Japanese post-marketing surveillance study in RA patients receiving tofacitinib did not detect new safety risks regarding serious infections, pneumonia by *Pneumocystis jirovecii*, tuberculosis (TB), or HZ. The IR for HZ and serious infections was higher for the first 3 months of treatment with tofacitinib, although it stabilized after the first year [25]. Pawar et al. [21], in a multidata base cohort study with data from public (Medicare) and private healthcare insurances in

the USA, showed an IR for serious infections of 3.1 (95% CI 3.0–3.2) for RA patients initiating tofacitinib. Tofacitinib showed similar adjusted HR for serious infection as ADA (1.06; 95% CI 0.9–1.3), certolizumab (1.02; 95% CI 0.8–1.3), golimumab (1.2; 95% CI 0.9–1.6), and tocilizumab (1.2; 95% CI 0.9–1.5), but lower than infliximab (0.81; 95% CI 0.7–1.0) and greater than etanercept (1.4; 95% CI 1.2–1.7) and abatacept (1.2; 95% CI 1.0–1.5). Of note, patients from Medicare had a mean age of 72 years and a crude incidence rate per 100 PYs of 7.89. In the Corrona RA Registry data set, incidence of infections and serious infections with tofacitinib initiators compared with bDMARD initiators was evaluated considering the age (< 65 vs. ≥ 65 years), and a higher SIE IR was found for older versus younger patients; the rate was similar between tofacitinib and bDMARD for both age groups [45].

Herpes Zoster Cases of HZ have been analyzed in clinical trials, including LTE studies. The risk of HZ seems to be increased in patients treated with tofacitinib, as well as with other JAK inhibitors, with respect to the therapy with tumor necrosis factor inhibitors (TNFi) [49]. The incidence of HZ is uniform over the time, without an increased risk with prolonged exposure to tofacitinib. Of note, the incidence of HZ is greater in the Asia-Pacific region than in Europe and the USA [50–52]. Winthrop et al. [49] evaluated whether concomitant treatment with cDMARD or GCC contributes to this risk in the long term in patients with RA

(approximately 17,000 PYs). The risk of developing HZ in patients receiving concomitant treatment with GCC was higher than in monotherapy with tofacitinib. The incidence of HZ was ten times lower with 5 mg BID tofacitinib in monotherapy than 10 mg BID in combination with cDMARDs and GCC. The mean IR for HZ in patients receiving tofacitinib 10 mg (4.1; 95% CI 3.3–5.2) was numerically higher than in those with 5 mg (3.3; 95% CI 2.6–4.3). The use of the approved dose of 5 mg and removal of concomitant therapies represent possible strategies for reducing this risk as long as the disease activity remains controlled. The AEs due to HZ were considered mainly non-serious and were treated by conventional antiviral agents.

Regarding real-life conditions, data from healthcare insurances in the USA (MarketScan and Medicare data between 2011 and 2016) [15, 18] confirmed the increased risk of HZ with the combination of tofacitinib and GCC, but not with MTX. The treatment without GCC showed the lowest incidence of HZ: 3.4/100 PYs with MTX versus 3.7/100 without MTX (about 4% of patients receiving tofacitinib per year). Glucocorticoids approximately double the incidence of HZ. Advanced age and female gender are some of the identified risk factors. Nevertheless, previous vaccination is strongly associated with a reduction of the risk [18]. On the other hand, Curtis et al. [14] also evaluated the risk for infection with HZ and herpes simplex virus (HSV) associated with tofacitinib compared with biologic agents (TNFi, abatacept, rituximab, and tocilizumab) by using healthcare insurance data in the USA between 2010 and 2014 (2526 patients who initiated treatment with these agents and had no previous history of HZ or HVS). The authors observed that the IR of HZ was doubled with tofacitinib (about 2 per 100 PYs) compared with biologics. The crude incidence of HZ associated with tofacitinib was slightly higher than that found during the tofacitinib clinical development program (3.87/PYs). After adjusting the multivariate model for potential confounding factors such as age, use of GCC, and comorbidities, the risk for HZ with tofacitinib significantly increased compared with abatacept. The risk for

the remaining biologic agents was comparable among themselves and with abatacept. Observations from this analysis are in concordance with conclusions from clinical trials and provide comparative evidence to data in real-world settings. In the post-marketing study by Tamura et al. [25], the IR for HZ was similar to results in Japanese patients from clinical trials (3956 PYs, 36 months of exposure), and IR of serious infections was within the interval found in post-marketing studies with biologics for RA. The most frequent AEs were infections and infestations (by system organ class, 12.5%) and HZ (by preferred term, 3.7%).

Opportunistic Infections and Tuberculosis Opportunistic infections associated with tofacitinib include mycobacterial and fungal ones, multidermatomal HZ, and viral infections associated with immunosuppression [1]. Patients with RA have a higher risk of developing opportunistic infections, especially in geographic regions in Asia. Risk of opportunistic infections in patients with RA and data up to 2013 from phase II and III clinical trials and LTE studies (a total of 5671 patients, 12,664 PY, and 48 countries worldwide) has been evaluated [53]. The authors identified 60 opportunistic infections, all of them in patients receiving tofacitinib. The most frequent opportunistic infection was TB ($n = 26$). However, it was rare in countries with low baseline incidence of TB, whereas frequent (80% of cases) in those with high incidence. A total of 263 patients with diagnosis of latent TB infection (LTBI) from phase III studies received concurrent treatment with isoniazid and tofacitinib, and none of them developed TB. As described for biologic agents, it is important to exclude TB before starting treatment with tofacitinib and to treat the LTBI with isoniazid during the treatment because it is well tolerated and is effective for preventing TB. Rifampin reduces the bioavailability of tofacitinib. Thus, isoniazid is the standard treatment; periodic tests need to be performed to evaluate liver function. None of the > 200 patients treated following this scheme (and completing isoniazid treatment) developed a clinically significant hepatitis or an active TB. Souto et al. [54], in a systematic

review and meta-analysis, analyzed the risk for active TB in 100 RCTs (75,000 patients) and 63 LTE studies (80,774 PYs) involving biologic agents and tofacitinib. The results showed concordance and low heterogeneity. A total of 119 cases of active TB were detected. RCTs are not sufficiently sensitive to determine the risk of reactivation of LTBI. In LTE studies, the IR for TB was $> 40/100,000$ with tofacitinib and biologic agents, excepting rituximab. Despite the shown benefit of the LTBI treatment, the risk/benefit balance seems not to support the implementation of widespread recommendations to prevent the reactivation of LTBI (treatment with isoniazid), for instance, in patients with low risk of TB and high risk of liver toxicity. For this reason, implementation should be considered individually in clinical practice [55]. Regarding the risk of fungal infection, Chen et al. [56], in a study with BALB/c mice, showed that treatment with tofacitinib increases the susceptibility to *Candida albicans* infection and thus to systemic and mucosal infections. Data highlighted the significant increased risk for opportunistic fungal infections associated with long-term treatment with tofacitinib in humans. Tamura et al. [26] reported *Pneumocystis jirovecii* in 0.4% of cases. Cytokines implicated in the function and homeostasis of lymphocytes are demonstrated to signal via JAK [57]. Thus, inhibitors of JAK are associated with lymphopenia and thus with the higher likelihood of infections. Vollenhoven et al. [44] also showed that the rate of opportunistic infections (such as HZ) tends to increase when the absolute lymphocyte count decreases. Nevertheless, the lack of enough cases did not allow making strong conclusions.

Hepatitis According to the summary of product characteristics of tofacitinib [1], patients with RA who developed hepatitis B or C were excluded from RCTs. Therefore, it was not possible to determine the effect of tofacitinib on the reactivation of the chronic viral hepatitis.

In real-life conditions, Chen et al. [30] compared hepatitis C viral replication in 32 patients with RA treated with tocilizumab, abatacept, and tofacitinib. The authors concluded that JAK inhibitors do not interfere with hepatitis C viral

replication, and thus the use of tofacitinib could be adequate in patients with RA and hepatitis C. Chen et al. [31] also retrospectively evaluated the risk of reactivation of hepatitis B virus (HBV) infection in a cohort of 116 patients with RA from Taiwan; 81 of them (69.8%) had HBV. Among patients with previous HBV infection, 6 were HBV carriers and the remaining 75 had resolved HBV. Among the six HBV carriers, two patients received pre-emptive antiviral treatment with nucleotide analogues and four patients did not. HBV reactivation occurred in two of the four patients without treatment and none of the two treated, stressing the importance of antiviral prophylaxis to prevent the reactivation of HBV. Treatment with tofacitinib seems safe in patients with resolved HBV infections [58].

Malignancies

There is concern about the risk of malignancies associated with immunosuppression [56]. Considering data from clinical trials and LTE studies, the risk of malignancies in patients with RA receiving 5 mg tofacitinib BID is similar to that reported for bDMARDs and cDMARDs. Data from clinical trials and LTE studies (5671 patients, and 12,664 PYs of exposure) have shown that the rate of malignancies does not increase with time exposure to tofacitinib, and the global risk for malignancies was similar to that expected in the RA population [59]. Diverse ISS data from the tofacitinib clinical development program for RA, meta-analysis, and network meta-analysis have confirmed such results [60, 61]. The risk of JAK/STAT inhibitor treatment for recurrent cancer in patients with previous malignancies is unknown (because these patients were excluded from clinical trials). The number of lymphoma events during the tofacitinib clinical development program (phase I, II, III clinical trials and LTE studies) has been published [62]. Lymphoma is the most frequent malignancy in patients with RA. Its IR was 0.10, and it did not increase over the time of exposure (19 cases of 6194 patients; 19,406 PYs of exposure; 3.4 years of mean treatment duration). In data coming from the ISS up to 9.5 years,

malignancies (excluding NMSC) occurred in 177 patients [2.5%; IR: 0.8 (95% CI 0.7–0.9)], NMSC in 129 patients [1.8%; IR: 0.6 (95% CI 0.5–0.7)] and lymphomas in 12 patients [0.2%; IR: 0.05 (95% CI 0.03–0.09)] [11].

Regarding real-world data, Tamura et al. [26], in the interim analysis of post-marketing reported cases in Japanese patients with RA treated with tofacitinib (3 years, up to November 2017), found that the rate of malignancies and deaths was similar to those in the clinical development program. A total of 3929 patients received tofacitinib and 25 developed a malignancy during the first 6 months of treatment (12 cases associated with the treatment), being the second-leading cause of death (5 out of 21 deaths). In the US Corrona register, Kremer et al. [63] compared the 5-year IRs of events of special interest, including malignancy, among patients who initiated tofacitinib (1999; 4505 PYs) or bDMARDs (6354 patients; 16,670 PYs). Of patients initiating tofacitinib and bDMARD, 88% and 59% had received previously a bDMARD. The IRs were similar between groups and for trimmed/matched analyses, in total 1.0 (95% CI 0.7–1.6) for total cancer excluding NMSC and 1.0 (95% CI 0.7–1.5) for NMSC. The adjusted HR was 1.04 (95% CI 0.7–1.6) for total cancer excluding NMSC and 1.0 (95% CI 0.7, 1.5) for NMSC. Data from a 3-year post-marketing study [24] [24] showed an estimated IR for neoplasm events by 6-month intervals ranging from 0.14 to 0.69 per 100 patient years, with an overall rate of 0.5 per 100 patient-years, which was highest after the first year and stabilized subsequently.

Gastrointestinal Perforations

Data from the ORAL Sequel (LTE) study [12], with an up to 9.5-year follow-up, reported 22 cases of gastrointestinal (GI) perforations. Perforations occurred in the large intestine (excluding the anus and rectum, $n = 13$), gastroduodenal area ($n = 3$), anus and rectum ($n = 2$), small intestine ($n = 1$), and other non-specified locations ($n = 3$). All patients received concomitant treatment with nonsteroidal anti-inflammatory drugs or GCC, medications

known to be associated with the development of GI perforations. In the last report from ISS, GI perforations occurred in 28 patients (0.4%; IR: 0.1; 95% CI 0.1–0.2) [11].

Xie et al. [16] described the risk of GI perforations in RA patients receiving various therapies in real-world settings. The incidence with tofacitinib was 1.3/1000 PYs, which was higher than for TNFi (0.8/1000 PYs). The incidence with tocilizumab, abatacept, and rituximab was 1.6, 1.1, and 0.7, respectively. The risk of lower GI perforations remained high after adjusting for age, sex, nonsteroidal anti-inflammatory drugs, GCC, peptic ulcer, and other GI conditions. This increased risk could be related to IL-6 inhibition. Real-world data from the US Corrona Registry showed an age- and gender-standardized IR for GI perforations of 0.05 in patients receiving tofacitinib, similar to those treated with bDMARDs (IR: 0.05) and cDMARDs (IR: 0.04) [64].

Interstitial Lung Disease

Interstitial lung disease (ILD) is an important extra-articular manifestation of RA. Different clinical trials have reported cases of ILD in patients with RA receiving tofacitinib, some of them fatal [1]. The relationship between JAK/STAT inhibition and ILD is so far unknown. In a pooled post hoc analysis of data from the tofacitinib clinical development program, Citera et al. [65], analyzed the IR of ILD in patients with active RA receiving tofacitinib. A total of 42 patients (0.6%, out of 7061; 23,394 PYs) had an ILD event during treatment with tofacitinib. Incidence rates were higher in patients older than 65 years and from Asia (compared with non-Asian ones). In phase I, II, III, IV and LTE studies, the incidence of ILD events reported after tofacitinib treatment was 0.18, and ILD events were associated with known risk factors for ILD in RA. In patients with ILD events (case-matched control analysis), the ILD group had a numerically higher proportion of patients with some characteristics such as Asian (31.0% versus 17.6% non-Asian), smokers (50.0% versus 39.5% ex-smokers), rheumatoid factor positive (89.2% versus 71.0% negative), anti-CCP antibody positive (54.8% versus 46.7% negative), higher baseline erythrocyte sedimentation rate

(57.0 versus 46.9 mm/h, control) and C-reactive protein (25.4 versus 15.4 mg/L control) and previous MTX treatment (90.5% versus 79.5%, without), csDMARDs (61.9% versus 55.2%), TNF inhibitors (26.2% versus 18.6%), and concomitant GCC (71.4% versus 52.9%).

Regarding real-world data, Xie et al. [17], in a comparative study, evaluated the risk of ILD in 150,225 patients with RA receiving biologic agents or csDMARD with data from Medicare 2006–2014 and Market Scan (2010–2015). The overall IR for ILD was 4.8 per 1000 PYs. Crude IRs varied between 3.1 (95% CI 1.2–8.1) for tofacitinib and 8.4 (95% CI 7.3–9.6) for infliximab in Medicare and between 0.6 (95% CI 0.1–4.1) for certolizumab and 3.9 (95% CI 2.1–7.2) for infliximab in Market Scan. Case series have also been published reporting RA patients with previous ILD who received tofacitinib to treat the disease [66, 67]. Conversely, Sendo et al. [68], in a study with SKG mice (animal model of RA that develops ILD), demonstrated that tofacitinib increased the myeloid-derived suppressor cells (MDSCs) and decreased the progression of ILD compared with controls. This potential benefit of tofacitinib on ILD in an experimental model of RA merits further evaluation in patients with RA, so it will be evaluated in the PULMORA phase IV study [69], a randomized, actively controlled, open-label, assessor-blinded, multicenter 48-week phase IV independent trial to evaluate the effects of tofacitinib versus methotrexate on interstitial pulmonary abnormalities.

Cardiovascular AEs

Data from the ISS for up to 9.5 years indicated that MACEs were reported in 85 patients (1.3%; IR: 0.4 [95% CI 0.3–0.5]) [11]. Charles-Schoeman et al. [70] evaluated the risk for CV events with tofacitinib using pooled data from six phase III studies and two LTE studies over 7 years in RA patients. The IR for MACE was 0.4 per 100 PYs. A protective association with subsequent MACEs was found with an increased HDL cholesterol level and decreased total cholesterol to HDL cholesterol ratio, but no impact was shown for LDL cholesterol or total cholesterol. McInnes et al. [71], in a randomized phase II, placebo controlled, multicenter phase

II study, open-label for tofacitinib and blinded for atorvastatin, revealed that atorvastatin can decrease the increased levels of lipids induced by tofacitinib, without reducing its efficacy in RA. Nurmohamed et al. [72], in a systematic review on the impact of biologic agents and tofacitinib in CV risk factors, found no increase in number of CV events with these medications. Similarly, Xie et al. [73], in another systematic review and meta-analysis, compared the impact of JAK inhibitors on risk of CV events in patients with RA. They analyzed data from 26 RCTs and 11,799 patients and showed that there is no significant association between tofacitinib and risk of CV events (Odds ratio 1.0; 95% CI 0.6–1.8). Souto et al. [74], in a systematic review and meta-analysis of RCTs, demonstrated that the mean increase in the HDL and LDL cholesterol levels was higher in patients with RA receiving tofacitinib than biologic agents. In ORAL Surveillance, the IR for CV mortality within 28 days of the last treatment was 0.5 per 100 PYs (95% CI 0.2–0.8) for tofacitinib 10 mg, 0.2 per 100 PYs (95% CI 0.1–0.5) for tofacitinib 5 mg, and 0.2 per 100 PYs (95% CI 0.1–0.4) for TNF inhibitors. To date, this study only has provided IR data for CV mortality and not for general CV events. Previous data from IR for CV mortality derive from ISS after 9.5 years (as adjudicated MACE, including CV death, of 0.4; 95% CI 0.3–0.5) [11] and 9.5 years of experience (IR: 0.1; 95% CI 0.1–0.2) [12]. Compared to TNF inhibitors, the incident rate ratio was 2.1 (95% CI 0.8–6.2) with tofacitinib 10 mg and 1.1 (95% CI 0.4–3.7) with tofacitinib 5 mg in these patients who were at least 50 years of age and had one or more CV risk factors [1].

Regarding real-world studies, data from a 3-year post-marketing study (Cohen et al. [24]) revealed a decrease in IR for CV events from 1.6 per 100 patient-years at the first 6-month interval to 0.3 at the final 6-month interval. The most frequent events were: myocardial infarction (29 cases), cardiac failure/cardiac failure congestive (21), cardiac disorder (19), atrial fibrillation (17), cardiac arrest (5), coronary artery disease (4), pericardial effusion (4), and tachycardia (3 cases). Data from the prospective, observational 5-year study embedded in the

ongoing US Corrona Registry showed that, in 1544 patients initiating tofacitinib (2138 PYs) and 7083 with bDMARD (9904 PYs), rates of MACE were similar in both groups, HR 0.6 (95% CI 0.3–1.18) [22]. Kume et al. [27], in a prospective cohort study in real-world settings, found a tendency to a possible beneficial effect on atherosclerosis in patients with active RA receiving tofacitinib (despite serum cholesterol increased) as measured by carotid intima-media thickness.

Deep Venous Thrombosis and Pulmonary Thromboembolism

Long-term extension studies and phase III studies have not shown an increased risk of VTE with tofacitinib. Final data for the ORAL Sequel LTE study for up to 9.5 years in patients with RA showed an IRs for deep venous thrombosis (DVT) of 0.1 (95% CI 0.1–0.3) for tofacitinib 5 mg BID and 0.1 (95% CI 0.1–0.2) for 10 mg BID [12]. The IRs for pulmonary embolism (PE) was 0.1 (95% CI 0.1–0.3) for tofacitinib 5 mg BID and 0.1 (95% CI 0.1–0.2) for 10 mg BID. Data from the ISS up to 9.5 years showed that DVT was reported in 36 patients (0.5%; IR: 0.2 [95% CI 0.1–0.2]) and PE in 28 patients (0.4%; IR: 0.1 [95% CI 0.1–0.2]) [11]. Mease et al. [75], analyzing data from phase I, II, and III RCTs and LTE studies [including 12,410 tofacitinib-treated patients from the development programs (RA: $n = 7964$; psoriasis, PsO: $n = 3663$; PsA: $n = 783$)], reported that IRs of venous thromboembolism and arterial thromboembolism are generally higher in patients with cardiovascular or VTE risk factors. In RA, PsO, and PsA programs, with 5 and 10 mg tofacitinib, the IR for DVT (0.17; 95% CI 0.09–0.27; 0.15, 95% CI 0.09–0.22), PE (0.12, 95% CI 0.06–0.22; 0.13; 95% CI 0.08–0.21), and arterial thromboembolism (ATE, 0.32, 95% CI 0.22–0.46; 0.38; 95% CI 0.28–0.49) were similar. These AEs, along with thromboembolic events, were lower in patients who did not show baseline cardiovascular or VTE risk factors. In LTE studies and ISS, including all patients ages [70], a relationship between tofacitinib (5 mg BID) and VTEs, including DVT and PE, was not found.

The phase IV ORAL Surveillance study was performed as an FDA requirement to study the

CV safety profile of tofacitinib in RA patients at least 50 years old and with at least one additional CV risk factor. EMA's safety committee has informed on 17 cases of PE out of 3123 patient-years with the tofacitinib 10 mg twice daily dose and 9 cases of PE out of 3317 patient-years with the tofacitinib 5 mg twice daily dose compared with 3 cases out of 3319 patient-years with a TNF inhibitor [76]. The IR for PE was 0.5 per 100 PYs (95% CI 0.3–0.9) for tofacitinib 10 mg, 0.3 per 100 PYs (95% CI 0.1–0.5) for tofacitinib 5 mg, and 0.09 per 100 PYs (95% CI 0.02–0.26) for TNF inhibitors [1]. Compared with TNF inhibitors, the HR for PE was 6.0 (95% CI 1.8–20.3) for tofacitinib 10 mg and 3.0 (95% CI 0.8–11.1) for tofacitinib 5 mg. Regarding DVT, the IR was 0.4 per 100 PYs (95% CI 0.2–0.7) for tofacitinib 10 mg, 0.3 per 100 PYs (95% CI 0.1–0.6) for tofacitinib 5 mg, and 0.2 per 100 PYs (95% CI 0.1–0.4) for TNF inhibitors [1]. Compared with TNF inhibitors, HR was 2.1 (95% CI 0.8–5.7) with tofacitinib 10 mg and 1.7 (95% CI 0.6–4.6) with tofacitinib 5 mg. The IR for PE was greater in patients treated with tofacitinib 10 mg twice daily in Study A3921133 (0.54; 95% CI 0.32–0.87) versus patients with baseline CV risk factors treated with tofacitinib 10 mg twice daily in the RA clinical program (0.24; 95% CI 0.13–0.41) [75, 76]. According to these data, tofacitinib should be used with caution in patients with known risk factors for VTE [1], such as those with heart failure, cancer, or any inherited blood coagulation disorder [76, 77]. Verden et al. [78] evaluated postmarketing reporting rates for related thromboembolic risks with three inhibitors of JAK (tofacitinib, tofacitinib extended-release, and ruxolitinib), and found no raised rates for DVT and PE. Nevertheless, they showed a trend toward higher-than-expected reporting rates.

Regarding real-world settings, IR for PE reported in the Corrona Registry [22] (including tofacitinib-naïve/bDMARD treated and tofacitinib treated) with baseline CV risk factors were similar to those observed among the corresponding patients in the tofacitinib development program. No signals of disproportionate reporting of DVT, PE, or ATE with tofacitinib were identified in the DA Adverse Event Reporting System (FAERS) database [75]. Yun

et al. [19], in a retrospective study using data from 2010–2015 US MarketScan claims, compared the risk of VTEs between patients with RA who initiated treatment with tofacitinib and ADA. The authors identified a total of 6022 initiators for ADA (4798 PYs) and 2155 for tofacitinib (1523 PYs). The authors detected 60 VTEs (20 in tofacitinib users and 40 in ADA users) and concluded that the risk was comparable between the two treatments (IR with tofacitinib: 1.3; 95% CI 0.8–2.0 versus IR with ADA: 0.83; 95% CI 0.6–1.1; HR of VTE for tofacitinib: 1.07; 95% CI 0.5–2.1). Desai et al. [20], in a recent observational cohort study using administrative claims data from the Truven MarketScan (2012–2016) and Medicare (and data from 50,865 patients with RA who started treatment with tofacitinib or TNFi), concluded that the incidence of DVT in these patients is infrequent (< 1 per 100 person-years). The absolute rates of VTE in routine care RA patients were low and comparable to those observed in pre-marketing trials of baricitinib and tofacitinib. Moreover, patients from Medicare insurance had a mean age of 71 years and a crude incidence rate per 100 PYs of 1.12 with tofacitinib (95% CI 0.5–2.3 versus 0.9; 95% CI 0.8–1.1 with TNF inhibitors). Cohen et al. [24], in the 3-year post-marketing study, reported 15 cases of pulmonary embolism and 9 of pulmonary thrombosis. Liang et al. [79] evaluated the incidence of inpatient VTEs in treated patients with RA by using a US claims database. The age and sex standardized IR for VTE was 0.9 per 100 PYs (95% CI 0.7–1.0). Results from a pharmacovigilance analysis performed by the World Health Organization considering the ongoing clinical debate on the safety profile of tofacitinib and baricitinib showed that patients who switched to another bDMARD or tsDMARD had a higher risk than csDMARD and first bDMARD or tsDMARD users [80]. 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 TEV (e.g., treatment with antithrombotic agents). Further risk factors potentially associated with risk of blood clots in lungs are having heart failure, having inherited blood clotting disorders, having had blood clots in the

veins, having cancer and planning to have or having recently had major surgery [81]. They concluded that, to date, real-world evidence regarding the safety of JAK inhibitors is lacking, and with the inherent limitations of pharmacovigilance data, the results of the study suggest that the thromboembolic safety of JAK inhibitors requires ongoing real-world assessment to determine whether a class and dose relationship exists. Thus, real-world assessments are needed to determine the safety of JAK inhibitors.

Mortality

In patients who received tofacitinib in phase II, III, and LTE studies, the overall all-cause mortality rate was 0.3 per 100 PYs (95% CI 0.2–0.4) and 0.5 per 100 PYs (95% CI 0.4–0.7) if deaths occurring at any time after the last dose are included [41]. Mortality rates were similar between phase III and LTE studies, and within phase III ones, among groups receiving tofacitinib (5 and 10 mg, BID), ADA, and placebo. Causes of death in phase III studies included: infection (6 cases), non-CV causes (3 cases, 1 of them receiving placebo), cardiac events (2 cases, 1 of them receiving ADA), cancer (1 case), trauma (1 case), or unknown cause (1 case). In the LTE studies causes were: infection (6 cases), cancer (6 cases), cardiac events (3 cases), non-CV causes (2 cases), suicide (2 cases), or unknown cause (1 case) [41]. Wollenhaupt et al. [12], in the LTE study of up to 9.5 years with tofacitinib, reported an IR for all-cause mortality of 0.3 (95% CI 0.2–0.4). In the interim results of the Oral Surveillance study, there were 28 deaths from all causes out of 3140 PYs in the tofacitinib 10 mg BID arm and 19 deaths from all causes out of 3324 PYs in the tofacitinib 5 mg BID arm compared with 9 cases out of 3323 PYs in the TNF inhibitor arm [75]. The mortality within 28 days of the last treatment was higher in patients treated with tofacitinib than in those taking TNF inhibitors [1]. The IRs were: 0.9 (95% CI 0.6–1.3) for tofacitinib 10 mg, 0.6 (95% CI 0.3–0.9) for tofacitinib 5 mg, and 0.3 (95% CI 0.1–0.5) for TNF inhibitors. Compared with TNF inhibitors, HR was 3.3 (95% CI 1.6–7.0) for tofacitinib 10 and 2.1 (95% CI 1.0–4.7) for

tofacitinib 5 mg. The main causes of mortality were: CV events, infections, and malignancies [1]. The IRs for fatal infections (within 28 days of treatment) were 0.18 (95% CI 0.07–0.39) with tofacitinib 5 mg BID, 0.22 (95% CI 0.09–0.46) with tofacitinib 10 mg BID, and 0.06 (95% CI 0.01–0.22) with TNF inhibitors [45].

Regarding real-world data, in the US Corrona Registry, the IR for death was 1.0 (95% CI 0.6–1.6), which was also similar for patients initiating bDMARDs [64]. Pope et al. [36], when describing the 3-year experience with tofacitinib in Canada, indicated that 27 patients (out of 1226 of those who discontinued tofacitinib, 2.2%) passed away during the treatment. Cohen et al. [25], in the 3-year post-marketing study, reported an overall mortality rate of 0.3 per 100 PYs. Causes of death were: infections (15 cases), CV events (8 cases), stroke (4 cases), pulmonary embolism (2 cases), ILD (2 cases), demyelination (1 case), Stevens-Johnson's syndrome (1 case), and surgical complications (1 case).

Risk Characterization and Relative Safety

A relatively large number of patients followed up for an adequate period of time and involving special populations is necessary to establish consistent conclusions about the safety of uncommon AEs. Tofacitinib RCTs and LTE studies and safety studies in special populations provide reassurance about the possibility of detecting additional unexpected adverse events [38]. The last ISS analysis included 7061 patients, representing 22,875 PY of tofacitinib exposure, with a median exposure of 3.1 years, and 30% of patients had > 5 years of exposure [11]. Study A3921133 contributes > 10,000 patients/year of exposure to tofacitinib in patients with CV risk factors [75]. Lee et al. [82] evaluated the relative efficacy and safety of tocilizumab, rituximab, abatacept, and tofacitinib in 1796 patients with RA having inadequate response to TNFi. By using a Bayesian network meta-analysis of RCTs, the authors found no significant differences regarding the number of withdrawals due to AEs. They suggested a comparable safety profile between biologic agents and tofacitinib. None of the treatments were associated with a significant risk of withdrawals due to AEs. Vieira et al. [83],

in another Bayesian network meta-analysis of tofacitinib versus biologic agents, also concluded that the treatment with 5 mg tofacitinib BID has AE rates comparable to those of abatacept, golimumab, tocilizumab, and rituximab during the 24 first weeks.

CONCLUSIONS

Tofacitinib has demonstrated a consistent safety profile during up to 9.5 years of experience in RCTs and LTE studies. Real-world evidence (since November 2012, including > 100,000 patients and an estimated exposure of 34,000 PYs) has not added new safety issues with respect to those found in the clinical development program. In general, the safety profile of tofacitinib is consistent with that of bDMARDs, with an increased risk of HZ that seems to be a class effect of JAK inhibitors. In patients aged > 65 years, a serious infection risk (fatal/non-fatal) was further increased with tofacitinib; therefore, the EMA recommended that older patients should receive tofacitinib when there is no suitable alternative treatment. In older patients with RA, additional risk factors should be evaluated (including age-related changes in pharmacokinetics and pharmacodynamics, comorbidities, polypharmacy, and drug compliance issues), and a specific risk assessment plan to minimize negative outcomes from therapies should be considered. The continuous follow-up of therapeutic agents is needed to adequately establish the safety profile for new mechanisms of action and the potential risks associated with their longer term use. Further research is required to complete the information presented here and verify these potential JAK inhibitor-associated risks.

ACKNOWLEDGEMENTS

Funding. This manuscript and the journal's Rapid Service Fee were funded by Pfizer, S.L.U.

Medical Writing and/or Editorial Assistance. Medical writing support was provided by

Meisys (Madrid, Spain) and was funded by Pfizer.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. JMA-G, FGL, MV, SG, and MM have contributed sufficiently to the work for them to be named as authors. The final manuscript has been read and approved by all the authors.

Disclosures. Jose Francisco García-Llorente declares no conflicts of interest. Jose María Álvaro-Gracia has received: consulting fees; speaker bureau fees from F Hoffmann-La Roche and Sanofi Genzyme; honoraria from AbbVie, BMS, Eli-Lilly, Galápagos, MSD, Novartis, Pfizer, Roche, Sanofi, and UCB; and research grants from MSD, Pfizer, Roche, and UCB. Mónica Valderrama, Susana Gomez, and Maria Montoro are employees of Pfizer, S.L.U.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES

1. European Medicines Agency, 2017. XELJANZ (tofacitinib citrate) 5 mg filmcoated tablets: summary of product characteristics. <https://www.ema.europa.eu>.
2. US Food and Drug Administration (2017) XELJANZ(R) (tofacitinib) tablets/XELJANZ(R) XR (tofacitinib) extended release tablets: prescribing information. Available from: <https://www.accessdata.fda.gov>.
3. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367:495–507.
4. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367:508–19.
5. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381:451–60.
6. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2013;159:253–61.
7. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014;370:2377–86.
8. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4,

- double-blind, head-to-head, randomised controlled trial. *Lancet*. 2017;390:457–68.
9. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum*. 2013;65:559–70.
 10. Fleischmann R, Wollenhaupt J, Takiya L, Maniccia A, Kwok K, Wang L, et al. Safety and maintenance of response for tofacitinib monotherapy and combination therapy in rheumatoid arthritis: an analysis of pooled data from open-label long-term extension studies. *RMD Open*. 2017;3:e000491.
 11. Cohen S, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the RA clinical development program. *RMD Open*. 2020;6:e001395.
 12. Wollenhaupt J, Lee EB, Curtis JR, Silverfield J, Terry K, Soma K, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther*. 2019;21:89.
 13. Barnish MS, Turner S. The value of pragmatic and observational studies in health care and public health. *Pragmat Obs Res*. 2017;8:49–55.
 14. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:1843–7.
 15. Curtis JR, Xie F, Yang S, Bernatsky S, Chen L, Yun H, et al. Risk for herpes zoster in tofacitinib-treated rheumatoid arthritis patients with and without concomitant methotrexate and glucocorticoids. *Arthritis Care Res (Hoboken)*. 2019;71(9):1249–54.
 16. Xie F, Yun H, Bernatsky S, Curtis JR. Brief Report: risk of gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, tocilizumab, or other biologic treatments. *Arthritis Rheumatol*. 2016;68:2612–7.
 17. Xie F, Annapureddy N, Chen L, Lobo JL, Oates JC, Shah A, et al. Rheumatoid arthritis and the risk for interstitial lung disease: a comparison of risk associated with biologic and conventional DMARDs. *Arthritis Rheumatol*. 2017;69:137.
 18. Curtis JR, Xie F, Yang S, Bernatsky S, Chen L, Yun H, Winthrop K. Risk for herpes zoster in tofacitinib-treated rheumatoid arthritis patients with and without concomitant methotrexate and glucocorticoids. *Arthritis Care Res (Hoboken)*. 2019;71(9):1249–1254. <https://doi.org/10.1002/acr.23769>.
 19. Yun H, Xie F, Chen L, Curtis JR. Risk of venous thrombotic events in rheumatoid arthritis patients initiating tofacitinib or adalimumab. *Arthritis Rheumatol*. 2018;70:224.
 20. Desai RJ, Pawar A, Weinblatt ME, Kim SC. Comparative risk of venous thromboembolism in rheumatoid arthritis patients receiving tofacitinib versus those receiving tumor necrosis factor inhibitors: an observational cohort study. *Arthritis Rheumatol*. 2019;71:892–900.
 21. Pawar A, Desai RJ, Gautam N, Kim SC. Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multidatabase cohort study. *Lancet Rheumatol*. 2020;2:84–98.
 22. Kremer J, Bingham C, Cappelli L, Greenberg J, Geier J, Madsen A, et al. Post-approval comparative safety study of tofacitinib and biologic DMARDs: five-year results from a US-based rheumatoid arthritis registry. *Ann Rheum Dis*. 2019;78:82–3.
 23. Kyburz D, Riek M, Herzog L, Scherer A, Gabay C, Dudler J, et al. Real-world use of tofacitinib in rheumatoid arthritis: data from the Swiss clinical quality management RA registry. *Arthritis Rheumatol*. 2016;68:1637.
 24. Cohen S, Curtis JR, DeMasi R, Chen Y, Fan H, Soonasra A, et al. Worldwide, 3-year, post-marketing surveillance experience with tofacitinib in rheumatoid arthritis. *Rheumatol Ther*. 2018;5:283–91.
 25. Tamura N, Kuwana M, Atsumi T, Takei S, Harigai M, Fujii T, et al. Infection events in Japanese patients with rheumatoid arthritis treated with tofacitinib: interim all-case post-marketing surveillance. *Arthritis Rheumatol*. 2018a;70:1516.
 26. Tamura N, Kuwana M, Atsumi T, Takei S, Harigai M, Fujii T, et al. Malignancy in Japanese patients with rheumatoid arthritis treated with tofacitinib: interim analysis of all-case post-marketing surveillance. *Arthritis Rheumatol*. 2018b;70:1515.
 27. Kume K, Amano K, Yamada S, Kanazawa T, Ohta H, Hatta K, et al. Tofacitinib improves atherosclerosis despite up-regulating serum cholesterol in patients with active rheumatoid arthritis: a cohort study. *Rheumatol Int*. 2017;37:2079–85.
 28. Mueller R, Hasler C, Popp F, Mattow F, Durmisi M, Souza A, et al. Effectiveness, tolerability, and safety of tofacitinib in rheumatoid arthritis: a retrospective analysis of real-world DATA from the ST.

- Gallen and-Aarau RA-Cohort. *Arthritis Rheumatol*. 2018;70:586.
29. Hsieh SC, Chen YH, Chen WS, Tsai WC, Hu JC, Chen HC, et al. Real-world use of tofacitinib compared with tumor necrosis factor inhibitors in a cohort of 211 patients with rheumatoid arthritis: data from a drug-based registry study in Taiwan. *Arthritis Rheumatol*. 2018;70:629.
30. Chen YM, Huang WN, Liao TL, Chen JP, Yang SS, Chen HH, et al. Comparisons of hepatitis C viral replication in patients with rheumatoid arthritis receiving tocilizumab, abatacept and tofacitinib therapy. *Ann Rheum Dis*. 2019;78:849–50.
31. Chen YM, Huang WN, Wu YD, Lin CT, Chen YH, Chen DY, et al. Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib: a real-world study. *Ann Rheum Dis*. 2018;77:780–2.
32. Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. *Rheumatology (Oxford)*. 2012;51:7–43.
33. Vashisht P, Sayles H, Cannella AC, Mikuls TR, Michaud K. Generalizability of patients with rheumatoid arthritis in biologic agent clinical trials. *Arthritis Care Res (Hoboken)*. 2016;68:1478–88.
34. Caporali R, Zavaglia D. Real-world experience with tofacitinib for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol*. 2019;37:485–95.
35. Pope J, Bessette L, Jones N, Fallon L, Woolcott J, Gruben D, et al. Experience with tofacitinib in Canada: patient characteristics and treatment patterns in rheumatoid arthritis over 3 years. *Rheumatol*. 2019. <https://doi.org/10.1093/rheumatology/kez324>.
36. Mueller RB, Hasler C, Popp F, Mattow F, Durmisi M, Souza A, et al. Effectiveness, tolerability, and safety of tofacitinib in rheumatoid arthritis: a retrospective analysis of real-world data from the St. Gallen and Aarau cohorts. *J Clin Med*. 2019;8:1548.
37. Bird P, Littlejohn G, Butcher B, Smith T, Pereira CDF, Witcombe D, et al. FRI0140 Evaluation of effectiveness and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia: an analysis from the OPAL-QUMI real world dataset. *Ann Rheum Dis*. 2019;78:740–1.
38. Curtis JR, Zhang R, Krishnaswami S, Anisfeld A, Chen Y, Strengholt S, et al. Use of a risk characterisation approach to contextualise the safety profile of new rheumatoid arthritis treatments: a case study using tofacitinib. *Clin Rheumatol*. 2017;36:683–8.
39. Kivitz AJ, Cohen S, Keystone E, van Vollenhoven RF, Haraoui B, Kaine J, et al. A pooled analysis of the safety of tofacitinib as monotherapy or in combination with background conventional synthetic disease-modifying antirheumatic drugs in a phase 3 rheumatoid arthritis population. *Semin Arthritis Rheum*. 2018;48:406–15.
40. Curtis JR, Wollenhaupt J, Chatzidionysiou K, Tas SW, Wang L, Shi H, et al. Patient characteristics associated with discontinuation of tofacitinib for the treatment of rheumatoid arthritis in open-label, long-term extension studies up to 9.5 years. *Arthritis Rheumatol*. 2018;70:1519.
41. Cohen S, Radominski SC, Gomez-Reino JJ, Wang L, Krishnaswami S, Wood SP, et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2014;66:2924–37.
42. Curtis JR, Schulze-Koops H, Takiya L, Mebus CA, Terry KK, Biswas P, et al. Efficacy and safety of tofacitinib in older and younger patients with rheumatoid arthritis. *Clin Exp Rheumatol*. 2017;35:390–400.
43. van Vollenhoven R, Lee EB, Strengholt S, Mojcik C, Valdez H, Krishnaswami S, et al. Evaluation of the short-, mid-, and long-term effects of tofacitinib on lymphocytes in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2019;71:685–95.
44. European Medicines Agency. Assessment report. Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data. INN/active substance: tofacitinib. https://www.ema.europa.eu/documents/referral/xeljanz-h-20-1485-c-4214-0017-assessment-report-article-20_en.pdf.
45. Winthrop KL, Citera G, Gold D, Henrohn D, Connell CA, Shapiro AB. Age-based (<65 vs ≥65 years) incidence of infections and serious infections with tofacitinib versus biological DMARDs in rheumatoid arthritis clinical trials and the US Corrona RA registry. *Ann Rheum Dis*. 2020. <https://doi.org/10.1136/annrheumdis-2020-218992>.
46. Strand V, Ahadieh S, DeMasi R, Krishnaswami S, Geier J, Menon S, et al. THU0211 Meta-analysis of serious infections with baricitinib, tofacitinib and biologic dmards in rheumatoid arthritis. *Ann Rheum Dis*. 2017;76:284.
47. Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis Res Ther*. 2015;17:362.

48. Bechman K, Subesinghe S, Norton S, Atzeni F, Galli M, Cope AP, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58:1755–66.
49. Winthrop KL, Curtis JR, Lindsey S, Tanaka Y, Yamaoka K, Valdez H, et al. Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. *Arthritis Rheumatol*. 2017;69:1960–8.
50. Chen LK, Arai H, Chen LY, Chou MY, Djauzi S, Dong B, et al. Looking back to move forward: a twenty-year audit of herpes zoster in Asia-Pacific. *BMC Infect Dis*. 2017;17:213.
51. Kim YJ, Lee CN, Lim CY, Jeon WS, Park YM. Population-based study of the epidemiology of herpes zoster in Korea. *J Korean Med Sci*. 2014;29(12):1706–10.
52. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open*. 2014;4(6):e004833.
53. Winthrop KL, Park SH, Gul A, Cardiel MH, Gomez-Reino JJ, Tanaka Y, et al. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:1133–8.
54. Souto A, Maneiro JR, Salgado E, Carmona L, Gomez-Reino JJ. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. *Rheumatology*. 2014;53:1872–85.
55. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. *Int J Infect Dis*. 2017;56:68–76.
56. Chen Y, Gong FY, Li ZJ, Gong Z, Zhou Z, Ma SY, et al. A study on the risk of fungal infection with tofacitinib (CP-690550), a novel oral agent for rheumatoid arthritis. *Sci Rep*. 2017;7:6779.
57. van Vollenhoven RF, Riese R, Krishnaswami S, Kawabata T, Fosser C, Rottinghaus S. Relationship between lymphocyte count and risk of infection in rheumatoid arthritis patients treated with tofacitinib. *Ann Rheum Dis*. 2013;72:250–1.
58. Serling-Boyd N, Mohareb AM, Kim AY, Hyle EP, Wallace ZS. The use of tocilizumab and tofacitinib in patients with resolved hepatitis B infection: a case series. *Ann Rheum Dis*. 2020. <https://doi.org/10.1136/annrheumdis-2020-218289>.
59. Sivaraman P, Cohen SB. Malignancy and Janus kinase inhibition. *Rheum Dis Clin North Am*. 2017;43:79–93.
60. Curtis JR, Lee EB, Kaplan IV, Kwok K, Geier J, Benda B, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. *Ann Rheum Dis*. 2016;75:831–41.
61. Maneiro JR, Souto A, Gomez-Reino JJ, editors. Risks of malignancies related to tofacitinib and biological drugs in rheumatoid arthritis: systematic review, meta-analysis, and network meta-analysis. *Seminars in arthritis and rheumatism*. Amsterdam: Elsevier; 2017.
62. Mariette X, Chen C, Biswas P, Kwok K, Boy MG. Lymphoma in the tofacitinib rheumatoid arthritis clinical development program. *Arthritis Care Res (Hoboken)*. 2018;70:685–94.
63. Kremer J, Bingham C, Cappelli L, Greenberg J, Madsen A, Geier J, et al. Comparison of malignancy and mortality rates between tofacitinib and biologic DMARDs in clinical practice: five-year results from a US-based rheumatoid arthritis registry. *Arthritis Rheumatol*. 2019;71:2874.
64. Kremer J, Cappelli LC, Etzel CJ, Greenberg J, Geier J, Madsen A, et al. Real-world data from a post-approval safety surveillance study of tofacitinib vs biologic DMARDs and conventional synthetic DMARDs: five-year results from a US-based rheumatoid arthritis registry. *Arthritis Rheumatol*. 2018;70:1542.
65. Citera G, Mysler E, Madariaga H, Cardiel MH, Castañeda O, Fischer A, et al. Incidence rates of interstitial lung disease events in tofacitinib-treated rheumatoid arthritis patients: post hoc analysis from 21 clinical trials. *J Clin Rheumatol*. 2020. <https://doi.org/10.1097/RHU.0000000000001552>.
66. Bejarano M, Tamborenea MN, Goñi MA, Saldarriaga L, Pisoni C, Garcia Salinas R, et al. AB0418 Interstitial lung disease in patients with rheumatoid arthritis treated with tofacitinib. *Ann Rheum Dis*. 2019;78:1672.
67. Saldarriaga-Rivera LM, López-Villegas VJ. Janus kinase inhibitors as a therapeutic option in rheumatoid arthritis and associated interstitial lung disease. Report of four cases. *Rev Colomb Reumatol*. 2019;26:137–9.
68. Sendo S, Saegusa J, Yamada H, Nishimura K, Morinobu A. Tofacitinib facilitates the expansion of myeloid-derived suppressor cells and ameliorates interstitial lung disease in SKG mice. *Arthritis Res Ther*. 2019;21:184.

69. ClinicalTrials.gov. Effects of tofacitinib vs methotrexate on rheumatoid arthritis interstitial lung disease (PULMORA). ClinicalTrials.gov Identifier: NCT04311567. <https://clinicaltrials.gov/ct2/show/NCT04311567>.
70. Charles-Schoeman C, DeMasi R, Valdez H, Soma K, Hwang LJ, Boy MG, et al. Risk factors for major adverse cardiovascular events in phase III and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2019;71:1450–9.
71. McInnes IB, Kim HY, Lee SH, Mandel D, Song YW, Connell CA, et al. Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. *Ann Rheum Dis*. 2014;73:124–31.
72. Nurmohamed M, Choy E, Lula S, Kola B, DeMasi R, Accossato P. The impact of biologics and tofacitinib on cardiovascular risk and outcomes in patients with rheumatic disease: a systematic literature review. *Drug Saf*. 2018;41:1–16.
73. Xie W, Huang Y, Xiao S, Sun X, Fan Y, Zhang Z. Impact of Janus kinase inhibitors on risk of cardiovascular events in patients with rheumatoid arthritis: systematic review and meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2019;78:1048–54.
74. Souto A, Salgado E, Maneiro JR, Mera A, Carmona L, Gómez-Reino JJ. Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis. *Arthritis Rheumatol*. 2015;67:117–27.
75. Mease P, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. *Ann Rheum Dis*. 2020;79:1400–13.
76. EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots EMA/608520/2019. https://www.ema.europa.eu/en/documents/referral/xeljanz-article-20-procedure-ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots_en.pdf.
77. European Medicines Agency. Increased risk of blood clots in lungs and death with higher dose of Xeljanz (tofacitinib) for rheumatoid arthritis EMA/180287/2019. https://www.ema.europa.eu/en/documents/press-release/increased-risk-blood-clots-lungs-death-higher-dose-xeljanz-tofacitinib-rheumatoid-arthritis_en.pdf.
78. Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. *Drug Saf*. 2018;41:357–61.
79. Liang H, Danwada R, Guo D, Curtis JR, Kilpatrick RD, Hendrickson B, et al. Incidence of inpatient venous thromboembolism in treated patients with rheumatoid arthritis and the association with switching biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) in the real-world setting. *RMD Open*. 2019;5:e001013.
80. Vallejo-Yagüe E, Weiler S, Micheroli R, Burden AM. Thromboembolic safety reporting of tofacitinib and baricitinib: an analysis of the WHO Vigibase. *Drug Saf*. 2020. <https://doi.org/10.1007/s40264-020-00958-9>.
81. European Medicines Agency. Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs. <https://www.ema.europa.eu/en/news/restrictions-use-xeljanz-while-ema-reviews-risk-blood-clots-lungs>
82. Lee YH, Bae SC. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials. *Int J Rheum Dis*. 2016;19:1103–11.
83. Vieira MC, Zwillich SH, Jansen JP, Smiechowski B, Spurden D, Wallenstein G. Tofacitinib versus biologic treatments in patients with active rheumatoid arthritis who have had an inadequate response to tumor necrosis factor inhibitors: results from a network meta-analysis. *Clin Ther*. 2016;38:2628–41.