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COMMENTARY

Risk Stratification of Patients with Psoriatic Arthritis and Ankylosing Spondylitis for Treatment with Tofacitinib: A Review of Current Clinical Data

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ABSTRACT

In this commentary, we review clinical data which helps inform individualized benefit–risk assessment for tofacitinib in patients with psoriatic arthritis (PsA) and ankylosing spondylitis (AS). ORAL Surveillance, a safety trial of patients ≥ 50 years of age with rheumatoid arthritis (RA) and cardiovascular risk factors, found increased rates of safety outcomes (including major adverse cardiovascular events [MACE], malignancies excluding non-melanoma skin cancer, and venous thromboembolism) with tofacitinib versus tumor necrosis factor inhibitors (TNFi). Post hoc analyses of ORAL Surveillance have identified subpopulations with different relative risk versus TNFi; higher risk with tofacitinib was confined to patients ≥ 65 years of age and/or long-time current/past smokers, and specifically for MACE, patients with a history of atherosclerotic cardiovascular disease (ASCVD). In patients without these risk factors, risk differences between tofacitinib and TNFi could not be detected. Given differences in demographics, pathophysiology, and comorbidities, we sought to examine whether the risk stratification observed in RA is also appropriate for PsA and

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AS. Data from the PsA tofacitinib development program show low absolute risk of safety outcomes in patients < 65 years of age and never smokers, and low MACE risk in patients with no history of ASCVD, consistent with results from ORAL Surveillance. No MACE, malignancies, or venous thromboembolism were reported in the tofacitinib AS development program. The mechanism of the ORAL Surveillance safety findings is unknown, and there are no similar prospective studies of sufficient size and duration. Accordingly, it is appropriate to use a precautionary approach and extrapolate differentiating risk factors identified from ORAL Surveillance (age ≥ 65 years, long-time current/past smoking, and history of ASCVD) to PsA and AS. We recommend an individualized approach to treatment decisions based on these readily identifiable risk factors, in line with updated labeling for Janus kinase inhibitors and international guidelines for the treatment of PsA and AS.

Trial Registration: NCT02092467, NCT01262118, NCT01484561, NCT00147498, NCT00413660, NCT00550446, NCT00603512, NCT00687193, NCT01164579, NCT00976599, NCT01059864, NCT01359150, NCT02147587, NCT00960440, NCT00847613, NCT00814307, NCT00856544, NCT00853385, NCT01039688, NCT02281552, NCT02187055, NCT02831855, NCT00413699, NCT00661661, NCT01877668, NCT01882439, NCT01976364, NCT00678210, NCT01710046, NCT01241591, NCT01186744, NCT01276639, NCT01309737, NCT01163253, NCT01786668, NCT03502616.

Keywords: Age; Ankylosing spondylitis; Cardiovascular disease; Psoriatic arthritis; Tofacitinib; Smoking

Key Summary Points

In the ORAL Surveillance trial, in patients with rheumatoid arthritis (RA), risk of safety outcomes (including major adverse cardiovascular events [MACE], malignancies [excluding non-melanoma skin cancer], and venous thromboembolism [VTE]) was higher with tofacitinib versus tumor necrosis factor inhibitors (TNFi), and higher risk was confined to patients who were ≥ 65 years of age, long-time current/past smokers, or had a history of atherosclerotic cardiovascular disease (ASCVD; specifically for MACE).

Comparable prospective trials assessing long-term risk of safety outcomes with tofacitinib versus TNFi or other advanced therapies have not been completed in patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS).

The tofacitinib clinical development program showed low absolute risk of safety outcomes in patients with PsA, particularly in those who were < 65 years of age and never smokers, and low risk of MACE in those without a history of ASCVD; in the AS clinical development program, there were no MACE, malignancies, or VTE events.

While differences in demographics, pathophysiology, and comorbidities exist between RA, PsA, and AS, these data suggest that the differentiating risk factors for safety outcomes with tofacitinib versus TNFi in RA (age, long-time current/past smoking, and history of ASCVD) are applicable to patients with PsA, and we also recommend that they apply to AS.

An individualized approach to risk assessment is recommended for patients with PsA and AS, irrespective of treatment.

BACKGROUND

In 2012, the US Food and Drug Administration (FDA) approved tofacitinib, the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). The FDA required the completion of a post-authorization safety study to compare two doses of tofacitinib (5 and 10 mg twice daily [BID]) with the standard of care in advanced therapy at the time, tumor necrosis factor inhibitors (TNFi). The study that followed, ORAL Surveillance, was a randomized, event-driven safety trial in patients with RA, designed to assess non-inferiority of tofacitinib relative to TNFi for risk of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer [NMSC]) [1]. To ensure enough safety events of interest accrued, the study population was enriched for patients with elevated cardiovascular (CV) risk; patients had to be $\geq$ 50 years of age with $\geq$ 1 additional CV risk factor to enroll. The primary results indicated that rates of MACE and malignancies (excluding NMSC), as well as venous thromboembolism (VTE; secondary endpoint), were higher with the combined tofacitinib doses (5 and 10 mg BID) versus TNFi [1]. In this commentary, 'safety outcomes' refers to the three types of events listed above.

Data in risk-enriched populations similar to that of ORAL Surveillance are not available for other JAK inhibitors versus TNFi or other advanced therapies, and also in other conditions treated with tofacitinib, including psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Given that the mechanism of the safety findings is unknown and prospective dedicated safety studies of sufficient size and duration other than ORAL Surveillance have not been performed, a precautionary approach would suggest applying the findings to patients with risk factors across all JAK inhibitors and all approved disease states, including PsA and AS, until data establish this is not appropriate.

There are important differences between PsA, AS, and RA in demographics (e.g., age at diagnosis, smoking prevalence), pathophysiology, and comorbidities (e.g., CV risk) [2–8], which manifest into higher absolute risk of safety outcomes including MACE [6, 7, 9–11], malignancies [12, 13], and VTE [14] in RA versus PsA or AS. However, rates of MACE, malignancies, and VTE appear to be similar between PsA, AS, and RA populations in patients receiving conventional and/or advanced treatments after adjusting for known risk factors such as age, sex, smoking, hypertension, diabetes, etc. [6, 7, 9, 12–14]. This suggests that the prevalence of individual risk factors influences the differences between these conditions for the risk of safety outcomes. Accordingly, and given the shared inflammatory burden across RA, PsA, and AS, an individualized approach to CV risk assessment is recommended across these diseases [10].

In this review, we explore the rationale for extrapolation of the findings of ORAL Surveillance to PsA and AS, using a precautionary approach. Furthermore, we review evidence to support individualized benefit–risk assessment with tofacitinib. 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.

KEY LEARNINGS FROM ORAL SURVEILLANCE: RELATIVE RISK FOR SAFETY OUTCOMES WITH TOFACITINIB VERSUS TNFI

Post hoc analyses of ORAL Surveillance aimed to identify risk factor(s) that could explain the higher risk of safety outcomes observed with tofacitinib versus TNFi in the overall study population. In this review, we distinguish between *absolute risk factors*—risk factors that impact incidence rates (IRs) of safety outcomes regardless of treatment—and *differentiating risk factors*—risk factors that impact relative risk with tofacitinib versus TNFi.

Firstly, multivariable modeling identified absolute risk factors for safety outcomes in the full ORAL Surveillance patient population (i.e., across treatment groups). Risk factors identified in these analyses were consistent with prior studies in the general population and in patients with RA, and included older age

Table 1 Relative risk of major safety outcomes in patients with RA treated with tofacitinib or TNFi without and with differential risk factors: data from ORAL Surveillance

Outcome	Subgroup			
	< 65 years old *and* never smoked		≥ 65 years old *or* current/past, long-time smoker	
	HR (95% CI), tofacitinib vs. TNFi	NNH (PY), tofacitinib vs. TNFi	HR (95% CI), tofacitinib vs. TNFi	NNH (PY), tofacitinib vs. TNFi
Malignancies (excluding NMSC)	1.16 (0.53, 2.55)	1485	1.55 (1.05, 2.30)	190
MACE	0.98 (0.42, 2.31)	−8892	1.41 (0.93, 2.15)	262
VTE	0.77 (0.28, 2.17)	−1421	5.19 (1.86, 14.46)	186
	No history of ASCVD		History of ASCVD	
	HR (95% CI), tofacitinib vs. TNFi	NNH (PY), tofacitinib vs. TNFi	HR (95% CI), tofacitinib vs. TNFi	NNH (PY), tofacitinib vs. TNFi
MACE	1.14 (0.73, 1.78)	1113	1.98 (0.95, 4.14)	78

Data previously published in [18] and [19]. All data are for combined tofacitinib doses. NNH was calculated based on reciprocal of the IR difference of tofacitinib versus TNFi. A positive NNH indicated the number of PY of tofacitinib exposure needed for one more patient to report an additional event versus TNFi; a negative NNH indicated the number of PY of TNFi exposure needed for one more patient to report an additional event versus tofacitinib. A larger NNH value (either positive or negative) indicates a smaller difference in absolute risk between tofacitinib and TNFi

ASCVD atherosclerotic cardiovascular disease, *CI* confidence interval, *HR* hazard ratio, *IR* incidence rate, *MACE* major adverse cardiovascular events, *NMSC* non-melanoma skin cancer, *NNH* number needed to harm, *PY* patient-years, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor, *VTE* venous thromboembolism

(≥ 65 years) and smoking for MACE and malignancies (excluding NMSC); and history of VTE, age ≥ 65 years, and body mass index (BMI) ≥ 35 kg/m^2 for VTE [15–17].

Subsequently, absolute risk factors were further explored to determine whether they were specifically associated with the increased risk of safety outcomes with tofacitinib versus TNFi in ORAL Surveillance. These analyses identified age ≥ 65 years and ever smoking (currently or in the past) as differentiating risk factors. In ORAL Surveillance, more than 90% of tofacitinib-treated patients with a history of smoking (currently or in the past) were long-term smokers who had smoked for > 10 years [18]; therefore, in this context, ever smoking largely corresponds to long-time smoking. Thus, the difference in risk between tofacitinib and TNFi was confined to patients with one or both risk factors (i.e., age ≥ 65 years and/or long-time current/past smokers) (Table 1, Fig. 1) [18]. In patients without these two differentiating risk factors (i.e., those who were < 65 years of age and never smokers), a difference in risk for safety outcomes was not detected between tofacitinib and TNFi (Table 1), and the absolute risk was also low (Fig. 1).

A separate post hoc analysis focusing on risk of MACE identified history of atherosclerotic CV disease (ASCVD; comprising coronary artery disease, cerebrovascular disease, and peripheral artery disease) as an absolute and differentiating risk factor for tofacitinib versus TNFi (Table 1, Fig. 2) [19]. Furthermore, in patients without a history of ASCVD, categorized using a 10-year risk calculator incorporating age, sex, race, smoking status, systolic blood pressure, antihypertensive treatment, total cholesterol, high-density lipoprotein cholesterol, and diabetes, there was no detectable difference in risk of

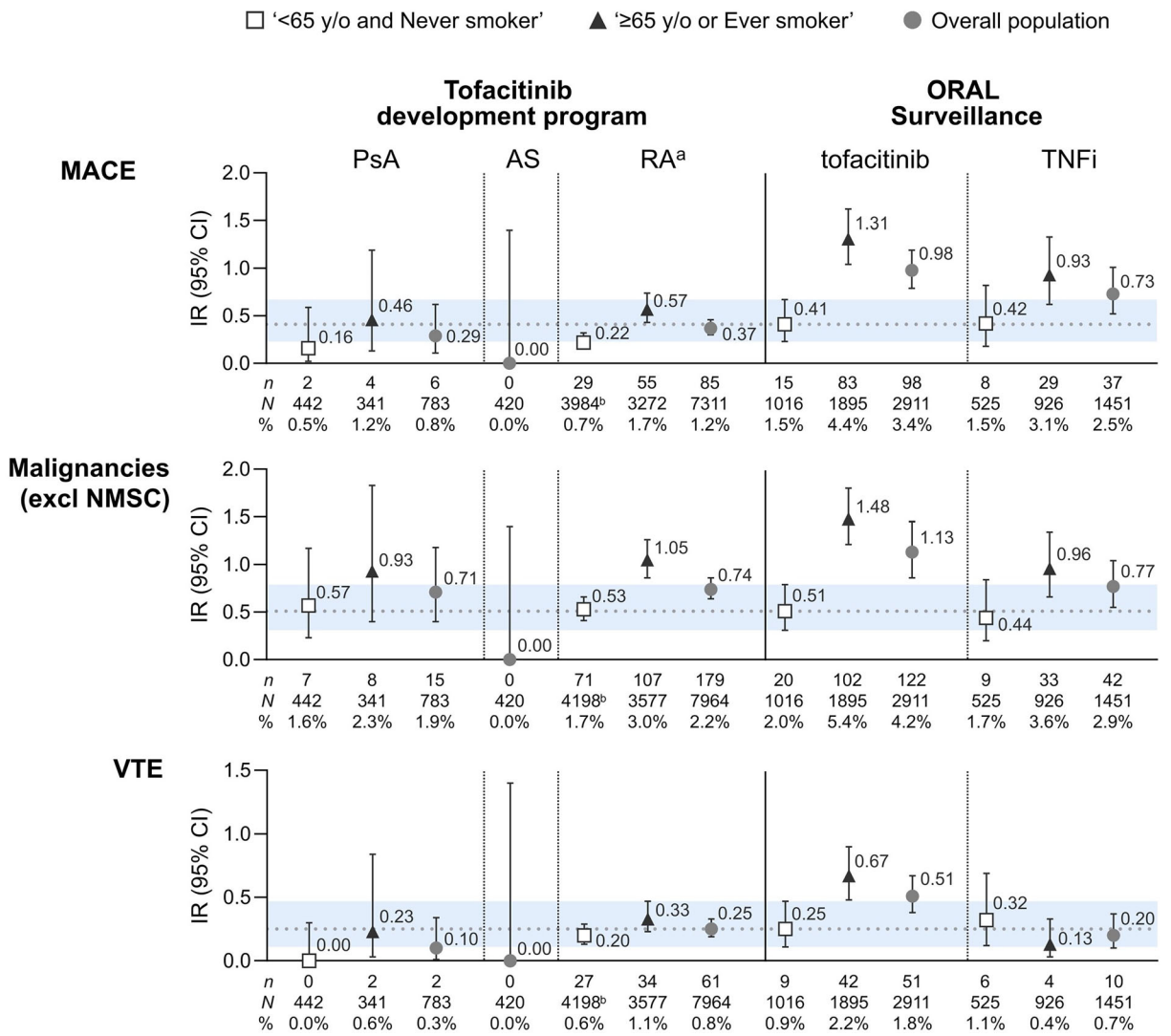

Fig. 1 Risk of MACE, malignancies (excluding NMSC), and VTE in the tofacitinib PsA, AS, and RA clinical development programs and ORAL Surveillance by age and smoking history**.** Figure adapted from Kristensen LE, et al. Ann Rheum Dis. 2023;82:901–910. https://doi.org/10.1136/ard-2022-223715. Data from the tofacitinib AS clinical development program previously reported by Deodhar et al. [20]. *Horizontal dotted line* and *blue shaded area* represent the IR (95% CI) in tofacitinib-treated patients who were < 65 years of age and never smokers in ORAL Surveillance. IRs express the number of patients with first events per 100 patient-years. All data are for combined tofacitinib doses. [a]Excluding ORAL Surveillance. [b]In the tofacitinib RA clinical development program, 2.7% (N = 214) of patients had unknown smoking status. Patients < 65 y/o with unknown smoking status were not included in the '< 65 y/o and never smoker' group. *AS* ankylosing spondylitis, *CI* confidence interval, *IR* incidence rate, *MACE* major adverse cardiovascular events, *n* number of patients with events, *N* number of evaluable patients, *NMSC* non-melanoma skin cancer, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor, *VTE* venous thromboembolism, *y/o* years of age

MACE with tofacitinib versus TNFi across risk categories (low-borderline, intermediate, or high) [19].

Aside from ORAL Surveillance, there is a substantial tofacitinib RA development program [23] comprising 23 clinical trials with up

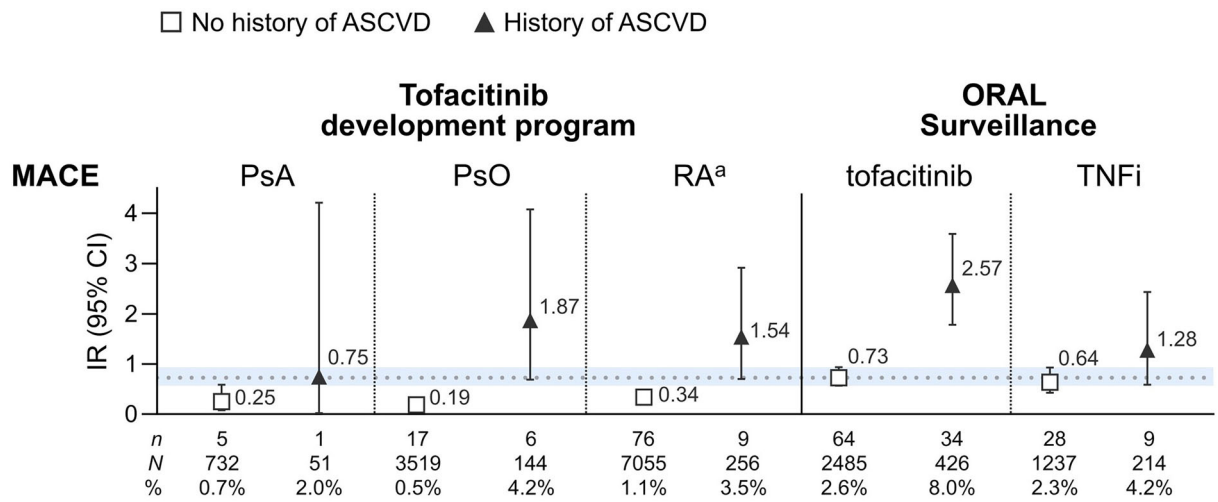

Fig. 2 Incidence of MACE (per 100 patient-years) by history of ASCVD in the tofacitinib PsA, PsO, and RA clinical development programs and ORAL Surveillance. No events of MACE occurred in the AS clinical development program. ORAL Surveillance data previously published [19]. RA data previously published for individual tofacitinib doses [21]; PsA and PsO data for patients with a history of ASCVD previously published [22]. *Horizontal dotted line* and *blue shaded area* represent the IR (95% CI) in tofacitinib-treated patients who had no history of ASCVD in ORAL Surveillance. IRs express the number of patients with first events per 100 patient-years. All data are for combined tofacitinib doses. [a]Excluding ORAL Surveillance. *AS* ankylosing spondylitis, *ASCVD* atherosclerotic cardiovascular disease, *CI* confidence interval, *IR* incidence rate, *MACE* major adverse cardiovascular events, *n* number of patients with event, *N* number of evaluable patients, *PsA* psoriatic arthritis, *PsO* psoriasis, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor

to 10.5 years of safety observations (Table 2). Analyses in the tofacitinib RA development program have confirmed the low absolute risk of safety outcomes in patients who were < 65 years of age and never smokers, and for MACE, patients with no history of ASCVD (Fig. 1) [18, 21]. Notably, in the wider RA clinical development program, there were not enough TNFi-treated patients with long-term follow-up to allow for a head-to-head comparison with tofacitinib. However, side-by-side comparison of data suggests that absolute risk of safety outcomes in patients receiving tofacitinib in the RA clinical development program who were < 65 years of age and never smokers was low in relation to overall, unenriched RA populations from randomized clinical trials (RCTs) of other RA treatments including TNFi [23–28].

APPLYING THE ORAL SURVEILLANCE FINDINGS TO PSA AND AS

ORAL Surveillance was specifically designed to assess non-inferiority of tofacitinib versus TNFi for MACE and malignancies (excluding NMSC), and a risk-enrichment protocol was applied to ensure that enough events accrued within a reasonable timeframe [1]. No studies like ORAL Surveillance have been conducted in PsA and AS. In the absence of direct evidence from such studies, it is important to assess whether the ORAL Surveillance findings should be extrapolated to tofacitinib-treated patients with PsA and AS. Notably, international guidelines for PsA and AS have been updated based on ORAL Surveillance to reinforce the importance of an

Table 2 Tofacitinib treatment exposure and risk factor subgroups in the PsA, AS, and RA clinical development programs and ORAL Surveillance

	Tofacitinib development program			ORAL Surveillance (RA), combined tofacitinib groups
	PsA	AS	RA[a]	
Overall population				
N	783	420	7964	2911
Exposure (patient-years)	2038	233	23,497	10,922
Follow-up; mean, max (years)	2.6, 4.8	0.6, 1.0	3.0, 10.5	3.8, 6.1
Subgroups, *n* (%)				
History of ASCVD	51 (6.5)	15 (3.6)	274 (3.4)	426 (14.6)
≥ 65 years of age	72 (9.2)	13 (3.1)	1270 (15.9)	891 (30.6)
Ever smoked	298 (38.1)	203 (48.3)	2754 (34.6)	1424 (48.9)
≥ 65 years of age or ever smoked	341 (43.6)	213 (50.7)	3577 (44.9)	1895 (65.1)
< 65 years of age and never smoked	442 (56.4)	207 (49.3)	4198 (52.7)	1016 (34.9)

Data from ORAL Surveillance and the PsA and RA clinical development programs were previously published (adapted from [18]). Patient-years were calculated from the first dose of tofacitinib to the last contact date in ORAL Surveillance, and from the first dose of tofacitinib to the last dose of tofacitinib for all other clinical development programs

AS ankylosing spondylitis, *ASCVD* atherosclerotic cardiovascular disease, *N* number of patients treated with tofacitinib, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

[a]Excluding ORAL Surveillance

individualized risk-factor based approach over a population-based approach in relation to JAK inhibitor treatment [29–32]. Similar conclusions by regulatory agencies led to updates to labeling for JAK inhibitors across indications.

The majority of safety data for tofacitinib originates from the RA development program and ORAL Surveillance (23,497 and 10,922 patient-years of tofacitinib exposure, respectively; Table 2). Compared with ORAL Surveillance, the tofacitinib PsA and AS development programs were limited in their ability to evaluate long-latency and relatively rare safety events (2038 and 233 patient-years of tofacitinib exposure, respectively; further details are provided in Table 2). This is partly due to shorter duration and lower patient numbers, but primarily since there was no risk enrichment. The proportion of tofacitinib-treated patients who were ≥ 65 years of age or ever smokers was lower in the PsA (44%) and AS (51%) development programs than in ORAL Surveillance (65%) (Table 2). Notably, there were relatively few patients ≥ 65 years of age in both the PsA (9%) and AS (3%) development programs, while almost a third of tofacitinib-treated patients in ORAL Surveillance were ≥ 65 years of age. Similarly, there were few patients with a history of ASCVD at baseline in the PsA (51/783; 7%) and AS (15/420; 4%) development programs compared with the combined tofacitinib groups in ORAL Surveillance (426/2911; 15%) (Table 2).

Data from the PsA Clinical Development Program

The PsA development program included two global phase 3 RCTs and a long-term extension (LTE) trial [33–35]. Rates of MACE, malignancies

(excluding NMSC), and VTE in the PsA development program are shown in Fig. 1, for all patients overall, and by age and smoking history. The proportions of patients who were < 65 years of age and never smokers were similar in the development programs for PsA and RA (excluding ORAL Surveillance) (Table 2); correspondingly, IRs for safety outcomes were similar across these two development programs when comparing the overall populations (Fig. 1). Furthermore, patients treated with tofacitinib in the PsA development program who were < 65 years of age and never smokers had similar absolute risk as the same subgroup of patients in ORAL Surveillance and the RA development program (Fig. 1). The absolute risk of safety outcomes with tofacitinib in patients with PsA who were < 65 years of age and never smokers (Fig. 1) was also generally comparable or lower relative to published IRs of safety outcomes in RCTs and LTE trials in patients with PsA treated with TNFi or interleukin-17 inhibitors (see Table S1 in the electronic supplementary material).

In tofacitinib-treated patients with PsA who were ≥ 65 years of age or ever smokers, the absolute risk of safety outcomes was numerically higher compared with patients who were < 65 years of age and never smokers, consistent with observations in the RA development program and ORAL Surveillance (Fig. 1), as well as in the general population [36, 37]. However, because of relatively few events, 95% confidence intervals of the IRs were wide, and it is difficult to evaluate absolute risk of safety outcomes in patients ≥ 65 years of age or ever smokers in the PsA development program versus the corresponding subgroup in ORAL Surveillance.

The impact of history of ASCVD on risk of safety outcomes has been explored in the PsA development program, as well as in phase 2, 3, and LTE trials of psoriasis (PsO), which included a larger number of patients (n = 3629; 4% of patients had a history of ASCVD) than the PsA development program [22]. In these cohorts, as in the RA development program and ORAL Surveillance, IRs of MACE were consistently ≥ 3 times higher in patients with a history of ASCVD compared with patients without a history of ASCVD (Fig. 2).

PsA and PsO are associated with high prevalence of metabolic syndrome (MetS) [38, 39], and international guidelines suggest considering MetS as a factor influencing both the management of these conditions [29, 30] and overall CV risk [40]. In the tofacitinib PsA and PsO development programs, IRs for MACE were higher in patients with MetS than those without [22], emphasizing the importance of adequate CV risk prevention measures for this patient group, regardless of the PsA treatment they received.

Data from the AS Clinical Development Program

The AS development program included one phase 2 and one phase 3 global RCT [20, 41, 42], but no LTE trial. No MACE, malignancies, or VTE were reported in the AS development program (Fig. 1). Therefore, it was not possible to assess the impact of age, smoking, or history of ASCVD on rates of these outcomes in patients with AS treated with tofacitinib. Of note, on average, patients in the AS development program were younger, less likely to have a history of ASCVD, and had lower baseline CV risk compared with those in ORAL Surveillance and the PsA program (Table 2) [18, 19, 21, 22]. Moreover, relatively few patients with AS received concomitant treatment with glucocorticoids and methotrexate [41]. However, based on the available data for RA and PsA, and the largely similar levels of background risk observed in PsA and AS populations [4, 6], it is appropriate to use a precautionary approach and assume that the same differentiating risk factors (age ≥ 65 years, long-time current/past smoking, and history of ASCVD) may impact risk of safety outcomes in tofacitinib-treated patients with AS.

BENEFIT OF TOFACITINIB TREATMENT IN PATIENTS WITH PSA AND AS

In addition to evaluating risk of safety outcomes, the potential benefits of tofacitinib treatment for individual patients must be considered as part of clinical decision-making. Recommendations for treatment of PsA and AS support a goal of low disease activity or remission using validated measures such as minimal disease activity and Ankylosing Spondylitis Disease Activity Score, respectively [30, 32]. The greater efficacy of tofacitinib relative to placebo in achieving and maintaining these treatment outcomes, along with other signs and symptoms of PsA and AS, have been previously described in the overall RCT populations [33, 34, 41]. Improvements in patient-reported outcomes versus placebo were observed within two weeks of initiating treatment in PsA and AS [41, 43]. Similar efficacy among tofacitinib and adalimumab across outcomes was reported in a phase 3 study of TNFi-naïve patients with PsA (OPAL Broaden), although the trial was not designed for direct comparisons among these active treatment groups [34].

The efficacy of tofacitinib in PsA and AS has been explored in diverse patient groups. Subgroup analyses of the PsA RCTs have demonstrated efficacy versus placebo across both sexes [44], all BMI categories [45], patients with and without MetS [46], and those with mild versus moderate/severe skin disease [47]. In AS, RCT subgroup analyses have shown similar efficacy across BMI categories [48] and in patients with normal or elevated CRP levels [49]. A post hoc analysis of response to tofacitinib in patients with PsA or AS by ever versus never smoker status showed comparable efficacy across measures of disease activity and patient-reported outcomes, with greater efficacy compared with placebo in both subgroups [50].

Notably, markers of disease activity have been associated with CV risk in RA, PsA, and AS [51–54]. In ORAL Surveillance, risk of MACE and VTE was numerically higher in patients with active disease (low, medium, or high disease activity) versus those in remission [55]. Accordingly, the European Alliance of Associations for Rheumatology recommendations emphasize the importance of optimal control of disease activity in patients with inflammatory joint disorders to reduce CV risk [10].

CONCLUSIONS

Prospective, dedicated safety studies of sufficient size and duration in PsA and AS with risk enrichment like ORAL Surveillance are not available for JAK inhibitors compared with TNFi or other advanced treatments. The mechanism of the ORAL Surveillance safety findings is unknown, and available data do not provide any signals to suggest that a precautionary approach should not be applied in PsA and AS. Hence, it is appropriate to conclude that results from ORAL Surveillance can be extrapolated to patients with PsA and AS. In this commentary, we reviewed clinical data to help inform individualized benefit–risk assessment for tofacitinib in patients with PsA and AS. Differentiating risk factors for MACE, malignancies (excluding NMSC), and VTE with tofacitinib versus TNFi have been identified from ORAL Surveillance (age $\geq$ 65 years, long-time current/past smoking, and history of ASCVD [only for MACE]), and in patients without these risk factors, differences in risk of safety outcomes between tofacitinib and TNFi could not be detected. We therefore recommend an individualized approach to treatment decisions based on these readily identifiable risk factors, which is in line with updated labeling for JAK inhibitors and international guidelines for the treatment of PsA and AS.

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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.

Declarations

Conflict of Interest. Lars Erik Kristensen has received grant/research support from Biogen, Janssen, Novartis, and UCB, and has received speaker's fees and/or consultancy fees from AbbVie, Amgen, Biogen, Bristol Myers Squibb, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer Inc, and UCB. Atul Deodhar has received grant/research support from AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, and UCB; and consulting fees from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer Inc, and UCB. Ying-Ying Leung has received speaker's fees from and acted as a consultant for AbbVie, Eli Lilly, Janssen, Novartis, and Pfizer Inc. Ivana Vranic, Mahta Mortezavi, Lara Fallon, and Arne Yndestad are employees and shareholders of Pfizer Inc. Cassandra D. Kinch was an employee and shareholder of Pfizer Inc at the time of this work. Dafna D. Gladman has acted as a consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead Sciences, Janssen, Novartis, Pfizer Inc, and UCB, and has received grants from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, and UCB.

Ethical Approval. 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.

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