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Communications

Review: Risk Stratification of Patients With Ulcerative Colitis for Treatment With Tofacitinib

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Lay Summary

Higher age (65 years or over), long-term smoking, or a previous cardiovascular event (such as heart attack) should be considered safety risks when considering treatment with tofacitinib versus tumor necrosis factor inhibitors for people with ulcerative colitis.

Key Words: ulcerative colitis, tofacitinib, safety

Introduction

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of ulcerative colitis (UC). The efficacy and safety of tofacitinib have previously been evaluated in patients with moderately to severely active UC in the tofacitinib UC clinical program, which was comprised of 3 Phase 2 and Phase 3 induction studies (NCT00787202; NCT01465763 [OCTAVE Induction 1]; NCT01458951 [OCTAVE Induction 2]),[1,2] a Phase 3 maintenance study (NCT01458574 [OCTAVE Sustain]),[2] an open-label, long-term extension study (NCT01470612 [OCTAVE Open]),[3] and a randomized Phase 3b/4 study (NCT03281304 [RIVETING]).[4]

ORAL Surveillance was a randomized, open-label, non-inferiority safety study (NCT02092467) in patients with rheumatoid arthritis (RA) that was designed to evaluate the risk of malignancies (excluding non-melanoma skin cancer [NMSC]) and major adverse cardiovascular events (MACE) with tofacitinib 5 and 10 mg twice daily versus tumor necrosis factor inhibitors (TNFi).[5] In contrast to other tofacitinib clinical trials, ORAL Surveillance was conducted in a risk-enriched population to ensure enough safety events occurred in a reasonable timeframe, and patients had to be ≥50 years old and have ≥1 additional cardiovascular risk factor.[5] Primary results of ORAL Surveillance found an increased rate of MACE, venous thromboembolism (VTE), and malignancies (excluding NMSC), hereafter these events are collectively referred to as major safety outcomes, and all-cause death with tofacitinib versus TNFi.[5]

Importantly, studies with a similar design to ORAL Surveillance do not currently exist for tofacitinib or other JAK inhibitors versus TNFi or other advanced treatments in UC. In this article, we describe the identification of differential risk factors of major safety outcomes with tofacitinib versus TNFi in ORAL Surveillance and compare patient risk profiles and results from ORAL Surveillance with those from the tofacitinib UC clinical program. We also discuss, in line with updated labeling for JAK inhibitors, how the results and identified differential risk factors from ORAL Surveillance apply to individualized risk assessment when considering tofacitinib as a treatment option for patients with UC.

Differential Risk Factors for Major Safety Outcomes With Tofacitinib Versus TNFi Identified From ORAL Surveillance

Following the primary results of ORAL Surveillance, post hoc analyses of ORAL Surveillance were carried out to evaluate the effect of patient characteristics on absolute risk (ie, incidence rates [IRs]; defined as the number of unique patients with events per 100 patient-years of exposure) of major safety outcomes, as well as differential risk (ie, relative risk with tofacitinib vs. TNFi). Identification of risk factors that accounted for the increased risk of major safety outcomes observed between tofacitinib and TNFi was important to minimize patient risk. In addition, it was important to determine whether the absence of said identified differential risk

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factors resulted in no detectable difference in risk between tofacitinib and TNFi.

Three risk factors were identified that accounted for the risk difference for major safety outcomes with tofacitinib versus TNFi (Figure 1).[6,7] Age ≥65 years and current or past smoking were identified as differential risk factors for malignancies (excluding NMSC), MACE, and VTE, and were associated with increases in absolute risk and relative risk of major safety outcomes with tofacitinib versus TNFi (Figures 1A and 2A). Prior history of atherosclerotic cardiovascular disease (ASCVD) was identified as another differential risk factor specifically for MACE with tofacitinib versus TNFi from ORAL Surveillance (Figures 1B and 2B).[7] Importantly, it was found that the current or past smokers in ORAL Surveillance were predominantly long-time smokers, >90% of current and past smokers had a smoking history of >10 years and a median smoking duration of >30 years.[6] Therefore, in this context, current or past smoking largely equated to long-time smoking.

Among patients in ORAL Surveillance without differential risk factors (<65 years of age and never smokers or without a history of ASCVD [for MACE]), risk difference for malignancies (excluding NMSC), MACE, or VTE could not be detected with tofacitinib versus TNFi (Figure 1), and the absolute risk (IR) of these events was low (IR < 1.0 for all outcomes; Figure 2).[6,7]

Risk Profiles in ORAL Surveillance and the Tofacitinib UC Clinical Program

Fundamental to the interpretation of results from ORAL Surveillance is that it enrolled a risk-enriched population of patients with RA (patients aged ≥50 years and with ≥1 cardiovascular risk factor).[5] Patients with RA and patients with UC are generally different in terms of demographics and comorbidity burden.[9–12] Consequently, patients who enrolled in ORAL Surveillance were very different in terms of baseline risk of major safety outcomes compared with those in the tofacitinib UC clinical program (Table 1). Only 12.6% of patients at the baseline of the OCTAVE Induction trials met the ORAL Surveillance inclusion criteria.[8] In total, 31.0% of patients in ORAL Surveillance were ≥65 years of age compared with 6.7% of patients in the tofacitinib UC clinical program.[5,13] In addition, 14.7% of patients in ORAL Surveillance had a history of ASCVD, a differential risk factor specifically for MACE, compared with only 3.9% of patients in the tofacitinib UC clinical program.[7,8]

The overall proportion of current/past smokers was higher in ORAL Surveillance versus the tofacitinib UC clinical program (48.2% vs. 36.0%, respectively), and the proportion of current smokers was higher (26.7% vs. 5.1%, respectively).[6] Smoking duration in the 2 populations was very different (Table 2). As discussed earlier, current or past smokers in ORAL Surveillance were predominantly long-time smokers (>90% smoked for >10 years; median smoking duration >30 years). In contrast, the smoking duration of current and past smokers in the tofacitinib UC clinical program was markedly shorter, with a median duration (range) of 14.5 (3.0–50.0) and 14.8 (0.0–51.0) years, respectively. In addition, 53.4% of current smokers and 62.1% of past smokers had smoked for >10 years.[14]

Differences in baseline risk factors other than those identified as differential risk factors were also observed between the ORAL Surveillance and tofacitinib UC clinical program populations. In total, 41.7% of patients had a body mass index (BMI) ≥30 kg/m^2 in ORAL Surveillance, while 13.8% of patients had a BMI >30 kg/m^2 in the tofacitinib UC clinical program.[5,13] In addition, a higher proportion of patients in ORAL Surveillance versus patients in the tofacitinib UC clinical program had a relevant medical history (history of diabetes mellitus: 17.4% vs. 4.1%, respectively; history of hypertension: 66.0% vs. 13.9%, respectively).[5,13]

Risk of Safety Outcomes in the Tofacitinib UC Clinical Program Versus ORAL Surveillance

The integrated summary of safety data from the tofacitinib UC clinical program demonstrated that the safety profile of tofacitinib was consistent over 9.2 years.[13,15,16] Moreover, except for herpes zoster, the absolute risk of major safety outcomes was consistent with IRs reported for other UC treatments, including TNFi and other biological therapies.[17] However, studies in the tofacitinib UC clinical program did not include any active comparator and the differential risk of safety outcomes versus TNFi could not be directly assessed. The tofacitinib UC clinical program was also limited in the ability to detect long latency events due to smaller patient numbers and lower exposure time in comparison to ORAL Surveillance. Here we compared the absolute risk of major safety outcomes in patients without and with differential risk factors in the tofacitinib UC clinical program versus ORAL Surveillance.

Patients Without Differential Risk Factors

As outlined above, in secondary analyses of ORAL Surveillance, a difference in risk of major outcomes between tofacitinib and TNFi was not detected in patients without differential risk factors (hazard ratios 0.77-1.16; Figure 1). The absolute risk (IR) of malignancies (excluding NMSC), MACE, and VTE with tofacitinib in the UC clinical program in the population of patients aged <65 years that had never smoked was similar to that for tofacitinib and TNFi in the population of patients without these differential risk factors in ORAL Surveillance (Figure 2A [symbol—open squares]).[6] In patients without a history of ASCVD (differential risk factor for MACE), absolute risk of MACE appeared to be lower in the tofacitinib UC clinical program than that observed with tofacitinib and TNFi in ORAL Surveillance (Figure 2B [symbol—open squares]).[7,8] In terms of absolute risk difference, the number needed to harm (NNH) indicated that 1485 and –1421 patient-years of tofacitinib exposure, respectively, would be needed among patients without differential risk factors to have one additional event of malignancy (excluding NMSC) or VTE versus TNFi (Figure 1).[6] For patients with RA and no history of ASCVD, the NNH versus TNFi for MACE was 1113.[7]

Patients With Differential Risk Factors

The increased risk of major safety outcomes with tofacitinib versus TNFi in ORAL Surveillance was confined to patients aged ≥65 years, long-time smokers, and, specifically for MACE, those with a history of ASCVD (hazard ratios 1.41–5.19; Figure 1).[6,7] The NNH indicated that 190 and

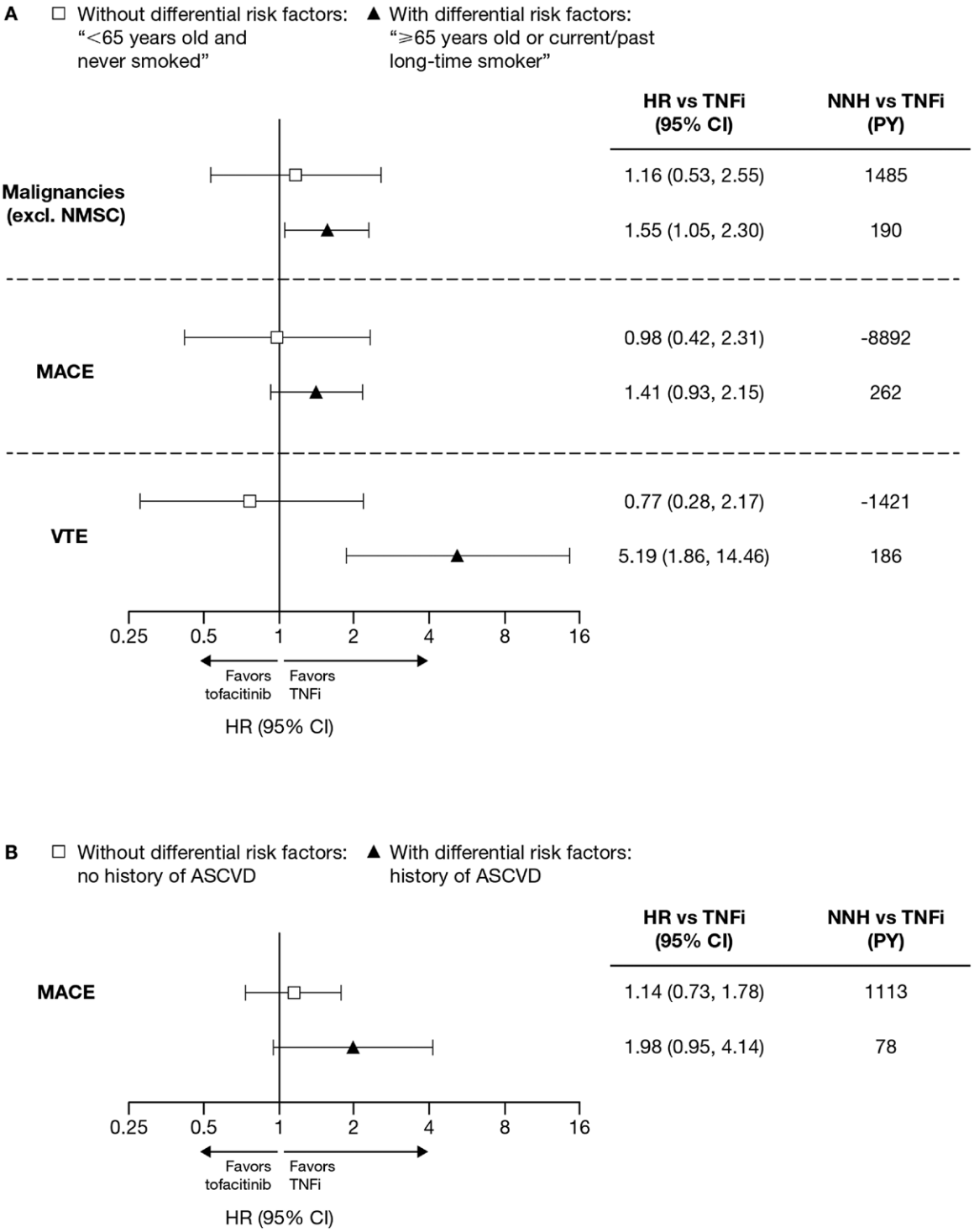

Figure 1. Relative risk of major safety outcomes in patients with RA treated with tofacitinib or TNFi in ORAL Surveillance by absence or presence of differential risk factors: (A) age and smoking history and (B) history of ASCVD (MACE only). Figure adapted from Kristensen et al.[6] and Charles-Schoeman et al.[7] 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. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; 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.

186 patient-years of tofacitinib exposure, respectively, would be needed among patients with RA aged ≥65 years or long-time smokers to have 1 additional event of malignancy (excluding NMSC) or VTE versus TNFi (Figure 1).[6] For patients with RA and a history of ASCVD, the NNH versus TNFi for MACE was 78.[7]

In patients with differential risk factors (age ≥65 years or long-time smokers), IRs for malignancies (excluding NMSC),

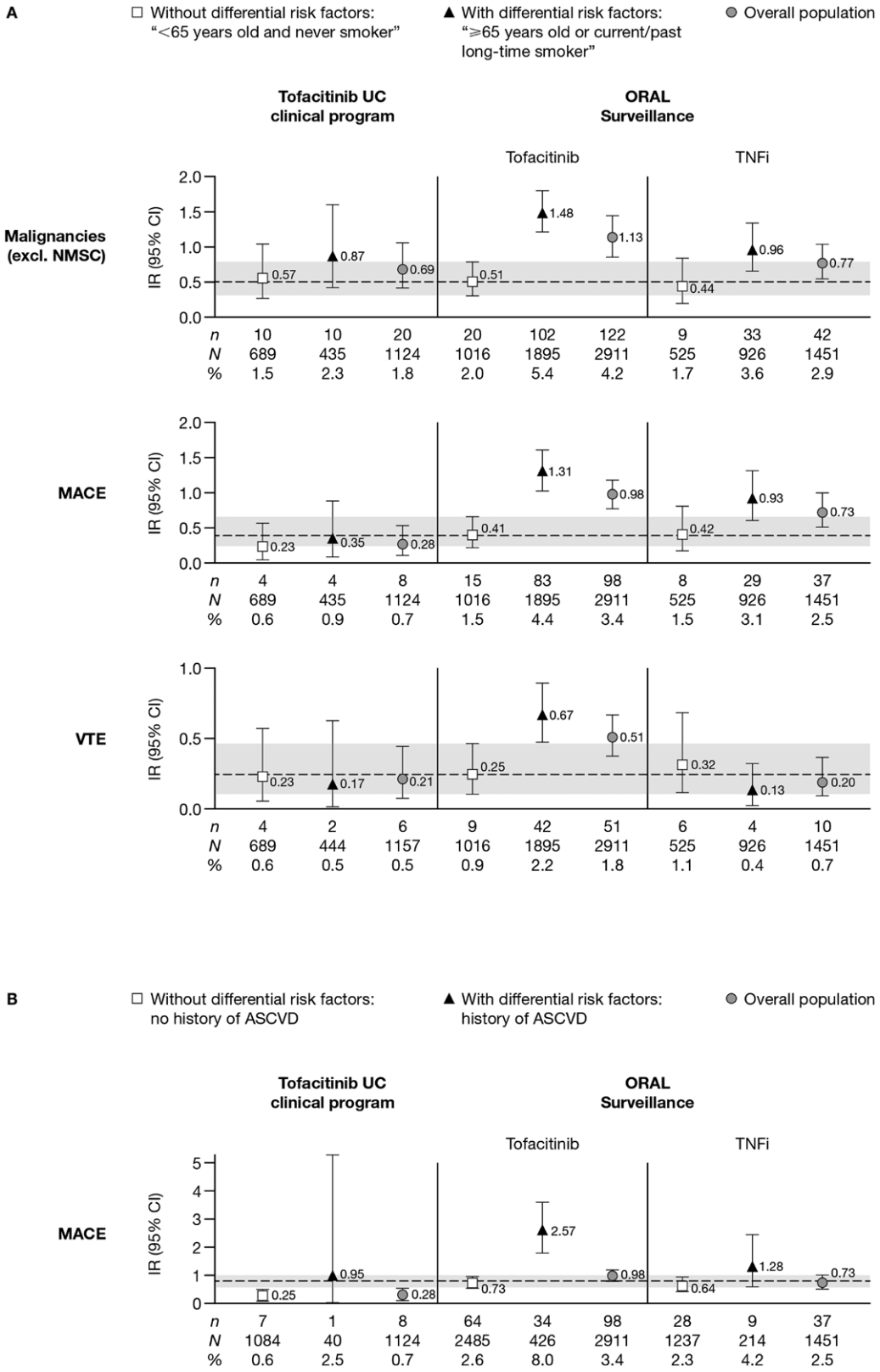

Figure 2. Risk of malignancies (excluding NMSC), MACE, and VTE in the tofacitinib UC clinical program and ORAL Surveillance by absence or presence of differential risk factors: (A) age and smoking history and (B) history of ASCVD (MACE only). Figure adapted from Kristensen et al.[6] Charles-Schoeman et al.,[7] and Schreiber et al.[8] All data are for combined tofacitinib doses. Horizontal dotted line and gray shaded area represent IR and 95% CI, respectively, in patients without differential risk factors treated with tofacitinib in ORAL Surveillance. The IR (95% CI) of MACE in patients with UC and no history of ASCVD was calculated based on data previously reported in Schreiber et al.[8] ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; IR, incidence rate (defined as the number of unique patients with events per 100 patient-years of exposure); MACE, major adverse cardiovascular events; *n*, number of patients with events; *N*, number of evaluable patients; NMSC, non-melanoma skin cancer; TNFi, tumor necrosis factor inhibitors; UC, ulcerative colitis; VTE, venous thromboembolism.

Table 1. Patients in ORAL Surveillance and the UC clinical program—prevalence of baseline risk factors and differential risk factors.

	ORAL Surveillance ($N = 4362$)[a]	Tofacitinib UC clinical program ($N = 1157$)
Age		
Mean (SD)	61.2 (7.1)	41.3 (13.9)
≥65 years of age, *n* (%)	1353 (31.0)	77 (6.7)
Smoking status, *n* (%)		
Current	1166 (26.7)	59 (5.1)
Past	937 (21.5)	357 (30.9)
Never	2259 (51.8)	740 (64.0)
Differential risk factors, *n* (%)		
≥65 years or ever smoked	1895 (65.1)[b]	444 (38.4)
<65 years and never smoked	1016 (34.9)[b]	713 (61.6)
History of ASCVD	640 (14.7)	45 (3.9)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; *n*, number of patients with characteristic; *N*, number of evaluable patients; SD, standard deviation; UC, ulcerative colitis.
Includes data previously reported by Ytterberg et al.,[5] Kristensen et al.,[6] Charles-Schoeman et al.,[7] and Sandborn et al.[13] All data are for combined tofacitinib doses.
[a]Data shown are for the overall ORAL Surveillance population unless stated otherwise.
[b]Data shown are for patients treated with tofacitinib only in ORAL Surveillance ($N = 2911$).

MACE, and VTEs with tofacitinib in the UC clinical program were numerically lower than the respective IRs observed with tofacitinib in ORAL Surveillance, but generally comparable with the respective IRs observed with TNFi in ORAL Surveillance (Figure 2A [symbol—black triangles]). However, the patient numbers, number of events, and patient-years of tofacitinib exposure were lower in the tofacitinib UC clinical program compared with ORAL Surveillance. Only 1 of 40 patients with a history of ASCVD in the tofacitinib UC clinical program had a MACE.[8] Accordingly, the statistical precision in the IR estimate was low, and it is difficult to compare this result with the data from ORAL Surveillance.

How Should Results From ORAL Surveillance Be Extrapolated to UC?

ORAL Surveillance enrolled a risk-enriched population of patients with RA that is very different from the UC populations included in clinical trials of tofacitinib and other forms of advanced treatment. Importantly, the mechanism of the safety findings in ORAL Surveillance is unknown, and there is a paucity of data on the risk with tofacitinib of major safety outcomes in patients with UC who have differential risk factors such as age ≥65 years, smoking, and history of ASCVD. In addition, while ORAL Surveillance enrolled a large group of long-time smokers (duration >10 years), most smokers in the tofacitinib UC clinical program had a shorter smoking duration. It is, therefore, difficult to compare the data from ORAL Surveillance and the tofacitinib UC clinical program directly. Accordingly, in the absence of a prospective dedicated safety trial of sufficient size and duration in patients with UC, the results from ORAL Surveillance and the identified differential risk factors for major safety outcomes should be considered when managing patients with UC as a precautionary approach.

A recent review discussing the management of safety risks associated with JAK inhibitors acknowledges the difficulties physicians can face when determining the best course of treatment for patients and that the clinical risk for individual patients can be based on many different factors.[18] The 3 differential risk factors identified for major safety outcomes with tofacitinib versus TNFi provide a simple framework for an individualized risk-factor-based approach to clinical decision-making on treatment with tofacitinib. In patients in ORAL Surveillance without any of these differential risk factors, no difference in risk with tofacitinib versus TNFi could be detected.

Notably, there may be other factors that contribute to the overall risk of malignancies (excluding NMSC), MACE, and VTEs, which are not considered to be associated with the differences in risk with tofacitinib versus TNFi identified in ORAL Surveillance. Such risk factors should be managed according to local guidelines or policies for all patients with UC.

Finally, it is important to emphasize that inadequate disease control in patients with UC is associated with a significant risk of major safety outcomes such as malignancies, MACE, and VTE.[19–25] Previous analyses of the tofacitinib UC clinical program did not observe any differences in efficacy outcomes when patients were stratified by differential risk factors for major safety outcomes such as smoking status or by age.[14,26]

Discussion and Conclusions

In ORAL Surveillance, an increased rate of malignancies (excluding NMSC), MACE, and VTE was observed with tofacitinib versus TNFi in patients with RA.[5] In subsequent analyses, 3 differential risk factors were identified. There are currently limited data on the safety of tofacitinib in patients with UC with such risk factors. The mechanism of the safety findings in RA is not known, and there are no comparable prospective safety studies of sufficient size and duration in UC. Accordingly, as a precautionary approach and in line with the updated labeling for JAK inhibitors, the results from ORAL Surveillance should be taken into consideration during the management of patients with UC. The identified differential risk factors for major safety outcomes with tofacitinib versus TNFi (age ≥65 years and long-time smoking, and history of ASCVD for MACE) provide a simple framework for an individualized risk-factor-based approach to clinical decision-making on treatment with tofacitinib.

Author Contributions

S.D.: Conceptualization (equal); visualization (equal); writing (equal)—original draft; and writing—review and editing (equal). J.P.: Conceptualization (equal); visualization (equal); writing (equal)—original draft; and writing—review and editing (equal). M.D.: Conceptualization (equal); visualization (equal); writing (equal)—original draft; and writing—review and editing (equal). X.G.: Conceptualization (equal); visualization (equal); writing

Table 2. Smoking duration and time since cessation in tofacitinib-treated current and past smokers in ORAL Surveillance and UC clinical program.

	ORAL Surveillance		Tofacitinib UC clinical program	
	Current smokers (*N* = 811)	Past smokers (*N* = 605)	Current smokers (*N* = 58)	Past smokers (*N* = 350)
Smoking duration (years)				
Mean (SD)	32.7 (13.1)	37.2 (13.0)	15.4 (10.0)	15.5 (10.8)[a]
Median (range)	35.0 (0.02–67.00)	39.0 (0.00–69.00)	14.5 (3.0–50.0)	14.8 (0.0–51.0)[a]
Smoking duration levels, *n* (%)				
>10 years	741 (91.4)	582 (96.2)	31 (53.4)	210 (62.1)[b]
>5–10 years	36 (4.4)	14 (2.3)	20 (34.5)	63 (18.6)[b]
>0–5 years	34 (4.2)	9 (1.5)	7 (12.1)	65 (19.2)[b]
Time since smoking cessation levels, *n* (%)				
≥10 years	NR	372 (61.5)	NR	149 (42.9)[c,d]
<10 years	NR	233 (38.5)	NR	198 (57.1)[c,e]
<5 years	NR	132 (21.8)	NR	111 (32.0)[c,f]

Abbreviations: *n*, number of patients in the specified category; *N*, number of patients treated in the smoker category; NR, not relevant; SD, standard deviation; UC, ulcerative colitis.
Includes data previously reported by: Kristensen et al.[6] and Rubin et al.[14]. All data are for combined tofacitinib doses.
[a]*N* = 348.
[b]*N* = 338.
[c]*N* = 347.
[d]Data based on >10 years.
[e]Data based on >0–10 years.
[f]Data based on >0–5 years.

(equal)—original draft; and writing—review and editing (equal). A.Y.: Conceptualization (equal); visualization (equal); writing (equal)—original draft; and writing—review and editing (equal). S.S.: Conceptualization (equal); visualization (equal); writing (equal)—original draft; and writing—review and editing (equal). M.C.: Conceptualization (equal); visualization (equal); writing (equal)—original draft; and writing—review and editing (equal).

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Conflicts of Interest

S.D. has received consulting fees from AbbVie, Allergan, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Gilead, Hospira, Janssen, Johnson & Johnson, MSD, Mundipharma, Pfizer Inc, Roche, Sandoz, Takeda, TiGenix, UCB, and Vifor Pharma. J.P. has received personal fees from AbbVie, Alimentiv, Athos, Atomwise, Boehringer Ingelheim, Celsius, Ferring, Galapagos, Genentech/Roche, GSK, Janssen, Mirum, Nimbus, Pfizer Inc, Progenity, Prometheus, Protagonist, Revolo, Sanofi, Sorriso, Surrozen, Takeda, and Wasserman. M.C.D. has received consulting fees from AbbVie, Abivax, AstraZeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Gilead, Janssen, Johnson & Johnson, Pfizer Inc, Prometheus Laboratories, Sphyre, and Takeda. X.G. and A.Y. are employees and shareholders of Pfizer Inc. S.S. has received consulting fees from AbbVie, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Dr. Falk Pharma, Eli Lilly, Ferring, Fresenius, Galapagos, Genentech, Gilead, GSK, I-MAB Biopharma, Janssen, Merck, Novartis/Sandoz, Pfizer Inc, Protagonist, Takeda, and Theravance Biopharma. M.C. has served as a speaker, consultant, or research or education funding from AbbVie, Biogen, Dr. Falk Pharma, Eli Lilly, Ferring, Gilead, Hospira, Janssen, MSD, Pfizer Inc, Shire Pharmaceuticals, Takeda, and Tillotts Pharma.

Data Availability

No new data were generated or analyzed in support of this review.

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