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Observations and Research

Association Between Smoking Status and the Efficacy and Safety of Tofacitinib in Patients with Ulcerative Colitis

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of ulcerative colitis (UC). This analysis assessed the impact of cigarette smoking on tofacitinib efficacy and safety in the UC clinical program.

Methods: Efficacy endpoints and adverse events (AEs) were evaluated by smoking status (ever smokers [current and ex-smokers] and never smokers) in the phase (P)2 induction study (baseline demographics and safety only), P3 studies (OCTAVE Induction 1&2, OCTAVE Sustain, OCTAVE Open), and P3/4b RIVETING study.

Results: This post hoc analysis included 1156 patients (ever smokers, *n* = 416 [36.0%; current smokers, *n* = 59 (5.1%); ex-smokers, *n* = 357 (30.9%)]; never smokers, *n* = 740 [64.0%]; median [range] treatment duration 654 [1–2712] and 615.5 [1–2850] days, respectively). Similar proportions of ever smokers and never smokers achieved efficacy endpoints. AEs were reported in 88.7% of ever smokers and 83.8% of never smokers. Overall, 60.6% of ever smokers had an infection (serious infections, 5.5%; herpes zoster [nonserious and serious], 10.8%; *Clostridioides difficile* infection, 12.0%; lower respiratory tract infection, 19.5%: corresponding values among never smokers were 53.1%, 3.9%, 6.8%, 8.5%, and 11.4%). Major adverse cardiovascular events were reported in 1.0% of ever smokers and 0.7% of never smokers and thromboembolism events (venous and arterial) in 1.0% of ever smokers and 0.9% never smokers. Deaths, malignancies (excluding non-melanoma skin cancer [NMSC]), and NMSC occurred infrequently in ever smokers (0.5%, 2.5%, and 3.7%, respectively) and never smokers (0.1%, 1.5%, and 1.0%, respectively). Colorectal cancer was reported in 0.6% of never smokers; no cases occurred in ever smokers.

Conclusions: Efficacy and safety of tofacitinib were generally similar in ever smokers and never smokers. Overall, serious AEs and, as expected, infections were more frequent in ever smokers versus never smokers. This may inform treatment selection and monitoring strategies.

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Lay Summary

This study assessed how cigarette smoking affected tofacitinib treatment in patients with ulcerative colitis. Outcomes were similar in patients who smoked and did not smoke. Infections were more common in patients with smoking history versus those who had never smoked.

Key Words: cigarette, inflammatory bowel disease, Janus kinase inhibitor, ulcerative colitis

Introduction

Inflammatory bowel disease is a chronic intestinal disorder comprising Crohn's disease and ulcerative colitis (UC), which results from interactions between genetic and environmental factors, and influences the intestinal immune response.[1] Cigarette smoking is an environmental factor known to interfere with the development and clinical course of UC and Crohn's disease in opposite ways. UC has been shown to predominantly affect nonsmokers and ex-smokers, and smoking has consistently been shown to have a protective effect against

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the development and severity of UC, while smokers with Crohn's disease have a worse disease course.[2] However, the protective effects of smoking are temporary, and the relative risk of developing UC increases following smoking cessation.[3] Smoking represents a major cause of preventable mortality,[4] and patients with inflammatory bowel disease should be advised to stop smoking due to overall harm to health.[5]

In several studies of biologic therapies for the treatment of inflammatory bowel disease, smoking has been recognized as a risk factor for the development of extraintestinal manifestations,[6] infections,[7] and colorectal cancer.[8] However, it is less clear whether smoking status affects the efficacy of therapeutic options in patients with UC, with the majority of studies finding no relationship between smoking and treatment outcome.[9–11] Moreover, there is anecdotal evidence to suggest that ex-smokers may have medication-resistant UC, compared with never smokers.[12,13]

Tofacitinib is an oral Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib were evaluated in a series of clinical trials, including a phase 2 induction study (NCT00787202), 2 identical phase 3 induction studies (OCTAVE Induction 1 and 2; NCT01465763 and NCT01458951), a phase 3 maintenance study (OCTAVE Sustain; NCT01458574), an open-label, long-term extension study (OCTAVE Open; NCT01470612), and a phase 3b/4 study (RIVETING; NCT03281304).[14–18] Here, we investigated the impact of smoking status on the efficacy and safety of tofacitinib 5 or 10 mg twice-daily (BID) treatment in the UC clinical program.

Methods

Patients and Studies

This post hoc analysis included data from the tofacitinib UC clinical program, and the detailed study design of each study has previously been reported.[14–18] Briefly, in the phase 2 induction study, patients (aged ≥18 years) with moderately to severely active UC were randomized to receive placebo or tofacitinib 0.5, 3, 10, or 15 mg BID.[14] Only patients who received tofacitinib 10 mg BID in the phase 2 induction study are included in this analysis. In OCTAVE Induction 1 and 2, patients (aged ≥18 years) with moderately to severely active UC, who had previously failed, or were intolerant to, treatment with corticosteroids, immunosuppressants, and/or tumor necrosis factor inhibitors (TNFi), were randomized to receive placebo or tofacitinib 10 or 15 mg BID. Randomization to tofacitinib 15 mg BID was discontinued following a protocol amendment; therefore, this analysis only included those patients in the OCTAVE Induction 1 and 2 studies randomized to receive placebo or tofacitinib 10 mg BID.[15] Patients who completed OCTAVE Induction 1 and 2 with a clinical response (a decrease from induction study baseline Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1) were eligible to enroll into OCTAVE Sustain. In OCTAVE Sustain, patients were re-randomized to receive placebo or tofacitinib 5 or 10 mg BID.[15] OCTAVE Open was an open-label, long-term extension study (≤7.0 years of treatment) that enrolled patients who completed OCTAVE Induction 1 or 2 without a clinical response (nonresponders), and patients who had either completed OCTAVE Sustain or withdrawn early after experiencing treatment failure (an increase from OCTAVE Sustain baseline total Mayo score of ≥3 points, plus an increase in rectal bleeding subscore and endoscopic subscore of ≥1 point, after ≥8 weeks of treatment).[16] Dose assignment in OCTAVE Open was based on remission (total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0) status at baseline; patients in remission received tofacitinib 5 mg BID, and all others received 10 mg BID. Patients from OCTAVE Open who had received tofacitinib 10 mg BID for ≥2 consecutive years, were in stable remission for ≥6 months, and corticosteroid free for ≥4 weeks, were eligible to enroll in RIVETING, and were randomized to receive tofacitinib 5 or 10 mg BID.[17]

Efficacy Assessments

Efficacy endpoints were derived from Mayo scores and were based on centrally read endoscopic subscores in OCTAVE Induction 1 and 2, and OCTAVE Sustain, and were derived from locally read endoscopic subscores in OCTAVE Open and RIVETING. Efficacy endpoints were reported at week 8 of OCTAVE Induction 1 and 2, week 52 of OCTAVE Sustain, month 36 of OCTAVE Open, and month 6 of RIVETING.

Efficacy endpoints in all trials included clinical response, endoscopic improvement (Mayo endoscopic subscore of 0 or 1; defined as mucosal healing in the study protocols), remission, and partial Mayo score remission (partial Mayo score of ≤2 with no individual subscore >1). Efficacy endpoints were summarized by initial treatment allocation.

Safety Assessments

Safety endpoints evaluated in this analysis included treatment-emergent adverse events (AEs), serious AEs (SAEs; an AE that was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or death), and selected AEs of interest in cigarette smokers (which included serious infections [infections meeting SAE-reporting criteria or that required parenteral antimicrobial therapy], opportunistic infections [excluding tuberculosis and herpes zoster with 2 adjacent dermatomes], herpes zoster, tuberculosis, malignancies [excluding nonmelanoma skin cancer (NMSC)], NMSC, major adverse cardiovascular events [MACE], venous thromboembolic events, and arterial thromboembolic events). Opportunistic infections, tuberculosis, malignancies, and cardiovascular events were evaluated by adjudication committees.

Safety was assessed in all patients who received ≥1 dose of tofacitinib 5 or 10 mg BID in any study included in the analysis. Patients were characterized based on the average daily tofacitinib dose: A predominant dose (PD) of tofacitinib 5 mg BID (an average daily dose <15 mg) and a PD of tofacitinib 10 mg BID (an average daily dose ≥15 mg).

Statistical Analysis

Data are described descriptively. Efficacy and safety data were summarized by induction study baseline cigarette smoking status; patients were classified as ever smokers (current smoker or ex-smoker) or never smokers.

The proportions of patients meeting efficacy endpoints are reported for the full analysis set (all patients who received ≥1 dose of placebo or tofacitinib 5 or 10 mg BID in any study, excluding the phase 2 induction study). Patients

with missing data in OCTAVE Induction 1 and 2, OCTAVE Sustain, and RIVETING were treated as nonresponders. In OCTAVE Open, patients with missing data were treated as nonresponders, but with the last observation carried forward after a patient advanced to a follow-up study.

The proportion of patients with treatment-emergent AEs, SAEs, and selected AEs of interest was calculated. Events were counted up to 28 days after the last dose of study treatment.

Results

Baseline Demographics and Clinical Characteristics

This analysis included 1156 patients; at induction study baseline, 416 (36.0%) were ever smokers (current smokers, $n = 59$ [5.1%]; ex-smokers, $n = 357$ [30.9%]) and 740 (64.0%) were never smokers (Table 1). Overall, in current smokers, the mean duration of smoking was 15.4 years and the majority (53.4%) had smoked for >10 years (Table S1). Overall, in ex-smokers, patients had stopped smoking for a mean duration of 12.3 years; more patients had stopped smoking for >10 years (42.9%) than >0–5 years (32.0%) and >5–10 years (25.1%). Moreover, overall, ex-smokers had smoked for a mean duration of 15.5 years, with the majority (62.1%) smoking for >10 years (Table S1). Baseline disease activity characteristics were generally similar between ever smokers and never smokers, although ever smokers were more often male, older, more likely to have longer disease duration, prior TNFi use, a prior history of myocardial infarction, diabetes mellitus, or ischemic or coronary heart disease, and more likely to have comorbid chronic obstructive pulmonary disease (COPD), compared with never smokers (Table 1).

Efficacy

For both ever smokers and never smokers, a numerically higher proportion of tofacitinib-treated patients achieved efficacy endpoints, compared with placebo-treated patients, at week 8 of OCTAVE Induction 1 and 2 and week 52 of OCTAVE Sustain (Figure 1A and 1B). When stratified by smoking status, the proportions of tofacitinib-treated patients who achieved efficacy endpoints at week 8 of OCTAVE Induction 1 and 2 and week 52 of OCTAVE Sustain, were generally similar in ever smokers and never smokers. In OCTAVE Induction 1 and 2, the treatment effect of tofacitinib 10 mg BID versus placebo for remission was greater in never smokers versus ever smokers.

At month 36 of OCTAVE Open, a numerically higher proportion of patients treated with tofacitinib 5 mg BID achieved efficacy endpoints compared with tofacitinib 10 mg BID (Figure 1C). Conversely, at month 6 of RIVETING, a numerically higher proportion of patients treated with tofacitinib 10 mg BID achieved efficacy endpoints compared with tofacitinib 5 mg BID (Figure 1D). However, smoking status did not affect the achievement of efficacy endpoints in OCTAVE Open and RIVETING.

When stratified by prior TNFi exposure status, the proportion of patients who achieved efficacy endpoints was generally higher in patients without prior TNFi exposure than those with prior TNFi exposure, regardless of smoking status (Figure S1, Supplementary Data Content). This observation was consistent across OCTAVE studies, regardless of treatment (tofacitinib 5 or 10 mg BID, or placebo).

Safety

SAEs occurred with similar frequency among treatment groups (tofacitinib 5 mg BID and tofacitinib 10 mg BID), regardless of smoking status. Overall, SAEs occurred with a higher frequency in ever smokers versus never smokers (Table 2).

Deaths

Overall, there were 3 deaths: 2 patients were ever smokers and 1 patient had never smoked; all patients were in the PD of tofacitinib 10 mg BID group. The cause of death in the never smoker was an aortic dissection (not considered to be treatment related). The 2 ever smoker patients were ex-smokers, and causes of death (considered to be treatment related) were recorded as hepatic angiosarcoma in the first patient and pulmonary embolism secondary to metastatic cholangiocarcinoma in the second patient.

Selected AEs of interest in cigarette smokers

Extraintestinal manifestations were reported in 101 (24.8%) ever smokers and 148 (20.7%) never smokers (Table 3).

Overall, 252 (60.6%) ever smokers and 393 (53.1%) never smokers had an infection (classified as any infection), of which 23 (5.5%) and 29 (3.9%) were serious infections, respectively. In total, 45 (10.8%) ever smokers and 50 (6.8%) never smokers had herpes zoster (nonserious and serious); 50 (12.0%) ever smokers and 63 (8.5%) never smokers had a *Clostridioides difficile* infection; and 81 (19.5%) ever smokers and 84 (11.4%) never smokers had a lower respiratory tract infection. Adjudicated opportunistic infections (excluding tuberculosis and herpes zoster with 2 adjacent dermatomes) were reported in 13 (3.2%) ever smokers and 18 (2.5%) never smokers; there were no reported cases of tuberculosis.

Adjudicated MACE were reported in 4 (1.0%) ever smokers and 5 (0.7%) never smokers. Among the ever smokers, 2 (0.5%) patients had a pulmonary embolism, and, among never smokers, 1 (0.1%) patient had a deep vein thrombosis and 4 (0.5%) patients had a pulmonary embolism; all patients were in the PD of tofacitinib 10 mg BID group. Two (0.5%) ever smokers and 2 (0.3%) never smokers had arterial thromboembolism.

Malignancies (excluding NMSC) occurred in 10 (2.5%) ever smokers and 11 (1.5%) never smokers. Malignancies in patients who were ever smokers included 2 patients with breast cancer and 1 patient each with lung cancer, lymphoma or lymphoproliferative disease, and melanoma; and in never smokers included 4 patients with colorectal cancer, and 1 patient each with lymphoma or lymphoproliferative disease and melanoma. Overall, NMSC was reported in 15 (3.7%) ever smokers and 7 (1.0%) never smokers.

Discussion

In this post hoc descriptive analysis of data from the tofacitinib UC clinical program (including 1156 patients), we demonstrated that tofacitinib efficacy and safety were generally similar in ever smokers and never smokers of cigarettes, but it is noted that overall, SAEs and infections were more frequent in ever smokers versus never smokers.

Table 1. Baseline demographics and clinical characteristics in the tofacitinib UC clinical program, by cigarette smoking status.

	Ever smokers			Never smokers		
	PD tofacitinib 5 mg BID	PD tofacitinib 10 mg BID	Tofacitinib all	PD tofacitinib 5 mg BID	PD tofacitinib 10 mg BID	Tofacitinib all
Female, *n*/*N* (%)[a]	25/63 (39.7)	126/353 (35.7)	151/416 (36.3)	61/139 (43.9)	266/601 (44.3)	327/740 (44.2)
Age (years), mean (SD)[b]	50.3 (14.3)	46.4 (13.5)	47.0 (13.6)	41.9 (13.8)	37.2 (12.6)	38.0 (12.9)
[*N*]	[63]	[353]	[416]	[139]	[601]	[740]
Race, *n*/*N* (%)						
White	45/63 (71.4)	283/353 (80.2)	328/416 (78.8)	115/139 (82.7)	483/601 (80.4)	598/740 (80.8)
Black	0/63 (0.0)	3/353 (0.8)	3/416 (0.7)	1/139 (0.7)	6/601 (1.0)	7/740 (0.9)
Asian	11/63 (17.5)	43/353 (12.2)	54/416 (13.0)	17/139 (12.2)	73/601 (12.1)	90/740 (12.2)
Other	5/63 (7.9)	7/353 (2.0)	12/416 (2.9)	4/139 (2.9)	26/601 (4.3)	30/740 (4.1)
Unknown	2/63 (3.2)	17/353 (4.8)	19/416 (4.6)	2/139 (1.4)	13/601 (2.2)	15/740 (2.0)
BMI (kg/m^2), mean (SD)[b]	26.8 (6.5)	25.9 (4.8)	26.1 (5.1)	24.5 (4.7)	24.1 (4.8)	24.2 (4.8)
[*N*]	[63]	[353]	[416]	[139]	[600]	[739]
Total Mayo score[b]						
Mean (SD)	7.9 (2.6)	8.9 (1.9)	8.7 (2.0)	7.8 (2.5)	8.7 (1.7)	8.5 (1.9)
[*N*]	[63]	[352]	[415]	[139]	[600]	[739]
≥3, *n*/*N* (%)	58/63 (92.1)	346/352 (98.3)	404/415 (97.3)	131/139 (94.2)	595/600 (99.2)	726/739 (98.2)
Partial Mayo score[b]						
Mean (SD)	5.5 (2.1)	6.3 (1.6)	6.1 (1.7)	5.5 (2.0)	6.1 (1.5)	6.0 (1.6)
[*N*]	[63]	[352]	[415]	[139]	[600]	[739]
≥2, *n*/*N* (%)	57/63 (90.5)	344/352 (97.7)	401/415 (96.6)	128/139 (92.1)	593/600 (98.8)	721/739 (97.6)
Mayo endoscopic score[b]						
Mean (SD)	2.4 (0.7)	2.6 (0.5)	2.6 (0.6)	2.4 (0.7)	2.6 (0.5)	2.6 (0.6)
[*N*]	[63]	[353]	[416]	[139]	[601]	[740]
≥2, *n*/*N* (%)	58/63 (92.1)	347/353 (98.3)	405/416 (97.4)	128/139 (92.1)	595/601 (99.0)	723/740 (97.7)
Baseline C-reactive protein, mg/L[a]						
Mean (SD)	4.2 (5.2)	11.8 (18.4)	10.6 (17.2)	10.7 (19.4)	11.1 (17.8)	11.0 (18.1)
[*N*]	[63]	[347]	[410]	[136]	[594]	[730]
>3, *n*/*N* (%)	25/63 (39.7)	241/347 (69.5)	266/410 (64.9)	78/136 (57.4)	377/594 (63.5)	455/730 (62.3)
>6, *n*/*N* (%)	14/63 (22.2)	170/347 (49.0)	184/410 (44.9)	45/136 (33.1)	252/594 (42.4)	297/730 (40.7)
Extent of disease, *n*/*N* (%)[a]						
Proctosigmoiditis	12/62 (19.4)	59/344 (17.2)	71/406 (17.5)	22/139 (15.8)	70/576 (12.2)	92/715 (12.9)
Left-sided colitis	26/62 (41.9)	116/344 (33.7)	142/406 (35.0)	43/139 (30.9)	195/576 (33.9)	238/715 (33.3)
Extensive colitis/pancolitis	24/62 (38.7)	168/344 (48.8)	192/406 (47.3)	74/139 (53.2)	311/576 (54.0)	385/715 (53.8)
Proctitis	0/62 (0.0)	1/344 (0.3)[c]	1/406 (0.2)[c]	0/139 (0.0)	0/576 (0.0)	0/715 (0.0)

Table 1. Continued

	Ever smokers			Never smokers		
	PD tofacitinib 5 mg BID	PD tofacitinib 10 mg BID	Tofacitinib all	PD tofacitinib 5 mg BID	PD tofacitinib 10 mg BID	Tofacitinib all
Disease duration ≥6 years, *n*/*N* (%)[b]	35/63 (55.6)	208/353 (58.9)	243/416 (58.4)	72/139 (51.8)	289/601 (48.1)	361/740 (48.8)
Baseline corticosteroid use, *n*/*N* (%)[b]	26/63 (46.0)	157/353 (44.5)	186/416 (44.7)	53/139 (38.1)	284/601 (47.3)	337/740 (45.5)
Prior corticosteroid use, *n*/*N* (%)[a]	59/63 (93.7)	311/353 (90.1)	370/416 (90.7)	126/139 (90.6)	520/601 (90.1)	646/740 (90.2)
Prior TNFi use, *n*/*N* (%)[a,d]	29/63 (46.0)	218/345 (63.2)	247/408 (60.5)	62/139 (44.6)	303/577 (52.5)	365/16 (51.0)
Prior TNFi failure, *n*/*N* (%)[a,d]	26/63 (41.3)	211/345 (61.2)	237/408 (58.1)	58/139 (41.7)	288/577 (49.9)	346/16 (48.3)
Prior immunosuppressant use, *n*/*N* (%)[a,d]	48/63 (76.2)	269/345 (78.0)	317/408 (77.7)	89/139 (64.0)	432/577 (74.9)	521/16 (72.8)
Prior immunosuppressant failure, *n*/*N* (%)[a,d]	46/63 (73.0)	262/345 (75.9)	308/408 (75.5)	85/139 (61.2)	420/577 (72.8)	505/16 (70.5)
Medical history[b]						
History of myocardial infarction, *n*/*N* (%)	3/63 (4.8)	5/353 (1.4)	8/416 (1.9)	1/139 (0.7)	2/601 (0.3)	3/740 (0.4)
History of diabetes mellitus, *n*/*N* (%)	6/63 (9.5)	23/353 (6.5)	29/416 (7.0)	4/139 (2.9)	14/601 (2.3)	18/740 (2.4)
History of ischemic heart disease, *n*/*N* (%)	3/63 (4.8)	9/353 (2.5)	12/416 (2.9)	2/139 (1.4)	7/601 (1.2)	9/740 (1.2)
History of coronary heart disease, *n*/*N* (%)	0/63 (0.0)	6/353 (1.7)	6/416 (1.4)	0/139 (0.0)	1/601 (0.2)	1/740 (0.1)
Smoking history						
Time since started smoking (years), mean (SD); median [min–max][d,e]	12.4 (6.8); 13.0 [5.0–20.0]	15.7 (10.2); 15.0 [3.0–50.0]	15.4 (10.0); 14.5 [3.0–50.0]	NA	NA	NA
[*N*]	[5]	[53]	[58]			
Time since stopped smoking (years), mean (SD); median [min–max][d,f]	14.7 (11.2); 13.0 [1.0–48.0]	12.4 (10.0); 10.0 [0.0–46.0]	12.8 (10.2); 10.0 [0.0–48.0]	NA	NA	NA
[*N*]	[58]	[292]	[350]			
COPD status, *n*/*N* (%)[b]						
Yes	1/63 (1.6)	9/353 (2.5)	10/416 (2.4)	0/139 (0.0)	1/601 (0.2)	1/740 (0.1)
No	62/63 (98.4)	344/353 (97.5)	406/416 (97.6)	139/139 (100)	600/601 (99.8)	739/740 (99.9)

Abbreviations: BID, twice daily; BMI, body mass index; COPD, chronic obstructive pulmonary disease, *N*, number of patients treated in the treatment group; *n*, number of patients in the specified category; NA, not applicable; PD, predominant dose; SD, standard deviation; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.
[a]Data are from screening of phase 2 or phase 3 induction studies (OCTAVE Induction 1 and 2).
[b]Data are from day 1 (start of active treatment in the tofacitinib UC clinical program).
[c]This patient was enrolled as a protocol deviation.
[d]Excludes phase 2.
[e]Current smokers only.
[f]Ex-smokers only.

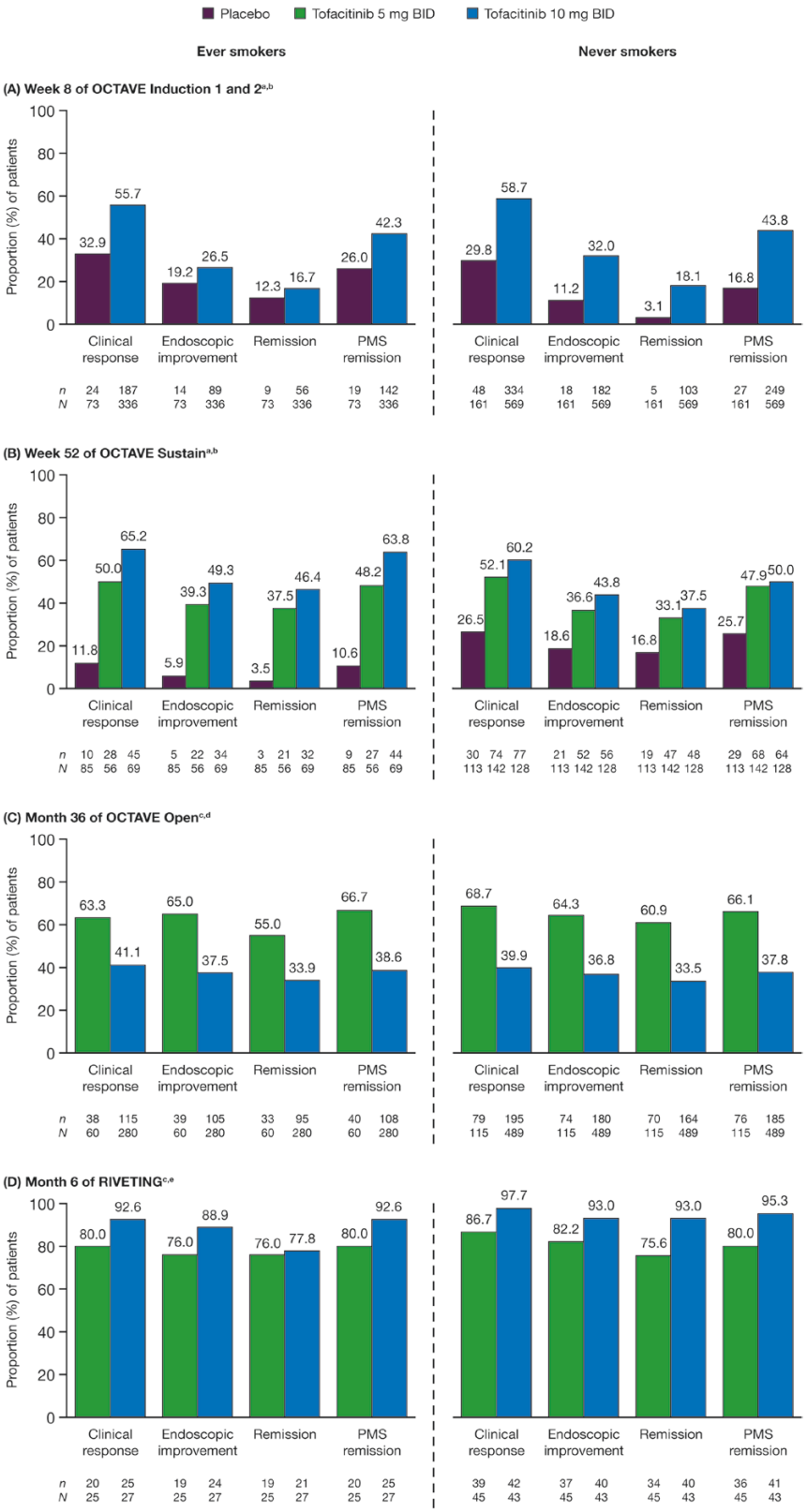

Figure 1. Proportion of patients who achieved efficacy endpoints in (A) OCTAVE Induction 1 and 2, (B) OCTAVE Sustain, (C) OCTAVE Open, and (D) RIVETING, by smoking status (full analysis set). Abbreviations: BID, twice daily; *N*, number of patients in the specified category with nonmissing data; *n*, number of patients with the specified response within the given category; PMS, partial Mayo score. Cigarette smoking status was determined at the baseline of the induction studies. [a]Central read endoscopy. [b]Nonresponder imputation was applied after a patient discontinued. [c]Local read endoscopy. [d]Nonresponder imputation, last observation carried forward was applied after a patient discontinued and the patient advanced to a subsequent study up to the visit they would have reached if that had stayed in the study. [e]Patients with missing scores were treated as nonresponders. Patients in the tofacitinib 5 mg BID group with dose escalation were treated as nonresponders for visits after dose escalation.

Table 2. Summary of safety in the tofacitinib UC clinical program, by cigarette smoking status.

	Ever smokers			Never smokers		
	PD tofacitinib 5 mg BID *N* = 63	PD tofacitinib 10 mg BID *N* = 353	Tofacitinib all *N* = 416	PD tofacitinib 5 mg BID *N* = 139	PD tofacitinib 10 mg BID *N* = 601	Tofacitinib all *N* = 740
Total patient-years of exposure	249.1	854.3	1103.4	534.0	1362.1	1896.1
Treatment duration (days), median (range)	1504 (52–2712)	506 (1–2694)	654 (1–2712)	1,684 (57–2850)	376 (1–2758)	615.5 (1–2850)
Treatment-emergent AEs						
Patients with AEs, *n* (%)	62 (98.4)	307 (87.0)	369 (88.7)	127 (91.4)	493 (82.0)	620 (83.8)
Patients with SAEs, *n* (%)	16 (25.4)	88 (24.9)	104 (25.0)	25 (18.0)	106 (17.6)	131 (17.7)
Deaths, *n* (%)	0 (0.0)	2 (0.6)	2 (0.5)	0 (0.0)	1 (0.2)	1 (0.1)
Discontinuation due to AEs, *n* (%)	12 (19.0)	99 (28.0)	111 (26.7)	27 (19.4)	141 (23.5)	168 (22.7)
Most common reasons for discontinuation:						
Worsening UC	2 (3.2)	53 (15.0)	55 (13.2)	12 (8.6)	69 (11.5)	81 (10.9)
Lymphopenia	0 (0.0)	2 (0.6)	2 (0.5)	2 (1.4)	4 (0.7)	6 (0.8)
Anemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	4 (0.7)	5 (0.7)
Anal abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	4 (0.5)

Abbreviations: AE, adverse event; BID, twice daily; *N*, number of patients treated in the treatment group; *n*, number of patients in the specified category; PD, predominant dose; SAE, serious AE; UC, ulcerative colitis.

Table 3. Proportions of selected AEs of interest in cigarette smokers[a] in the tofacitinib UC clinical program.

	Ever smokers			Never smokers		
	PD tofacitinib 5 mg BID *N* = 63	PD tofacitinib 10 mg BID *N* = 353	Tofacitinib all *N* = 416	PD tofacitinib 5 mg BID *N* = 139	PD tofacitinib 10 mg BID *N* = 601	Tofacitinib all *N* = 740
Extraintestinal manifestations, *n* (%)[b]	15 (23.8)	86 (24.9)	101 (24.8)	32 (23.0)	116 (20.1)	148 (20.7)
Infections, *n* (%)						
All infections	47 (74.6)	205 (58.1)	252 (60.6)	89 (64.0)	304 (50.6)	393 (53.1)
Serious infections	4 (6.3)	19 (5.4)	23 (5.5)	6 (4.3)	23 (3.8)	29 (3.9)
Herpes zoster (nonserious and serious)	8 (12.7)	37 (10.5)	45 (10.8)	14 (10.1)	36 (6.0)	50 (6.8)
Opportunistic infections[b,c,d]	4 (6.3)	9 (2.6)	13 (3.2)	4 (2.9)	14 (2.4)	18 (2.5)
Clostridioides difficile infection	8 (12.7)	42 (11.9)	50 (12.0)	13 (9.4)	50 (8.3)	63 (8.5)
Lower respiratory tract infection	18 (28.6)	63 (17.8)	81 (19.5)	24 (17.3)	60 (10.0)	84 (11.4)
MACE, *n* (%)[b,c]	2 (3.2)	2 (0.6)	4 (1.0)	2 (1.4)	3 (0.5)	5 (0.7)
Malignancies, *n* (%)[b,c,e]						
Malignancies (excluding NMSC)	2 (3.2)	8 (2.3)	10 (2.5)	1 (0.7)	10 (1.7)	11 (1.5)
Colorectal cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	4 (0.6)
Lung cancer	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer	1 (1.6)	1 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoma and lymphoproliferative disease	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.7)	0 (0.0)	1 (0.1)
Melanoma	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.1)
NMSC	4 (6.3)	11 (3.2)	15 (3.7)	1 (0.7)	6 (1.0)	7 (1.0)
Thromboembolic events, *n* (%)						
Thromboembolism	1 (1.6)	3 (0.8)	4 (1.0)	2 (1.4)	5 (0.8)	7 (0.9)
Deep vein thrombosis[f]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pulmonary embolism[f]	0 (0.0)	2 (0.6)	2 (0.5)	0 (0.0)	4 (0.7)	4 (0.5)
Arterial thromboembolism[g]	1 (1.6)	1 (0.3)	2 (0.5)	2 (1.4)	0 (0.0)	2 (0.3)

Abbreviations: AE, adverse event; BID, twice daily; MACE, major adverse cardiovascular events; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of patients treated in the treatment group; *n*, number of patients in the specified category; NMSC, non-melanoma skin cancer; PD, predominant dose; UC, ulcerative colitis.
[a]Events that occurred >28 days after the last dose of study drug were excluded.
[b]Excludes data from phase 2 (ever smokers: PD tofacitinib 10 mg BID, *N* = 345; tofacitinib all, *N* = 408; and never smokers: PD tofacitinib 10 mg BID, *N* = 577; tofacitinib all, *N* = 716).
[c]Adjudicated events.
[d]Excludes tuberculosis and herpes zoster with 2 adjacent dermatomes.
[e]No events of pancreatic cancer or prostate cancer.
[f]Adjudicated events from OCTAVE Open and RIVETING, plus selected events from the phase 2 induction study, OCTAVE Induction 1 and 2, and OCTAVE Sustain, from the narrow Standardized MedDRA query for embolic and thrombotic events.
[g]Selected events from the narrow Standardized MedDRA query for embolic and thrombotic events (v23.0).

Cigarette smoking is recognized to interfere with the course of UC; some studies have noted that active smoking results in a more benign course of disease compared with nonsmokers, and smoking cessation may be associated with new-onset UC and may negatively impact the course of the disease.[3] Smoking was not predictive of the primary response to TNFi or vedolizumab in a systematic review of patients with inflammatory bowel disease.[19] Conversely, real-world data from patients with UC treated with vedolizumab demonstrated that current or former smoking was significantly associated with clinical remission at week 14.[20]

The treatment effect of tofacitinib compared with placebo in OCTAVE Induction 1 and 2, and OCTAVE Sustain, has previously been reported.[15] The data reported here demonstrate that, when stratified by smoking status, generally similar proportions of patients achieved efficacy endpoints.

In the general population, smoking is a known risk factor for infections.[21] A retrospective review of safety data from patients with inflammatory bowel disease treated with vedolizumab noted that active smokers were more likely to have respiratory infections and active smoking was independently associated with developing an infection; active smokers also had a 3-fold increased risk for infections with vedolizumab.[7] In contrast, a numerically similar proportion of ever smokers and never smokers had lower respiratory tract infections in this study, although it should be noted that the ever smoker group consisted predominantly of ex-smokers and not current smokers. Previous analyses of data from the tofacitinib UC clinical program showed an elevated risk of herpes zoster in patients with UC receiving tofacitinib compared with placebo and, in univariate analyses but not in a multivariate analysis, smoking was identified as a risk factor for herpes zoster.[22] However, in this study, the proportion of patients who had herpes zoster (nonserious and serious) was numerically similar in ever smokers and never smokers. Inflammatory bowel disease itself has been shown to be an independent risk factor for the development of *C. difficile* infection.[23,24] In addition, the incidence rates of *C. difficile* infection have been reported to be higher in current smokers compared with ex-smokers and never smokers, and similar between ex-smokers and never smokers.[25] In comparison, in this analysis, a numerically similar proportion of ever smokers and never smokers had a *C. difficile* infection.

Smoking is also associated with a risk of serious chronic disorders, including cardiovascular disorders, lung disease, COPD, and many forms of cancer.[26–28] Malignancies (excluding NMSC), NMSC, MACE, and venous thromboembolic events occurred infrequently in the tofacitinib UC clinical program, details of which have previously been reported.[17,18,29–31] In our study, the proportions of patients with these AEs were numerically similar between ever smokers and never smokers. Of note, the small sample size, duration of follow-up, and the relatively young age of patients, without a prominent risk profile, render the patient population suboptimal to explore the impact of smoking on MACE and pulmonary embolism events. Colorectal cancer is a severe complication of UC, and in a retrospective cohort study of patients with UC, smoking was identified as the main risk factor for the development of colorectal cancer.[8] Interestingly, in our study cohort, 4 never smokers had colorectal cancer, although this finding should be interpreted with caution due to the small number of patients included in this analysis.

An important component of the impact of UC is the development of extraintestinal manifestations,[32] and these have been shown to be associated with active smoking.[6] Data from a retrospective safety analysis of patients with UC treated with vedolizumab reported that active smokers at the time of vedolizumab initiation had an increased risk of noninfectious AEs; however, in this study, a numerically similar proportion of ever smokers and never smokers reported extraintestinal manifestations.

This study has some limitations. The studies included in this analysis were not designed to assess the impact of smoking status, and all assessments are descriptive, with no formal statistical analysis. Most patients in the ever smoker group were ex-smokers, and the number of current smokers was low; therefore, a robust analysis of the ever smokers stratified by current smokers and ex-smokers was not feasible (Tables S2 and S3, Supplementary Data Content). Consequently, these data should be interpreted with caution. However, it is noteworthy that the baseline clinical characteristics for the ever smoker group show that within the current smoker and ex-smoker subgroups, the time since smoking initiation, and the time since smoking cessation, respectively, varied widely. Therefore, this also suggests that analysis of data stratified by current and ex-smokers should be interpreted with caution, due to the heterogeneity within subgroups. Additionally, factors such as the degree of smoking (pack-years or dose exposure), time between smoking cessation and UC diagnosis, time between smoking cessation and initiation of tofacitinib, and smoking of other substances beyond cigarettes (eg, e-cigarettes, noncommercial tobacco) were not collected during the studies. Efficacy analyses were not adjusted for characteristics such as age and disease duration, and the low number of some AEs limits the interpretation of these data. Baseline differences between the ever smokers and never smokers in factors known to impact infection risk (eg, age, disease duration, treatment history, and comorbid COPD) were not adjusted for in this analysis.

Conclusions

This post hoc analysis of data from the tofacitinib UC clinical program suggested that tofacitinib efficacy and safety in patients with UC were generally similar in ever smokers and never smokers. Overall, SAEs and infections were more frequent in ever smokers versus never smokers; however, at baseline, there were differences in factors known to impact infection risk between the 2 groups. These findings may inform treatment selection and monitoring strategies in patients with UC and support the recommendation to stop or refrain from cigarette smoking.

Supplementary Data

Supplementary data are available at *Crohn's & Colitis 360* online.

Author Contributions

F.H.T. and S.G. conceived and designed the study. R.M. and M.J.C. analyzed and interpreted the data. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript for submission.

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Conflicts of Interest

D.T.R. has received grant support from Takeda and has served as a consultant for AbbVie, AltruBio, Arena Pharmaceuticals, Bellatrix Pharmaceuticals, Boehringer Ingelheim Ltd., Bristol Myers Squibb, Dizal Pharmaceuticals, Galapagos, Ichnos Sciences, InDex Pharmaceuticals, Iterative Health, Janssen Pharmaceuticals, Lilly, Pfizer Inc, Prometheus Biosciences, Reistone, S.A., and Syneos.

J.T. has served as an advisory board member for AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Galapagos, Janssen, and Pfizer Inc, has received research funding from AbbVie and Janssen, and has received lecture fees from AbbVie, Galapagos, Janssen, and Pfizer Inc.

M.R. has served as an advisory board member or consultant for AbbVie, Amgen, Celgene, Janssen, Miraca Labs, Pfizer Inc, Seres Therapeutics, Takeda, and UCB, has received research funding from AbbVie, Janssen, and Takeda, and has received unrestricted educational grants from AbbVie, Janssen, Pfizer Inc, Salix, Shire, Takeda, and UCB.

W.R. has served as a speaker for AbbVie, Celltrion, Falk Pharma GmbH, Ferring, Galapagos, Janssen, MSD, Pfizer Inc, Pharmacosmos, Roche, Shire, Takeda, and Therakos, has served as a consultant for AbbVie, Amgen, AOP Orphan, Arena Pharmaceuticals, Astellas, AstraZeneca, Bioclinica, Boehringer Ingelheim, Bristol Myers Squibb, Calyx, Celgene, Celltrion, Eli Lilly, Falk Pharma GmbH, Ferring, Galapagos, Gatehouse Bio Inc, Genentech, Gilead Sciences, Grünenthal, ICON, InDex Pharmaceuticals, Inova, Janssen, Landos Biopharma, MedAhead, MedImmune, Microbiotica, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, OMass, Otsuka, Parexel, Periconsulting, Pfizer Inc, Pharmacosmos, Protagonist, Provention, Quell Therapeutics, Sandoz, Seres Therapeutics, SetPoint Medical, Sigmoid, Sublimity, Takeda, Teva Pharmaceuticals, Therakos, Theravance, and Zealand, has served as an advisory board member for AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Galapagos, Janssen, Mitsubishi Tanabe Pharma Corporation, MSD, Pharmacosmos, Pfizer Inc, Sandoz, and Takeda, and has received research funding from AbbVie, Janssen, MSD, Sandoz, Sanofi, and Takeda.

L.P. has no conflicts of interest to declare.

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S.C.N. has served as a speaker for AbbVie, Ferring, Janssen, Menarini, Pfizer Inc, Takeda, and Tillotts, has received research funding from AbbVie, Ferring, and Olympus, and holds a directorship with Microbiota I-Center.

Ethical Considerations

All patients provided written informed consent, and all studies were conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Guidelines for Good Clinical Practice, and local regulations. Participating institutions provided Institutional Review Board approval prior to participation. All authors had access to the study data and reviewed and approved the final manuscript. This analysis included data from the following studies registered at ClinicalTrials.gov: phase 2 induction study (baseline demographics and safety only; NCT00787202); phase 3 studies OCTAVE Induction 1 and 2 (NCT01465763 and NCT01458951), OCTAVE Sustain (NCT01458574), and OCTAVE Open (NCT01470612); and the phase 3/4b RIVETING study (NCT03281304).

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.

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