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Safety of Tofacitinib for Treatment of Ulcerative Colitis, Based on 4.4 Years of Data From Global Clinical Trials

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BACKGROUND & AIMS: **Tofacitinib is an oral, small-molecule inhibitor of JAK approved in several countries for the treatment of ulcerative colitis (UC). We report integrated safety analyses of tofacitinib-treated patients with moderate to severe UC.**

METHODS: **Patients receiving placebo or tofacitinib (5 or 10 mg) twice daily were analyzed as 3 cohorts: induction (phase 2 and 3 induction studies, n = 1220), maintenance (phase 3 maintenance study, n = 592), and overall (patients receiving tofacitinib 5 or 10 mg twice daily in phase 2, phase 3, or open-label, long-term extension studies, n = 1157; 1613 patient-years' exposure). Incidence rates (IRs; patients with events per 100 patient-years of exposure) were evaluated for select adverse events.**

RESULTS: **In the maintenance cohort, IRs for select adverse events were similar among treatment groups, except for a numerically higher IR of herpes zoster infection among patients who received tofacitinib 5 mg twice daily (2.1; 95% CI, 0.4–6.0) and statistically higher IR among patients who received tofacitinib 10 mg twice daily (IR, 6.6; 95% CI, 3.2–12.2) vs placebo (IR, 1.0, 95% CI, 0.0–5.4). For the overall cohort (84% received average dose of tofacitinib 10 mg twice daily), IRs were: death, 0.2 (95% CI, 0.1–0.6); serious infections, 2.0 (95% CI, 1.4–2.8); opportunistic infections, 1.3 (95% CI, 0.8–2.0); herpes zoster infection, 4.1 (95% CI, 3.1–5.2); malignancy (excluding non-melanoma skin cancer), 0.7 (95% CI, 0.3–1.2); non-melanoma skin cancer, 0.7 (95% CI, 0.3–1.2); major adverse cardiovascular events, 0.2 (95% CI, 0.1–0.6); and gastrointestinal perforations, 0.2 (95% CI, 0.0–0.5).**

CONCLUSIONS: **In safety analyses of patients with moderate to severe UC treated with tofacitinib, we observed a dose relationship with herpes zoster infection. Although follow-up time was relatively short, the safety profile of tofacitinib for patients with UC appeared similar to that reported for patients with rheumatoid arthritis and for patients with UC treated with biologic agents, except for the higher IR of herpes zoster infection. ClinicalTrials.gov, no: NCT00787202, NCT01465763, NCT01458951, NCT01458574, and NCT01470612.**

Keywords: NMSC; Janus Kinase; Malignancies; Secondary Analysis.

Tofacitinib is an oral, small molecule Janus kinase inhibitor approved in several countries for the treatment of ulcerative colitis (UC). In 2 identical phase 3, placebo-controlled, 8-week UC induction studies,[1] tofacitinib 10 mg twice daily demonstrated induction efficacy versus placebo. Tofacitinib 5 and 10 mg twice daily also demonstrated robust efficacy versus placebo in a phase 3, placebo-controlled, 52-week maintenance study.[1] The long-term safety and efficacy of tofacitinib is being evaluated in an ongoing, open-label, long-term extension (OLE) study (NCT01470612; OCTAVE Open).

Abbreviations used in this paper: **CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; HZ, herpes zoster; IR, incidence rate; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; OIs, opportunistic infections; OLE, open-label, long-term extension; UC, ulcerative colitis.**

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Tofacitinib has been approved for the treatment of patients with moderately to severely active rheumatoid arthritis,[2] and safety in the rheumatoid arthritis population has been reported based on clinical trial data from >7000 patients and >22,000 patient-years of exposure accumulated through 9 years of treatment.[3–5]

To characterize the safety of tofacitinib in patients with UC, we performed an integrated analysis of tofacitinib UC clinical trials, pooling data from individual trials to maximize the duration of tofacitinib exposure evaluated. We focused on adverse events of special interest: serious infections, herpes zoster (HZ), opportunistic infections (OIs), malignancies (excluding nonmelanoma skin cancer [NMSC]), NMSC, major adverse cardiovascular events (MACE), and gastrointestinal (GI) perforations.

What You Need to Know

Background

Efficacy and safety of tofacitinib in patients with moderately to severely active ulcerative colitis (UC) have been reported in 8-week phase 2 and phase 3 induction studies, a 52-week phase 3 maintenance study, and an open-label, long-term extension study.

Findings

A dose relationship of herpes zoster (HZ) was observed with tofacitinib therapy.

Incidence rates for serious infections, HZ, opportunistic infections, malignancies, major adverse cardiovascular events, and gastrointestinal perforations did not increase with longer treatment duration.

Tofacitinib safety in UC was consistent with that observed in other tofacitinib clinical development programs.

Implications for patient care

These findings support the use of tofacitinib 5 mg twice daily and 10 mg twice daily as a long-term treatment option for patients with moderately to severely active UC.

Methods

Studies and Treatments

Data were pooled from patients with UC treated with placebo, tofacitinib 5 mg twice daily, and tofacitinib 10 mg twice daily in phase 2,[6] phase 3,[1] and OLE studies (Figure 1, Table 1).

Ethics Approval

All studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines, and were approved by the institutional review boards and/or independent ethics committees at each of the investigational centers participating in the studies, or a central institutional review board. All patients provided written informed consent.

Analysis Cohorts

Safety data were analyzed as 3 cohorts. The induction cohort included patients who received placebo or tofacitinib 10 mg twice daily in phase 2 or phase 3 induction studies, and compared the short-term safety profile of tofacitinib versus placebo as induction therapy. The maintenance cohort included patients who received placebo, tofacitinib 5 mg twice daily, or tofacitinib 10 mg twice daily in OCTAVE Sustain, and compared the longer term safety profile of tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo as maintenance therapy. The overall cohort included patients who received tofacitinib 5 or 10 mg twice daily in any phase 2, phase 3, or OLE study. The overall cohort assessed tofacitinib safety during the entire UC program.

The laboratory cohort evaluated changes in laboratory parameters over time and comprised 2 phases: the induction phase (patients from the induction cohort) and the postinduction phase (patients in OCTAVE Sustain who previously received tofacitinib 10 mg twice daily induction therapy).

Safety Assessments

Proportions of patients with adverse events, serious adverse events, and discontinuations caused by adverse events were calculated for each cohort. Adverse event and serious adverse event criteria are provided in the Supplementary Material.

Serious infections were defined as any treated infections that required parenteral antimicrobial therapy, hospitalization for treatment, or met other criteria that required the infection to be classified as a serious adverse event. Patients with serious infections were required to discontinue the studies (with appropriate follow-up). OIs were adjudicated according to prespecified criteria. HZ that was classified as disseminated (diffuse rash [>6 dermatomes], or had nonskin organ involvement) or multidermatomal (involving nonadjacent or 3–6 adjacent dermatomes) were considered HZ OIs. See the Supplementary Material for further details on adjudication committees.

Statistical Analyses

For induction and maintenance cohorts, analyses were based on the study treatment received. For the overall cohort, analysis was based on all patients who received at least 1 dose of tofacitinib (either tofacitinib 5 mg twice daily or 10 mg twice daily [ie, the Tofacitinib

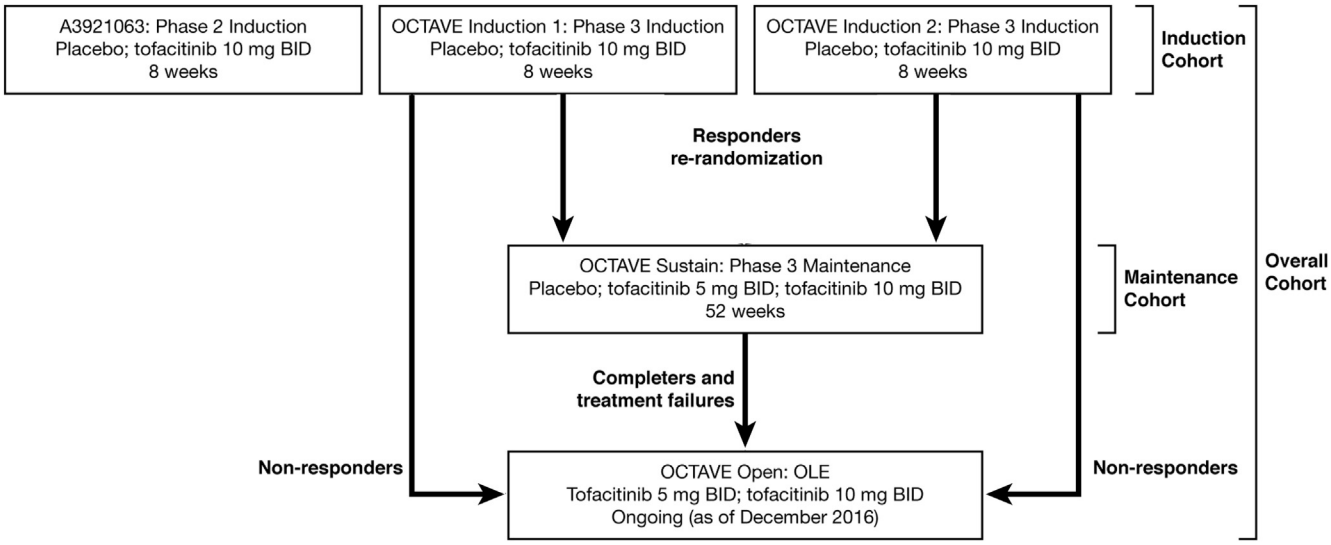

Figure 1. Overview of the tofacitinib UC clinical development program showing phase 2, phase 3, and OLE studies, and transfer of patients from induction studies to maintenance and/or OLE studies. Clinical response in OCTAVE Induction 1 and 2 was defined as a decrease from baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1. In A3921063, patients received placebo, or tofacitinib 0.5, 3, 10, or 15 mg twice daily. This analysis included only treatment experience with placebo, tofacitinib 5 mg twice daily, and tofacitinib 10 mg twice daily. OCTAVE Induction 1 and 2 initially included a tofacitinib 15 mg twice daily treatment arm, which was discontinued following a protocol amendment. Patients who received tofacitinib 15 mg twice daily in OCTAVE Induction 1 and 2 are not included in the induction cohort. However, patients who received induction treatment with tofacitinib 15 mg twice daily and subsequently received at least 1 dose of tofacitinib 5 mg twice daily or 10 mg twice daily in either OCTAVE Sustain or OCTAVE Open were included in the overall cohort. Patients in remission at entry of OCTAVE Open received tofacitinib 5 mg twice daily; all other patients entering OCTAVE Open received tofacitinib 10 mg twice daily. Tapering of corticosteroids was mandatory in OCTAVE Sustain and in OCTAVE Open. Permitted concomitant therapies, corticosteroid tapering, and discontinuation and dose adjustment criteria in OCTAVE Open are described in the Supplementary Material. BID, twice daily; OLE, open-label, long-term extension; UC, ulcerative colitis.

All group]). For patients who received placebo in induction or maintenance studies, adverse events that occurred during the placebo treatment period were not counted in the overall cohort. The overall cohort was analyzed as a single treatment group, because patients could potentially be assigned to different study treatments across induction, maintenance, and/or OLE studies.

For the induction cohort, because of the short treatment duration (up to 8 weeks), evaluation of adverse events of special interest was performed based on the proportions of patients with ≥1 event. For the maintenance and overall cohorts, incidence rates (IRs) for adverse events of special interest were calculated based on the number of unique patients with ≥1 event per 100 patient-years of exposure. For malignancies (excluding NMSC), NMSC, MACE, and death, all events were included in IR calculations. For other adverse events, events occurring >28 days after the last dose of study treatment were not included in the primary IR calculations. 95% CI for IRs were computed using an exact method.

For the overall cohort, a Cox proportional hazards model evaluated risk factors for select adverse events of special interest (serious infections, OIs, HZ, and NMSC), where there were sufficient numbers of events to support a valid analysis. Statistical significance was declared for P values $< .05$. Risk factors evaluated, and further details of the modeling approach, are provided in the Supplementary Material.

Results

Patients and Tofacitinib Exposure

Demographics and disease characteristics were generally similar among the treatment groups in each cohort (Table 2). In the overall cohort, treatment duration was up to 4.4 years (median, 1.4 years; range, 0.0–4.4 years), with exposure of 1612.8 patient-years. Most patients (n = 971; 83.9%) in the overall cohort received tofacitinib 10 mg twice daily during most of their treatment duration.

Adverse Events, Serious Adverse Events, and Discontinuations Because of Adverse Events

In the induction cohort, the proportions of patients with adverse events (placebo, 55.0%; tofacitinib 10 mg twice daily, 54.9%), serious adverse events (placebo, 6.4%; tofacitinib 10 mg twice daily, 3.8%), and discontinuations because of adverse events (placebo, 5.0%; tofacitinib 10 mg twice daily, 3.8%) were generally similar across treatment groups. Across treatment groups in the maintenance cohort, proportions of patients with adverse events (placebo, 75.3%; tofacitinib 5 mg twice daily, 72.2%; tofacitinib 10 mg twice daily, 79.6%) and serious adverse events (placebo, 6.6%;

Table 1. Summary of Tofacitinib Phase 2, Phase 3, and OLE Studies in Patients With Active UC Included in This Integrated Safety Analysis

Study and study design	Patient population	Study treatments[a]
A3921063, NCT00787202[6] 8-week, double-blind, placebo-controlled, phase 2	Moderately to severely active disease (n = 194)	Placebo BID (n = 48); tofacitinib 0.5 mg BID (n = 31); 3 mg BID (n = 33); 10 mg BID (n = 33); 15 mg BID (n = 49)
OCTAVE Induction 1, NCT01465763[1] 8-week, double-blind, placebo-controlled, phase 3	Moderately to severely active disease (n = 614) Prior failure or intolerance to treatment with corticosteroids, immunomodulators, and/or tumor necrosis factor inhibitors	Placebo BID (n = 122); tofacitinib 10 mg BID (n = 476); tofacitinib 15 mg BID (n = 16)
OCTAVE Induction 2, NCT01458951[1] 8-week, double-blind, placebo-controlled, phase 3	Moderately to severely active disease (n = 547) Prior failure or intolerance to treatment with corticosteroids, immunomodulators, and/or tumor necrosis factor inhibitors	Placebo BID (n = 112); tofacitinib 10 mg BID (n = 429); tofacitinib 15 mg BID (n = 6)
OCTAVE Sustain, NCT01458574[1] 52-week, double-blind, placebo-controlled, phase 3	Patients completing OCTAVE Induction 1 or 2 with clinical response[b] (n = 593)	Placebo BID (n = 198); tofacitinib 5 mg BID (n = 198); tofacitinib 10 mg BID (n = 197)
OCTAVE Open, NCT01470612 OLE study; data as of December 2016 data cutoff	Patients who completed OCTAVE Induction 1 or 2 without clinical response, and patients who completed or who demonstrated treatment failure in OCTAVE Sustain	Tofacitinib 5 mg BID (patients in remission at study entry); tofacitinib 10 mg BID (all other patients) Dose adjustment was permitted after Month 2

BID, twice daily; OLE, open-label, long-term extension; UC, ulcerative colitis.

[a]This analysis included only treatment experience with placebo, tofacitinib 5 mg BID, and tofacitinib 10 mg BID. OCTAVE Induction 1 and 2 initially included a tofacitinib 15 mg BID treatment arm, which was discontinued following a protocol amendment. Patients who received tofacitinib 15 mg BID in OCTAVE Induction 1 and 2 are not included in the induction cohort. However, patients who received induction treatment with tofacitinib 15 mg BID and subsequently received at least 1 dose of tofacitinib 5 mg BID or 10 mg BID in either OCTAVE Sustain or OCTAVE Open were included in the overall cohort.

[b]A decrease from baseline in total Mayo score of $\geq$3 points and $\geq$30%, plus a decrease in rectal bleeding subscore of $\geq$1 point or an absolute rectal bleeding subscore of 0 or 1.

Table 2. Patient Demographics, Baseline Disease Characteristics, and Drug Exposure for Patients in the Tofacitinib UC Program for Each Cohort

	Induction cohort		Maintenance cohort			Overall cohort (induction + maintenance + OLE)
	Placebo (n = 282)	Tofacitinib 10 mg BID (n = 938)	Placebo (n = 198)	Tofacitinib 5 mg BID (n = 198)	Tofacitinib 10 mg BID (n = 196)	Tofacitinib All (n = 1157)
Age, mean *y* (SD)	41.4 (14.4)	41.3 (13.8)	43.4 (14.0)	41.9 (13.7)	43.0 (14.4)	41.3 (13.9)
≥65 y, n (%)	21 (7.4)	62 (6.6)	18 (9.1)	13 (6.6)	17 (8.7)	77 (6.7)
Male, n (%)	155 (55.0)	557 (59.4)	116 (58.6)	103 (52.0)	110 (56.1)	679 (58.7)
Race, n (%)						
White	229 (81.2)	756 (80.6)	155 (78.3)	164 (82.8)	153 (78.1)	927 (80.1)
Black	4 (1.4)	6 (0.6)	3 (1.5)	2 (1.0)	0 (0.0)	10 (0.9)
Asian	28 (9.9)	114 (12.2)	26 (13.1)	23 (11.6)	25 (12.8)	144 (12.4)
Other	11 (3.9)	36 (3.8)	9 (4.5)	5 (2.5)	9 (4.6)	42 (3.6)
Unspecified	10 (3.5)	26 (2.8)	5 (2.5)	4 (2.0)	9 (4.6)	34 (2.9)
Geographic region, n (%)						
Asia	26 (9.2)	95 (10.1)	20 (10.1)	22 (11.1)	21 (10.7)	123 (10.6)
Eastern Europe	90 (31.9)	283 (30.2)	57 (28.8)	66 (33.3)	63 (32.1)	342 (29.6)
North America	53 (18.8)	187 (19.9)	45 (22.7)	39 (19.7)	44 (22.4)	241 (20.8)
Western Europe	79 (28.0)	281 (30.0)	55 (27.8)	47 (23.7)	57 (29.1)	344 (29.7)
Rest of the world	34 (12.1)	92 (9.8)	21 (10.6)	24 (12.1)	11 (5.6)	107 (9.2)
Disease duration, mean *y* (SD)	8.2 (6.8)	8.2 (7.0)	8.8 (7.5)	8.3 (7.2)	8.7 (7.0)	8.2 (7.0)
Mean Mayo score (SD)	8.9 (1.5)	9.0 (1.5)	3.3 (1.8)	3.3 (1.8)	3.4 (1.8)	8.6 (2.0)
C-reactive protein, median *mg/L* (range)	5.3 (0.1–205.1)	4.6 (0.1–208.4)	1.0 (0.1–45.0)	0.7 (0.1–33.7)	0.9 (0.1–74.3)	4.5 (0.1–208.4)
Prior tumor necrosis factor inhibitor failure, n (%)	124 (53.0)	465 (51.4)	89 (44.9)	83 (41.9)	92 (46.9)	583 (51.9)
Prior immunosuppressant treatment, n (%)	160 (68.4)	683 (75.5)	134 (67.7)	149 (75.3)	144 (73.5)	838 (74.6)
Steroid use at baseline, n (%)	127 (45.0)	430 (45.8)	100 (50.5)	101 (51.0)	86 (43.9)	523 (45.2)
Mean dose (prednisone equivalent), mg/day (SD)	16.9 (6.2)	16.0 (6.4)	15.9 (6.2)	14.9 (6.2)	14.5 (5.9)	16.0 (6.3)
Total exposure, patient-years	44.8	156.2	100.4	146.2	154.3	1612.8
Treatment duration, median *d* (range)	62 (7–80)	63 (1–96)	138 (14–382)	363.5 (22–420)	368 (1–399)	514 (1–1606)

BID, twice daily; OLE, open-label, long-term extension study; SD, standard deviation; UC, ulcerative colitis.

Table 3. Proportions of Adverse Events of Special Interest in the Induction Cohort

	Induction cohort		
	Placebo (n = 282)	Tofacitinib 10 mg BID (n = 938)	Difference versus placebo
	n (%)[a]	n (%)[a]	Percentage points (95% CI)
Serious infection event	0 (0.0)	8 (0.9)	0.9 (-0.4 to 1.7)
HZ	1 (0.4)	6 (0.6)	0.3 (-1.3 to 1.2)
OIs[b]	0 (0.0)	3 (0.3)	0.3 (-1.2 to 1.1)
OIs (excluding HZ)[b]	0 (0.0)	1 (0.1)	0.1 (-1.4 to 0.7)
Malignancy (excluding NMSC)[b]	0 (0.0)	0 (0.0)	0.0 (0.0 to 0.0)
NMSC[b]	0 (0.0)	2 (0.2)	0.2 (-1.3 to 0.9)
MACE[b]	0 (0.0)	2 (0.2)	0.2 (-1.3 to 0.9)
GI perforations[b]	1 (0.4)	1 (0.1)	-0.3 (-2.1 to 0.4)

BID, twice daily; CI, confidence interval; GI, gastrointestinal; HZ, herpes zoster; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; OIs, opportunistic infections.
[a]For the induction cohort, adverse events of special interest were evaluated based on the proportions of patients with ≥1 event.
[b]Adjudicated data do not include data from Study A3921063.

tofacitinib 5 mg twice daily, 5.1%; tofacitinib 10 mg twice daily, 5.6%) were similar.

In the induction cohort, the most frequently occurring adverse events were headache (placebo, 6.7%; tofacitinib 10 mg twice daily, 7.8%) and nasopharyngitis (placebo, 5.0%; tofacitinib 10 mg twice daily, 6.0%). In the maintenance cohort, the most frequently occurring adverse events were nasopharyngitis (placebo, 5.6%; tofacitinib 5 mg twice daily, 9.6%; tofacitinib 10 mg twice daily, 13.8%) and worsening UC (placebo, 35.9%; tofacitinib 5 mg twice daily, 18.2%; tofacitinib 10 mg twice daily, 14.8%). The most frequently occurring serious adverse event in each cohort was worsening UC.

Table 4. IRs of Adverse Events of Special Interest in the Maintenance and Overall Cohorts

	Maintenance cohort			Overall cohort (induction + maintenance + OLE)
	Placebo (n = 198)	Tofacitinib 5 mg BID (n = 198)	Tofacitinib 10 mg BID (n = 196)	Tofacitinib all (n = 1157)
	n (%) IR (95% CI)	n (%) IR (95% CI)	n (%) IR (95% CI)	n (%) IR (95% CI)
Serious infections	2 (1.0) 1.9 (0.2–7.0)	2 (1.0) 1.4 (0.2–4.9)	1 (0.5) 0.6 (0.0–3.5)	33 (2.9) 2.0 (1.4–2.8)
HZ	1 (0.5) 1.0 (0.0–5.4)	3 (1.5) 2.1 (0.4–6.0)	10 (5.1) 6.6 (3.2–12.2)	65 (5.6) 4.1 (3.1–5.2)
OIs[a]	1 (0.5) 1.0 (0.0–5.4)	2 (1.0) 1.4 (0.2–4.9)	4 (2.0) 2.6 (0.7–6.7)	21 (1.9) 1.3 (0.8–2.0)
OIs (excluding HZ)[a]	0 (0.0) 0.0 (0.0–3.6)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	4 (0.4) 0.2 (0.1–0.6)
Malignancy (excluding NMSC)[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	11 (1.0) 0.7 (0.3–1.2)
NMSC[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	3 (1.5) 1.9 (0.4–5.6)	11 (1.0) 0.7 (0.3–1.2)
MACE[a]	0 (0.0) 0.0 (0.0–3.6)	1 (0.5) 0.7 (0.0–3.8)	1 (0.5) 0.6 (0.0–3.5)	4 (0.4) 0.2 (0.1–0.6)
GI perforations[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	3 (0.3) 0.2 (0.0–0.5)

NOTE. With the exception of malignancy (excluding NMSC), NMSC, and MACE, IRs presented in the table exclude events that occurred >28 days after the last dose of study drug.
BID, twice daily; CI, confidence interval; GI, gastrointestinal; HZ, herpes zoster; IR, incidence rate, patients with ≥1 event per 100 patient-years; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; OIs, opportunistic infections; OLE, open-label, long-term extension study.
[a]Adjudicated data do not include data from Study A3921063.

Deaths

In the entire tofacitinib UC program, there were 4 deaths. One patient receiving tofacitinib 10 mg twice daily died of dissecting aortic aneurysm during OCTAVE Induction 1. Three patients receiving open-label tofacitinib 10 mg twice daily died during OCTAVE Open: causes of death were hepatic angiosarcoma, acute myeloid leukemia, and pulmonary embolism in the setting of cholangiocarcinoma metastasized to the peritoneum. IR for deaths in the overall cohort was 0.2 (95% CI, 0.1–0.6).

Serious Infections

In the induction cohort, serious infections occurred numerically more frequently with tofacitinib (0.9%) than with placebo (0.0%; Table 3). IRs for serious infections were similar between treatment groups in the maintenance cohort and in the overall cohort (Table 4). In the overall cohort, the serious infection IR was 2.0 (95% CI, 1.4–2.8).

In the overall cohort, there were 4 serious infection event terms reported more than once: appendicitis (n = 4), anal abscess (n = 2), serious HZ (n = 3), and *Clostridium difficile* infection (n = 2). No serious infections resulted in death. Based on Cox regression analysis, body weight (≥90 kg vs <90 kg) was identified as a significant risk factor for serious infections (hazard ratio [HR], 2.3; 95% CI, 1.1–4.8; $P = .0318$).

Herpes Zoster

In the maintenance cohort, IRs of HZ were numerically higher with tofacitinib 5 mg twice daily versus placebo and statistically higher with tofacitinib 10 mg twice daily versus placebo (Table 4), suggesting dose dependency of the risk of HZ.

In the overall cohort, there were 18 events of HZ adjudicated as OIs (15 were limited to cutaneous involvement, 2 were ophthalmic HZ, and 1 was HZ meningitis). Cox regression analysis identified older age (every 10 years; HR, 1.6; 95% CI, 1.3–1.9; $P < .0001$), prior tumor necrosis factor inhibitor failure (yes vs no; HR, 1.9; 95% CI, 1.2–3.2; $P = .0112$), and nonwhite race (white vs all other races; HR, 0.6; 95% CI, 0.4–1.0; $P = .0455$) as significant risk factors for HZ. The increased risk for HZ in nonwhite races was primarily caused by increased risk in Asian patients. The IR for HZ in Asian patients was 6.5 (95% CI, 3.6–10.9) versus 3.5 (95% CI, 2.5–4.7) in white patients. Further analyses of HZ events in the UC program have been reported by Winthrop et al.[7]

Opportunistic Infections

In the overall cohort, 22 OIs were reported in 21 patients. Most were HZ OIs, accounting for 18 of 22 events (81.8%). The IR of OIs in the overall cohort was 1.3 (95% CI, 0.8–2.0). The 4 non-HZ OIs were 1 case of cytomegalovirus colitis (occurring in OCTAVE Induction 2 with tofacitinib 10 mg twice daily) and 3 cases that occurred during OCTAVE Open (pulmonary cryptococcosis, n = 1; histoplasmosis, n = 1; cytomegalovirus hepatitis, n = 1). Further details of non-HZ OIs are provided in Supplementary Table 1. In the overall cohort, the IR of non-HZ OI was 0.2 (95% CI, 0.1–0.6).

Cox analysis for all OIs (including HZ OIs) identified older age (every 10 years; HR, 1.5; 95% CI, 1.2–2.1; $P = .0040$) as a significant risk factor.

Malignancies

Excluding nonmelanoma skin cancer. In the overall cohort, 11 patients had malignancies (excluding NMSC), all during OCTAVE Open. Of these 11 patients, 8 had received prior tumor necrosis factor inhibitor treatment, and all had received prior treatment with thiopurines. There was no pattern in the types of malignancy observed, with 1 case reported for each of the following cancers: cervical cancer, hepatic angiosarcoma, cholangiocarcinoma, cutaneous leiomyosarcoma, Epstein-Barr-virus-associated lymphoma, renal cell carcinoma, essential thrombocythemia, acute myeloid leukemia, adenocarcinoma of colon, lung cancer, and breast cancer. The patient with cholangiocarcinoma developed metastases to the peritoneum, which was reported as a second event. Three events resulted in death (hepatic angiosarcoma, cholangiocarcinoma, and acute myeloid leukemia). In the overall cohort, IR of malignancy (excluding NMSC) including all 11 patients with events was 0.7 (95% CI, 0.3–1.2).

Nonmelanoma skin cancer. In the overall cohort, IR of NMSC was 0.7 (95% CI, 0.3–1.2), based on 11 patients with events. Among the 11 patients with NMSC, 6 had prior history of NMSC, 10 had prior use of immunosuppressant therapies, and 10 had prior treatment with tumor necrosis factor inhibitors. Five patients had squamous cell carcinoma, 4 patients had basal cell carcinoma, and 2 patients had both squamous cell carcinoma and basal cell carcinoma events, resulting in a squamous cell carcinoma/basal cell carcinoma ratio of 7:6. All patients with squamous cell carcinoma had prior exposure to thiopurines, and most had prior history of NMSC. Cox regression analysis for NMSC identified age (every 10 years; HR, 2.2; 95% CI, 1.4–3.5; $P = .0003$) and prior tumor necrosis factor inhibitor failure (yes vs no; HR, 11.3; 95% CI, 1.4–88.3; $P = .0210$) as significant risk factors.

Major Adverse Cardiovascular Events

In the overall cohort, the IR of MACE was 0.2 (95% CI, 0.1–0.6), based on 4 patients with events. All 4 MACE (hemorrhagic stroke, aortic dissection, acute coronary syndrome, and myocardial infarction) were serious adverse events. The aortic dissection event resulted in

death. The hemorrhagic stroke event resulted in permanent tofacitinib discontinuation, and was reported as ongoing as of December 2016. The myocardial infarction and acute coronary syndrome events led to temporary discontinuation of tofacitinib and resolved. Based on medical history, pre-existing cardiovascular risk factors were identified for the acute coronary syndrome, myocardial infarction, and hemorrhagic stroke events.

Gastrointestinal Perforations

In the overall cohort, the IR of GI perforation was 0.2 (95% CI, 0.0–0.5), based on 3 patients with events. All 3 GI perforations were serious adverse events. One patient who received tofacitinib 10 mg twice daily in OCTAVE Induction 1 had perforation in the descending colon. The perforation occurred with the background of active UC inflammation, concomitant use of corticosteroids, and recent endoscopy. One patient in OCTAVE Open who received concomitant nonsteroidal anti-inflammatory drugs, had appendicitis that was adjudicated to be GI perforation. One patient in OCTAVE Open had perforated sigmoid colon. The perforation occurred at the site of the Epstein-Barr virus lymphoma described previously, and with the background of recent oral corticosteroids and recent endoscopy.

Laboratory Parameter Findings

In the UC program, there were no significant changes in laboratory parameters, except for elevations in lipid parameters (Supplementary Figure 1). No clinically meaningful changes were observed in the low-density lipoprotein/high-density lipoprotein ratio. Further details of changes in lipid parameters, hemoglobin, absolute lymphocyte count, and creatine kinase are presented in the Supplementary Material.

Discussion

This integrated safety analysis of tofacitinib UC clinical studies, including data from 1157 patients with UC treated with tofacitinib for up to 4.4 years, showed that tofacitinib was generally well-tolerated. Similar proportions of patients with adverse events and serious adverse events were observed in the placebo and tofacitinib groups in the induction and maintenance cohorts, and serious infections and malignancies were infrequent. In the overall cohort, the safety profile of tofacitinib was generally similar to that of tumor necrosis factor inhibitor therapies, except for the higher IR of HZ.

Increased rates of HZ have previously been observed with tofacitinib in other disease populations. In the UC maintenance cohort, a dose relationship in the risk of HZ was demonstrated. Most HZ events were limited to cutaneous involvement over 1 or 2 adjacent dermatomes, and did not require permanent discontinuation. In this study, multivariate Cox regression analyses identified advancing age, prior failure of tumor necrosis factor inhibitors, and nonwhite race as significant risk factors for HZ. Baseline corticosteroid use was not identified to be a statistically significant factor associated with HZ in this study in the context of mandatory corticosteroid taper in the UC phase 3 maintenance and OLE studies, but was found to be a significant risk factor in the larger rheumatoid arthritis experience.[8] In a study of live zoster vaccination in patients with rheumatoid arthritis, vaccine responses were not diminished by tofacitinib treatment.[9] Further studies (eg, with HZ subunit vaccines) are needed regarding the use of zoster vaccination in patients with inflammatory bowel disease.

Increased risk of certain types of malignancy has been reported in patients with inflammatory bowel disease receiving thiopurines, including lymphoma[10] and NMSC.[11] Of the 11 patients with malignancies (excluding NMSC) in this analysis, most had received prior therapy with thiopurines, and most had received prior tumor necrosis factor inhibitors. Similarly, 10 of 11 patients who had NMSC had prior treatment with thiopurines, and observational data have shown that risk of NMSC associated with thiopurines persists following their discontinuation.[11]

In the UC program, tofacitinib treatment was associated with increases in lipid levels (without changes in the low-density lipoprotein/high-density lipoprotein ratio) similar to prior observations in other patient populations. However, MACE occurred infrequently during the UC program. Three of the 4 MACE occurred in patients with pre-existing cardiovascular risk factors. In the tofacitinib rheumatoid arthritis clinical development program, IRs of cardiovascular events were low, despite changes in lipid parameters.[12]

Three GI perforations were observed in the UC program, 2 of which occurred in patients at risk for intestinal perforations, such as active severe UC or intestinal lymphoma. The IR of GI perforation in the overall cohort was not higher than that observed in the placebo group in the maintenance cohort.

In the UC program, the magnitude and time course of changes in laboratory parameters with tofacitinib (including increases in serum lipid and creatine kinase levels, and decreases in absolute lymphocyte count), when adjusted for the effect of placebo, appeared generally similar to those reported during the rheumatoid arthritis program.[3,4]

IRs of adverse events of special interest in the tofacitinib UC program were generally consistent with those reported in the rheumatoid arthritis program.[3,4] With the exception of the increased rate of HZ, the safety profile of tofacitinib in the UC overall cohort was also similar to that observed in UC clinical trials of vedolizumab[13] and tumor necrosis factor inhibitor

therapies.[14–17] Furthermore, tofacitinib safety was similar to that reported for tumor necrosis factor inhibitor–treated patients with UC from the external Truven MarketScan database.[5] Key exclusion criteria used in the tofacitinib UC clinical trials were applied when defining the Truven comparison cohort; however, it is acknowledged that direct comparison of clinical trial data with claims data is difficult. In the absence of head-to-head trials or actual real-world evidence, the Truven data may be useful in contextualizing the safety profile of tofacitinib with that of existing UC therapies.

Limitations of this analysis include the relatively short-term exposure to tofacitinib treatment in the UC program. In addition, the tofacitinib group in the overall cohort included patients who could have been assigned different tofacitinib doses across studies, and thus does not give a clear evaluation of dose dependency. Finally, because of the relatively low number of events observed, risk factor analysis was not performed for all adverse events of special interest. Nevertheless, the safety profile of tofacitinib in patients with UC was consistent with that observed in the tofacitinib rheumatoid arthritis program.[3–5]

In conclusion, the safety profile of tofacitinib in the UC clinical development program was manageable. Tofacitinib treatment in patients with UC was associated with dose-dependent risk of HZ. Compared with prior experience with tofacitinib in rheumatoid arthritis, no new or unexpected safety signals were identified. These safety findings support the long-term use of tofacitinib 5 and 10 mg twice daily in patients with moderately to severely active UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.11.035.

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meet the research criteria outlined on Pfizer.com. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers via a secured portal.

Conflicts of interest

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