Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-022-07794-0

ORIGINAL ARTICLE

Impact of Concomitant Corticosteroids on Tofacitinib Induction Efficacy and Infection Rates in Ulcerative Colitis

Gary R. Lichtenstein[1] · Benjamin L. Cohen[2] · Leonardo Salese[3] · Irene Modesto[4] · Wenjin Wang[3] · Gary Chan[3] · Haytham Mohamed Ahmed[5] · Chinyu Su[3] · Laurent Peyrin-Biroulet[6]

Received: 8 February 2022 / Accepted: 5 December 2022

Abstract

Background Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of ulcerative colitis.

Aim To report efficacy and infection rates in patients receiving tofacitinib induction treatment, by baseline corticosteroid status.

Methods We evaluated efficacy and safety data from OCTAVE Induction 1&2 in patients with moderately-to-severely active ulcerative colitis who received tofacitinib 10 mg twice daily or placebo for 8 weeks, based on induction baseline oral corticosteroid use (Corticosteroid-Yes/No) and dose (< 20/ ≥ 20 mg/day). Infections of interest included serious infections, herpes zoster (HZ), and adjudicated opportunistic infections (OIs).

Results At OCTAVE Induction 1&2 baseline, 478/1092 (43.8%) patients were receiving corticosteroids. Tofacitinib demonstrated significant induction efficacy versus placebo for both Corticosteroid-Yes and Corticosteroid-No. With adjustment for prior tumor necrosis factor inhibitor and immunosuppressant failure, there were no statistically significant differences in remission and clinical response rates for Corticosteroid-Yes versus Corticosteroid-No. Among tofacitinib-treated patients, HZ and OIs occurred more frequently in Corticosteroid-Yes versus Corticosteroid-No, regardless of dose (< 20 mg vs. ≥ 20 mg). Infection incidence rates (regardless of severity/seriousness) during tofacitinib induction were generally similar regardless of baseline corticosteroid use. The proportion of tofacitinib-treated patients with HZ was 0.2% for Corticosteroid-No versus 1.1% for Corticosteroid-Yes < 20 mg and 1.0% for Corticosteroid-Yes ≥ 20 mg. Two out of three patients had HZ OIs.

Conclusions Tofacitinib induction efficacy (clinical response and remission) was similar in baseline corticosteroid subgroups. Infections of interest were rare; HZ and OIs occurred more frequently among those receiving tofacitinib and corticosteroids versus those receiving tofacitinib without corticosteroids.

Trial Registration http://www.clinicaltrials.gov (NCT01465763[21/10/2011]; NCT01458951[21/10/2011]).

Keywords Induction therapy · Infections · Corticosteroid · Janus kinase inhibitor

Introduction

Ulcerative colitis is an idiopathic inflammatory disorder that affects the mucosal surface of the colon and rectum, characterized by a chronic and relapsing course [1]. Although corticosteroids are frequently used as induction therapy for patients with ulcerative colitis [2], they are not recommended for maintenance treatment, due to their lack of efficacy as a maintenance agent [2] and their association with multiple adverse effects [3]. This has led professional societies to advocate for a reduction in corticosteroid use, or a corticosteroid-sparing approach to ulcerative colitis management [2, 4]. Patients with immune-mediated disorders receiving corticosteroids are at increased risk of serious or opportunistic infections [5, 6]. In a long-term safety study of infliximab in patients with Crohn's disease, multivariate regression analyses indicated prednisone use to be a significant predictor of serious infection and mortality [6].

Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of ulcerative colitis. Tofacitinib efficacy and safety was demonstrated in two Phase 3 induction studies (OCTAVE Induction 1 and 2), a Phase 3 maintenance study (OCTAVE Sustain) [7], and an open-label, long-term extension study (OCTAVE Open) [8]. In OCTAVE

✉ Irene Modesto
irene.modesto@pfizer.com

Extended author information available on the last page of the article

Published online: 04 February 2023

Induction 1 and 2, patients were allowed stably dosed concomitant corticosteroids up to a maximum dose of 25 mg/day oral prednisone or equivalent; in the maintenance study, OCTAVE Sustain, tapering of corticosteroids was mandatory [7]. The risk of infectious events associated with ulcerative colitis pharmacotherapy is a crucial consideration for patients and physicians. It is important to understand whether concomitant corticosteroid use may affect the risk of infections in patients treated with tofacitinib. Winthrop et al. have recently reported the incidence of infections from the tofacitinib ulcerative colitis clinical program [9]. Here, we evaluated induction efficacy and risk of infections of interest with tofacitinib 10 mg twice daily (b.d.) treatment, stratified by baseline corticosteroid use in OCTAVE Induction 1 and 2.

Methods

Patients and Study Design

Full details of OCTAVE Induction 1 and 2 have been reported previously [7]. In brief, patients (≥ 18 years of age and had previously failed, or were intolerant to, treatment with corticosteroids, immunosuppressants, and/or tumor necrosis factor inhibitors [TNFi]) received tofacitinib 10 mg b.d. or placebo for 8 weeks (Fig. 1). Stably dosed concomitant corticosteroids (maximum of 25 mg/day oral prednisone or equivalent) and 5-aminosalicylates were permitted in OCTAVE Induction 1 and 2. Concomitant TNFi (8 weeks' washout) and immunosuppressants (azathioprine and 6-mercaptopurine) (2 weeks' washout) were prohibited.

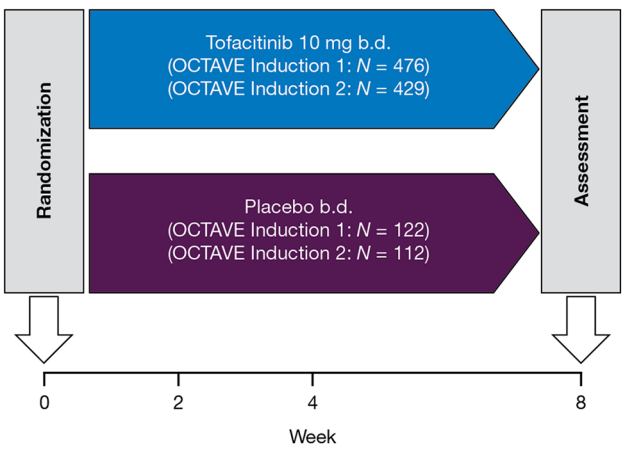


Fig. 1 Study design of OCTAVE Induction 1 and 2. Final complete efficacy assessment at Week 8. Treatment continued up to Week 9. *b.d.* twice daily, *N* number of patients included in each treatment group

All studies were conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines, and were approved by the Institutional Review Board and/or Independent Ethics Committee at each of the investigational centers, or a central Institutional Review Board. All patients provided written informed consent. OCTAVE Induction 1 and 2 are registered on http://www.clinicaltrials.gov (NCT01465763 and NCT01458951).

Key Measures

Efficacy endpoints were derived from the Mayo score, based on the centrally read endoscopic subscore. Remission, endoscopic improvement (defined as mucosal healing in the OCTAVE Induction 1 and 2 protocols), and clinical response endpoints were assessed following 8 weeks of treatment in patients with and without concomitant baseline corticosteroid use. Remission was defined as a total Mayo score of ≤ 2 with no individual subscore > 1, and a rectal bleeding subscore of 0. Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1. Clinical response was defined as a decrease from induction study 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.

Adverse events, which were classified with the use of the Medical Dictionary for Regulatory Activities, were recorded throughout the induction trials. Details on the adverse event reporting for this analysis are provided in Online Resource 1. Serious adverse events were defined as any events that: resulted in death; were life-threatening; resulted in a persistent or significant disability or incapacity; required patient hospitalization or prolongation of existing hospitalization; or resulted in a congenital anomaly or birth defect.

Infections of interest included herpes zoster, serious infections, and adjudicated opportunistic infections. Serious infections were defined, per protocol, as infections requiring parenteral antimicrobial therapy or hospitalization, or meeting other serious adverse event reporting criteria. Opportunistic infections were based on a review by an independent adjudication committee (see Online Resource 1). Herpes zoster events that were confirmed as opportunistic infections were classified as multidermatomal (non-adjacent or > 2 adjacent dermatomes that were not considered disseminated) or disseminated. All other herpes zoster events were limited to cutaneous involvement with ≤ 2 adjacent dermatomes. Infection events were counted up to 28 days beyond the last dose of tofacitinib or placebo.

Statistical Analysis

Efficacy and safety data were summarized by oral corticosteroid use at induction baseline (Yes/No) and oral corticosteroid dose, using < 20 mg/day or ≥ 20 mg/day to represent lower and higher doses of oral corticosteroids, respectively. These post hoc analyses are based on pooled data from OCTAVE Induction 1 and 2, with a focus on systemic corticosteroid exposure; therefore, patients receiving budesonide or beclomethasone were excluded. Efficacy endpoints are reported for the full analysis set (all patients who underwent randomization) and patients with missing binary efficacy data were treated as non-responders. Differences (95% confidence intervals [CIs]) from placebo were based on the normal approximation for the difference in binomial proportions. For a comparison of differences between tofacitinib and placebo, the *p* values were based on the Cochran–Mantel–Haenszel χ^2 test. A logistic regression model was used to compare the adjusted treatment effects (odds ratios) between corticosteroid dose subgroups, controlled for prior TNFi and immunosuppressant failure status. For between-subgroup comparisons of treatment effects, odds ratios and *p* values were obtained based on logistic regression models with prior TNFi failure, prior immunosuppressant failure, prior oral corticosteroid use, oral corticosteroid use at baseline, and treatment as covariates.

Table 1 Baseline demographics and disease characteristics stratified by baseline oral corticosteroid use

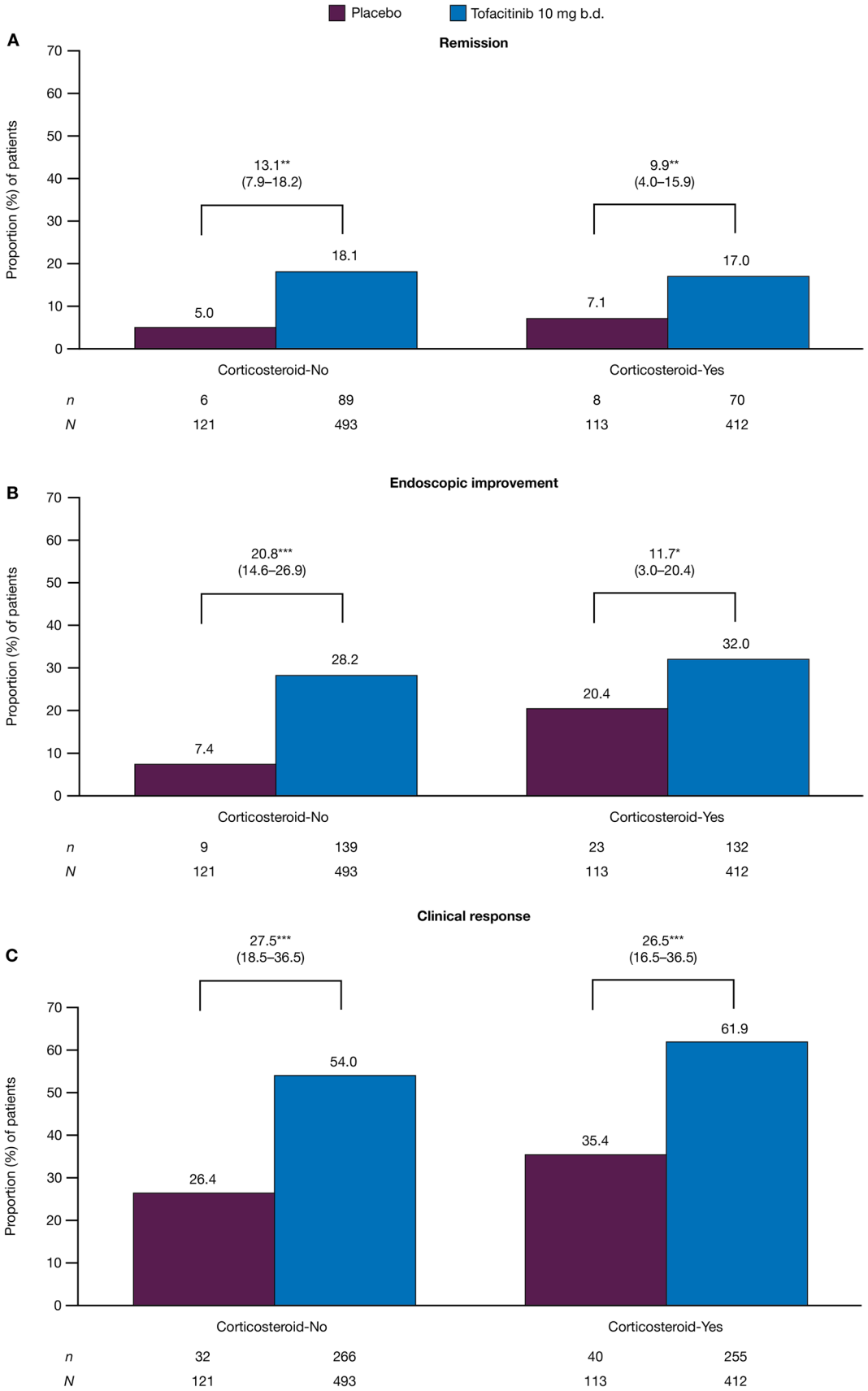
	Corticosteroid-Yes[a]				Corticosteroid-No	
	< 20 mg/day		≥ 20 mg/day			
	Placebo *N* = 48	Tofacitinib 10 mg b.d. *N* = 178	Placebo *N* = 54	Tofacitinib 10 mg b.d. *N* = 198	Placebo *N* = 121	Tofacitinib 10 mg b.d. *N* = 493
Age in years, mean (SD)	43.4 (16.6)	41.9 (15.7)	40.0 (13.8)	39.9 (13.6)	40.2 (13.7)	41.6 (13.3)
Female, *n* (%)	24 (50.0)	78 (43.8)	21 (38.9)	71 (35.9)	52 (43.0)	203 (41.2)
Smoking status, *n* (%)						
Never smoked	31 (64.6)	108 (60.7)	38 (70.4)	129 (65.2)	86 (71.1)	308 (62.5)
Current smoker	2 (4.2)	6 (3.4)	2 (3.7)	13 (6.6)	4 (3.3)	27 (5.5)
Ex-smoker	15 (31.3)	64 (36.0)	14 (25.9)	56 (28.3)	31 (25.6)	158 (32.0)
Total Mayo score at baseline, mean (SD)	9.3 (1.5)	8.9 (1.5)	8.6 (1.6)	9.2 (1.4)	9.1 (1.4)	8.9 (1.5)
Extent of disease, *n* (%)						
Proctosigmoiditis	5 (10.4)	28 (15.7)	8 (14.8)	24 (12.1)	21 (17.5)	78 (15.9)
Left-sided colitis	21 (43.8)	57 (32.0)	21 (38.9)	77 (38.9)	31 (25.8)	161 (32.8)
Pancolitis	22 (45.8)	93 (52.2)	25 (46.3)	97 (49.0)	68 (56.7)	251 (51.1)
Prior TNFi use, *n* (%)	31 (64.6)	113 (63.5)	29 (53.7)	96 (48.5)	61 (50.4)	249 (50.5)
Prior TNFi failure, *n* (%)	29 (60.4)	110 (61.8)	27 (50.0)	89 (44.9)	59 (48.8)	237 (48.1)
Prior immunosuppressant use, *n* (%)	38 (79.2)	141 (79.2)	36 (66.7)	151 (76.3)	80 (66.1)	364 (73.8)
Prior immunosuppressant failure, *n* (%)[b]	37 (77.1)	136 (76.4)	35 (64.8)	149 (75.3)	80 (66.1)	349 (70.8)
Prior corticosteroid use, *n* (%)[c]	47 (97.9)	174 (97.8)	54 (100)	190 (96.0)	105 (86.8)	413 (83.8)
Prior corticosteroid failure, *n* (%)	33 (68.8)	129 (72.5)	46 (85.2)	151 (76.3)	93 (76.9)	342 (69.4)
Baseline corticosteroid daily dose, *n* (%)						
< 15 mg/day	35 (72.9)	122 (68.5)	0 (0)	0 (0)	N/A	N/A
≥ 15 mg/day	13 (27.1)	56 (31.5)	54 (100)	198 (100)	N/A	N/A
5-aminosalicylates use at baseline, *n* (%)	38 (79.2)	118 (66.3)	39 (72.2)	143 (72.2)	82 (67.8)	363 (73.6)

b.d. twice daily, *Corticosteroid-No* not receiving baseline oral corticosteroids, *Corticosteroid-Yes* receiving baseline oral corticosteroids, *N* number of patients included in the subgroup, *n* number of unique patients with a particular characteristic, *N/A* not applicable, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitor

[a]Excludes patients who were receiving budesonide or beclomethasone

[b]Includes antineoplastic agents, azathioprine, cyclosporine, 6-mercaptopurine, methotrexate, methotrexate sodium, mycophenolate mofetil, tacrolimus, thioguanine

[c]Eight patients in the tofacitinib 10 mg b.d. group were newly started on oral corticosteroids at doses ≥ 20 mg/day


Placebo
Tofacitinib 10 mg b.d.
A
Remission
Proportion (%) of patients
70
60
50
40
30
20
10
0
13.1**
(7.9–18.2)
9.9**
(4.0–15.9)
18.1
17.0
5.0
7.1
Corticosteroid-No
Corticosteroid-Yes
n 6 89 8 70
N 121 493 113 412
B
Endoscopic improvement
Proportion (%) of patients
20.8***
(14.6–26.9)
11.7*
(3.0–20.4)
28.2
32.0
20.4
7.4
Corticosteroid-No
Corticosteroid-Yes
n 9 139 23 132
N 121 493 113 412
C
Clinical response
Proportion (%) of patients
27.5***
(18.5–36.5)
26.5***
(16.5–36.5)
61.9
54.0
35.4
26.4
Corticosteroid-No
Corticosteroid-Yes
n 32 266 40 255
N 121 493 113 412

◂**Fig. 2** The proportion of patients (95% CI): **A** in remission; **B** with endoscopic improvement; and **C** with a clinical response at Week 8 of OCTAVE Induction 1 and 2, by baseline oral corticosteroid status (FAS, NRI). *$p < 0.05$; **$p < 0.01$; ***$p < 0.0001$ versus placebo, based on Cochran–Mantel–Haenszel χ^2 test. Remission was defined as a total Mayo score of ≤ 2 with no individual subscore > 1, and a rectal bleeding subscore of 0. Endoscopic improvement (defined as mucosal healing in the OCTAVE Induction 1 and 2 protocols) was defined as a Mayo endoscopic subscore of 0 or 1. Clinical response was defined as a decrease from induction study 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. Differences (95% CIs) from placebo are based on the normal approximation for the difference in binomial proportions. *b.d.* twice daily, *Corticosteroid-No* not receiving baseline oral corticosteroids, *Corticosteroid-Yes* receiving baseline oral corticosteroids, *CI* confidence interval, *FAS* full analysis set, *N* number of patients in the subgroup, *n* number of patients with the specified response in the given subgroup, *NRI* non-responder imputation

Results

Baseline Demographics and Clinical Characteristics

Of 1139 patients enrolled into OCTAVE Induction 1 and 2, 983/1092 (90.0%) patients had prior corticosteroid use and 478/1092 (43.8%; excluding 47 patients receiving budesonide or beclomethasone) patients were receiving oral corticosteroids at baseline (Table 1). Among those receiving steroids, 47.3% (226/478) received a dose of < 20 mg/day and 52.7% (252/478) received a dose of ≥ 20 mg/day. Of those receiving baseline oral corticosteroids < 20 mg/day, 30.5% (69/226) were receiving a baseline daily dose of ≥ 15 mg/day (Table 1).

OCTAVE Induction 1 and 2 baseline characteristics were generally similar between treatment groups when stratified by baseline oral corticosteroid use and dose, although a numerically greater proportion of patients receiving baseline oral corticosteroids < 20 mg/day had prior TNFi and immunosuppressant use and failure versus those receiving baseline oral corticosteroids ≥ 20 mg/day and those without baseline corticosteroid use (Table 1).

Efficacy

Without adjustment for prior TNFi and immunosuppressant failure, a statistically significant treatment effect of tofacitinib 10 mg b.d. versus placebo was observed for remission, endoscopic improvement, and clinical response at Week 8, for patients with and without baseline oral corticosteroid use (Fig. 2). For example, 17.0% and 18.1% of patients treated with tofacitinib, with and without baseline oral corticosteroid use, respectively, achieved remission vs. 7.1% and 5.0% of patients treated with placebo ($p = 0.0089$ and $p = 0.0004$, respectively). The observed treatment effects (differences vs. placebo) for remission and endoscopic improvement, without adjustment for prior TNFi and immunosuppressant failure, were numerically greater for patients without baseline oral corticosteroid use versus patients with baseline oral corticosteroid use (remission: difference = 13.1 [95% CI 7.9–18.2] vs. 9.9 [95% CI 4.0–15.9], respectively; endoscopic improvement: 20.8 [95% CI 14.6–26.9] vs. 11.7 [95% CI 3.0–20.4], respectively; Fig. 2).

After adjustment for prior TNFi and immunosuppressant failure, the estimated treatment effects for remission and endoscopic improvement, in terms of adjusted odds ratios (tofacitinib 10 mg b.d. vs. placebo), were numerically greater for patients without baseline oral corticosteroid use versus patients with baseline oral corticosteroid use < 20 mg/day and ≥ 20 mg/day (remission: adjusted odds ratio = 4.5 [95% CI 1.9–10.5] vs. 2.9 [95% CI 0.8–10.1] and 3.2 [95% CI 1.1–9.6], respectively; endoscopic improvement: 5.2 [95% CI 2.5–10.6] vs. 2.3 [95% CI 1.0–5.4] and 1.5 [95% CI 0.8–3.1], respectively; Table 2). However, the differences in treatment effects between the subgroups were not statistically significant, except for endoscopic improvement at Week 8. For endoscopic improvement, the estimated treatment effect, in terms of adjusted odds ratio (tofacitinib 10 mg b.d. vs. placebo), was significantly greater in patients without baseline oral corticosteroid use versus patients with baseline oral corticosteroid use at ≥ 20 mg/day (unadjusted $p = 0.0163$). For clinical response, the adjusted odds ratios were similar for all three subgroups, and there were no statistically significant differences among the subgroups (Table 2).

For each of the three subgroups (< 20 mg/day, ≥ 20 mg/day, no baseline oral corticosteroid use), the odds ratios (tofacitinib 10 mg b.d. vs. placebo) were significantly greater than 1.0 for all endpoints at a significance level of 0.05, with the exception of remission in the subgroup of patients receiving baseline oral corticosteroids < 20 mg/day and endoscopic improvement in the subgroup of patients receiving baseline oral corticosteroids ≥ 20 mg/day (Table 2).

Overall Safety

In OCTAVE Induction 1 and 2, serious adverse events occurred with similar frequency among treatment groups, regardless of baseline oral corticosteroid use and dose subgroups (Fig. 3).

Infections of Interest

In OCTAVE Induction 1 and 2, infections of interest were generally infrequent, with similar frequency among those with baseline oral corticosteroids, regardless of dose (Fig. 4). There were five serious infections in patients who received tofacitinib 10 mg b.d.; none of these patients were receiving baseline oral corticosteroids. The five serious infections

Table 2 Summary of efficacy at Week 8 of OCTAVE Induction 1 and 2 by baseline oral corticosteroid use and dose (FAS, NRI)

	Placebo[a]	Tofacitinib 10 mg b.d.[a]	Difference from placebo (95% CI)	Adjusted odds ratio (95% CI)[b]	Odds ratio *p* value (tofacitinib vs. placebo)[b]	*p* value (tofacitinib vs. placebo) between subgroups: Corticosteroid-Yes vs. Corticosteroid-No	*p* value (tofacitinib vs. placebo) between subgroups: ≥ 20 mg vs. < 20 mg
Remission, *n*/*N* (%)							
Corticosteroid-Yes < 20 mg/day	3/48 (6.3)	28/178 (15.7)	9.5 (0.8–18.2)	2.9 (0.8–10.1)	0.0954	0.5754	0.8951
Corticosteroid-Yes ≥ 20 mg/day	4/54 (7.4)	40/198 (20.2)	12.8 (3.8–21.7)	**3.2 (1.1–9.6)**	0.0344	0.6487	
Corticosteroid-No	6/121 (5.0)	89/493 (18.1)	13.1 (7.9–18.2)	**4.5 (1.9–10.5)**	0.0007		
Endoscopic improvement, *n*/*N* (%)							
Corticosteroid-Yes < 20 mg/day	8/48 (16.7)	55/178 (30.9)	14.2 (1.7–26.8)	**2.3 (1.0–5.4)**	0.0482	0.1547	0.4498
Corticosteroid-Yes ≥ 20 mg/day	14/54 (25.9)	69/198 (34.8)	8.9 (–4.5–22.4)	1.5 (0.8–3.1)	0.2258	0.0163	
Corticosteroid-No	9/121 (7.4)	139/493 (28.2)	20.8 (14.6–26.9)	**5.2 (2.5–10.6)**	< 0.0001		
Clinical response, *n*/*N* (%)							
Corticosteroid-Yes < 20 mg/day	18/48 (37.5)	110/178 (61.8)	24.3 (8.9–39.7)	**2.8 (1.4–5.4)**	0.0027	0.6300	0.5583
Corticosteroid-Yes ≥ 20 mg/day	18/54 (33.3)	127/198 (64.1)	30.8 (16.6–45.0)	**3.7 (1.9–7.0)**	< 0.0001	0.8420	
Corticosteroid-No	32/121 (26.4)	266/493 (54.0)	27.5 (18.5–36.5)	**3.4 (2.2–5.3)**	< 0.0001		

Remission was defined as a total Mayo score of ≤ 2 with no individual subscore > 1, and a rectal bleeding subscore of 0. Endoscopic improvement (defined as mucosal healing in the OCTAVE Induction 1 and 2 protocols) was defined as a Mayo endoscopic subscore of 0 or 1. Clinical response was defined as a decrease from induction study 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. Differences (95% CIs) from placebo are based on the normal approximation for the difference in binomial proportions. Bold values are statistically significant ($p < 0.05$)

b.d. twice daily, *Corticosteroid-No* not receiving baseline oral corticosteroids, *Corticosteroid-Yes* receiving baseline oral corticosteroids, *CI* confidence interval, *FAS* full analysis set, *N* number of patients in the subgroup, *n* number of patients with the efficacy response in the given subgroup, *NRI* non-responder imputation, *TNFi* tumor necrosis factor inhibitor

[a]Excludes patients who were receiving budesonide or beclomethasone

[b]Between-subgroup comparisons of the adjusted odds ratios (tofacitinib vs. placebo). Odds ratios and *p* values were obtained based on the logistic regression model: endpoint response status = prior TNFi failure + prior immunosuppressant failure + treatment + oral corticosteroid use at baseline + treatment × oral corticosteroid use at baseline

comprised one event each of anal abscess, *Clostridium difficile* infection, furuncle, otitis externa, and pneumonia, all of which resolved.

Three patients who received tofacitinib 10 mg b.d., two of whom were receiving baseline oral corticosteroids, had opportunistic infections (based on adjudication). Two out of the three patients had herpes zoster opportunistic infections. One patient, who was receiving baseline oral corticosteroids at a dose of 7.5 mg/day, had a cytomegalovirus infection (mild in severity; onset day 56), and this event was ongoing at the end of the final study visit; tofacitinib treatment was not interrupted. This patient had a history of prior cytomegalovirus infection (based on evidence of cytomegalovirus in colonic biopsies). Two patients had herpes zoster opportunistic infections, both of which were considered to be moderate in severity. One patient who was not receiving oral corticosteroids had herpes zoster affecting non-adjacent or > 2 adjacent dermatomes, which was not considered disseminated; tofacitinib treatment was stopped temporarily and the herpes zoster event resolved. One patient who was receiving baseline oral corticosteroids at a dose of 20 mg/day had disseminated herpes zoster (> 6 dermatomes); tofacitinib treatment continued and herpes zoster was still present at the final study visit.

Five tofacitinib-treated patients had herpes zoster, compared with one placebo-treated patient. Four out of the five tofacitinib-treated patients were receiving baseline oral corticosteroids. Two patients who were receiving baseline oral

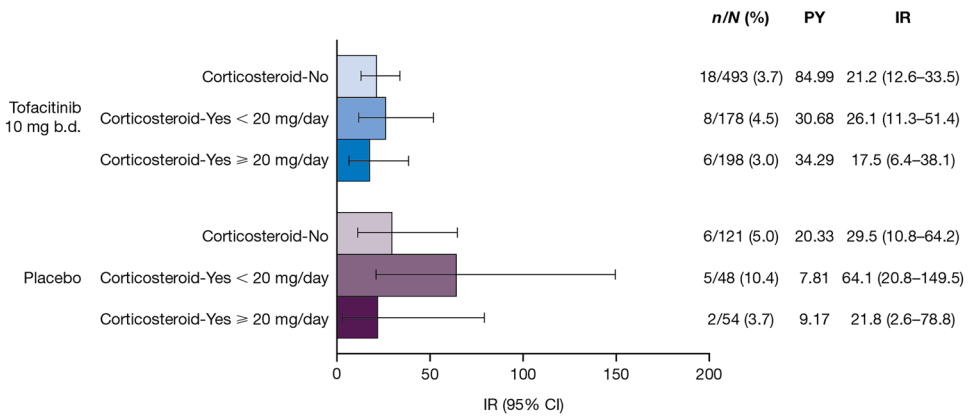


Fig. 3 Serious adverse events in OCTAVE Induction 1 and 2, by baseline oral corticosteroid use and dose. *b.d.* twice daily, *Corticosteroid-No* not receiving baseline oral corticosteroids, *Corticosteroid-Yes* receiving baseline oral corticosteroids, *CI* confidence interval, *IR* incidence rate (unique patients with events per 100 PY of exposure), *N* number of patients in the subgroup, *n* number of patients with events in the given subgroup, *PY* patient-years

corticosteroids < 20 mg/day had herpes zoster; one patient who was receiving baseline oral corticosteroids at a dose of 15 mg/day had herpes zoster that was confined to the skin and classed as mild, and one patient who was receiving baseline oral corticosteroids at a dose of 10 mg/day had disseminated herpes zoster (adjudicated as an opportunistic infection) that was moderate in severity. Both patients continued with tofacitinib treatment, and herpes zoster was still present at the final study visit. Two patients who were receiving oral corticosteroids ≥ 20 mg/day (doses of 20 and 25 mg/day) had herpes zoster (confined to the skin) that was moderate in severity and was still present at the final study visit. One patient (without baseline oral corticosteroid use) had herpes zoster affecting non-adjacent or > 2 adjacent dermatomes, which was not considered disseminated (adjudicated as an opportunistic infection); tofacitinib treatment was stopped temporarily and herpes zoster was still present at the final study visit. The placebo-treated patient (without baseline oral corticosteroid use) had herpes zoster that was mild in severity and resolved. None of the herpes zoster events were classed as serious adverse events.

Discussion

Tofacitinib demonstrated significant induction efficacy versus placebo for patients with and without baseline oral corticosteroid use. The treatment effects of tofacitinib versus placebo, without adjustment for prior TNFi and immunosuppressant failure, were numerically greater for patients without baseline oral corticosteroid use versus patients with baseline oral corticosteroid use. However, with adjustment for prior TNFi and immunosuppressant failure, there were no statistically significant differences in the remission and clinical response rate between patients with and without baseline oral corticosteroid use. For endoscopic improvement, with adjustment for prior TNFi and immunosuppressant failure, the estimated treatment effect (tofacitinib vs. placebo), in terms of odds ratio, was significantly greater in patients without baseline oral corticosteroid use versus patients with baseline oral corticosteroid use (≥ 20 mg/day). There were no statistically significant differences in the efficacy (remission, endoscopic improvement, and clinical response) of tofacitinib in patients receiving baseline oral corticosteroids < 20 mg/day versus ≥ 20 mg/day.

A similar observation was noted in patients with ulcerative colitis receiving vedolizumab; the difference from placebo was numerically higher in patients receiving vedolizumab monotherapy versus vedolizumab and corticosteroids combination therapy [10]. A meta-analysis of data from randomized trials of TNFi in patients with Crohn's disease concluded that patients who were receiving concomitant corticosteroids during TNFi induction therapy did not have higher rates of clinical improvement compared with patients not receiving concomitant corticosteroids during induction therapy [11]. Here, the treatment effect differences, without adjustment for prior TNFi and immunosuppressant failure, may be due to those patients receiving baseline oral corticosteroids, in which there was a higher proportion of prior TNFi and immunosuppressant failure, suggesting a more refractory group. However, data from the placebo group shows a numerically higher proportion of patients achieving endpoints with versus without concomitant baseline oral corticosteroids. It is possible that patients stopped their current treatment to enroll into these trials, oral corticosteroids were prescribed for symptom control, and this in turn led to a higher placebo response.

The use of corticosteroids in combination with other immunosuppressants and biologic agents has been shown to be associated with the development of opportunistic infections in patients with inflammatory bowel disease [12]. In a long-term safety study of infliximab in patients with inflammatory bowel disease, concomitant treatment with corticosteroids was the only independent risk factor for infections [13]. In an analysis of claims data from patients with Crohn's disease, treatment with corticosteroids was associated with an increased risk of infection [14]. In rheumatoid arthritis, corticosteroids have been shown to be dose-dependently

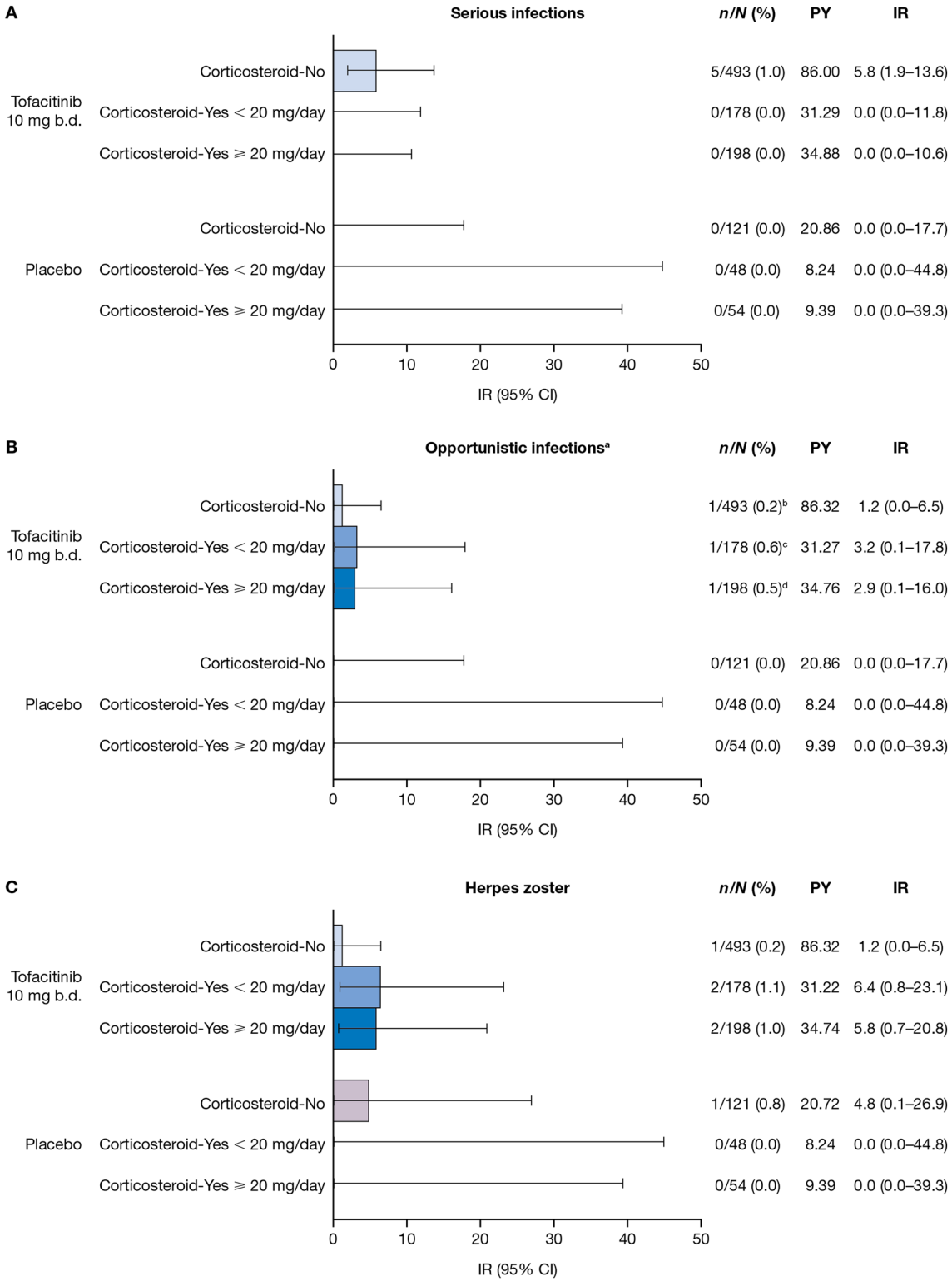


Fig. 4 Incidence rates of: **A** serious infections; **B** opportunistic infections; and **C** herpes zoster events in OCTAVE Induction 1 and 2, by baseline oral corticosteroid use and dose. [a]Excludes tuberculosis and herpes zoster with two adjacent dermatomes. [b]Herpes zoster (non-adjacent or > 2 adjacent dermatomes). [c]Cytomegalovirus infection. [d]Herpes zoster (disseminated). *b.d.* twice daily, *Corticosteroid-No* not receiving baseline oral corticosteroids, *Corticosteroid-Yes* receiving baseline oral corticosteroids, *CI* confidence interval, *IR* incidence rate (unique patients with events per 100 PY of exposure), *N* number of patients in the subgroup, *n* number of patients with events in the given subgroup, *PY* patient-years

linked to increased risk for both serious and non-serious infections [15–17].

Proportions of serious adverse events and infections of interest in OCTAVE Induction 1 and 2 were generally infrequent and similar between baseline oral corticosteroid doses (< 20 mg/day or ≥ 20 mg/day). Ulcerative colitis is a known risk factor for herpes zoster, and the use of corticosteroids, immunosuppressants, and TNFi significantly increased the risk of herpes zoster in patients with inflammatory bowel disease [18–22]. Furthermore, the reactivation of varicella zoster virus in patients with ulcerative colitis treated with tofacitinib has previously been reported [23]. Herpes zoster occurred in a higher proportion of patients receiving tofacitinib with baseline oral corticosteroid use compared with patients receiving tofacitinib without baseline oral corticosteroid use. Four out of the five patients who had herpes zoster while receiving tofacitinib were also receiving concomitant oral corticosteroids (three of which were confined to the skin). Three patients continued with tofacitinib therapy and one temporarily stopped tofacitinib treatment. Herpes zoster is theoretically preventable with vaccination, and guidance on the management and prevention in tofacitinib-treated patients with ulcerative colitis is available [19]. A non-herpes zoster opportunistic infection occurred in a patient receiving tofacitinib 10 mg b.d. and baseline oral corticosteroids. Further evaluation regarding the concomitant use of oral corticosteroids is needed; however, it is prudent to follow a corticosteroid-sparing approach to ulcerative colitis management, by reducing usage and tapering as per society recommendations [2, 4]. In addition, systemic corticosteroid use among patients with inflammatory bowel disease has been found to be a risk factor for adverse COVID-19 outcomes [24]. Therefore, maintaining remission with steroid-sparing treatments is important in managing patients with inflammatory bowel disease in the ongoing COVID-19 pandemic [24].

These were post hoc analyses and are limited by the relatively small number of events and short duration of follow-up (8 weeks). Serious infections are relatively rare, and large cohorts of treated patients are required to determine the incidence. The protocol for the maintenance study, OCTAVE Sustain, included mandatory tapering of corticosteroids, making the interpretation of efficacy and safety data by corticosteroid use challenging. OCTAVE Induction 1 and 2, and OCTAVE Sustain, were not designed to examine the incremental benefit of concomitant corticosteroid use.

In conclusion, the data reported here demonstrate efficacy of induction therapy with tofacitinib regardless of baseline oral corticosteroid use. In the short-term, during induction therapy with tofacitinib, infections of interest were rare, with herpes zoster and opportunistic infections occurring more frequently among those receiving tofacitinib and corticosteroids versus those receiving tofacitinib without corticosteroids, as expected [5, 6]. These findings confirm that tofacitinib can be used as monotherapy in patients with ulcerative colitis, but, importantly, physicians should follow local guidelines for steroid tapering.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-022-07794-0.

Acknowledgments These studies were sponsored by Pfizer. The authors would like to thank the patients, investigators, and study teams involved in OCTAVE Induction 1 and 2. Medical writing support, under the guidance of the authors, was provided by Helen Findlow, PhD, McCann Health Medical Communications, and was funded by Pfizer Inc, New York, NY, USA in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med*. 2015;163:461–464).

Author's contribution GRL, BLC, LS, IM, WW, GC, HMA, CS, and LP-B collected or interpreted the data and drafted and edited the manuscript. All authors approved the final draft of the manuscript for submission, including the authorship list.

Funding This study was sponsored by Pfizer. Medical writing support was funded by Pfizer Inc.

Data availability Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declarations

Competing interests GRL has received research support and/or funding from Celgene, Janssen Ortho Biotech, Pfizer Inc, Takeda, and UCB; consultancy fees from AbbVie, American Regent, Celgene, Cellceutix, Eli Lilly, Endo Pharmaceuticals, Ferring Pharmaceuticals, Gilead Sciences, Janssen Ortho Biotech, Merck, Morphic Therapeutics, Pfizer Inc, Prometheus Laboratories Inc, Romark, Salix/Valeant, Shire, Takeda, and UCB; honoraria from the American College of Gastroenterology, American Regent, Gastroenterology and Hepatology, Merck, Romark, Springer Science and Business Media, and Up-To-Date; and royalties from Professional Communications Inc and SLACK Inc. BLC has been an advisory board member for AbbVie; has received consultancy or speaker fees from AbbVie; and received support/and or funding from Celgene, Bristol-Myers Squibb, Cornerstones, Pfizer Inc, Sublimity Therapeutics, Takeda, TARGET RWE, and Vindico. LS, IM, WW, GC, HMA, and CS are employees and stockholders of Pfizer Inc. LP-B has received honoraria from AbbVie, Allergan, Alma, Amgen, Arena, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Enterome, Ferring Pharmaceuticals, Genentech, Gilead Sciences, Hikma, Index Pharmaceuticals, Janssen, MSD, Nestlé, Pfizer Inc, Pharmacosmos, Roche, Samsung Bioepis, Sandoz, Sterna, Takeda, and Tillotts; grants from AbbVie, MSD, and Takeda; and is a stockholder of CTMA.

Ethical approval All studies were conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. Study protocols were approved by the Institutional Review Board and/or Independent Ethics Committee at each of the investigational centers participating in the studies, or a central Institutional Review Board.

Consent to participate Informed consent was obtained from all individual participants included in the study.

References

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. *Lancet.* 2017;389:1756–1770.
2. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol.* 2019;114:384–413.
3. Salice M, Rizzello F, Calabrese C, Calandrini L, Gionchetti P. A current overview of corticosteroid use in active ulcerative colitis. *Expert Rev Gastroenterol Hepatol.* 2019;13:557–561.
4. Lamb CA, Kennedy NA, Raine T et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut.* 2019;68:s1–106.
5. Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. *Rheum Dis Clin North Am.* 2016;42:157–176.
6. Lichtenstein GR, Feagan BG, Cohen RD et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol.* 2012;107:1409–1422.
7. Sandborn WJ, Su C, Sands BE et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2017;376:1723–1736.
8. Sandborn WJ, Lawendy N, Danese S et al. Safety and efficacy of tofacitinib for treatment of ulcerative colitis: final analysis of OCTAVE Open, an open-label, long-term extension study with up to 7.0 years of treatment. *Aliment Pharmacol Ther.* 2022;55:464–478.
9. Winthrop KL, Loftus EV, Baumgart DC et al. Tofacitinib for the treatment of ulcerative colitis: analysis of infection rates from the ulcerative colitis clinical programme. *J Crohns Colitis.* 2021;15:914–929.
10. Colombel J-F, Loftus EV Jr, Siegel CA et al. P433 Efficacy of vedolizumab with concomitant corticosteroid or immunomodulator use in patients with ulcerative colitis from GEMINI 1 [abstract]. *J Crohns Colitis.* 2015;9:S296–S297.
11. Faleck DM, Shmidt E, Huang R et al. Effect of concomitant therapy with steroids and tumor necrosis factor antagonists for induction of remission in patients with Crohn's disease: a systematic review and pooled meta-analysis. *Clin Gastroenterol Hepatol.* 2021;19:238-245.e234.
12. Toruner M, Loftus EV Jr, Harmsen WS et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology.* 2008;134:929–936.
13. Fidder H, Schnitzler F, Ferrante M et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut.* 2009;58:501–508.
14. Marehbian J, Arrighi HM, Hass S, Tian H, Sandborn WJ. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J Gastroenterol.* 2009;104:2524–2533.
15. Grijalva CG, Kaltenbach L, Arbogast PG, Mitchel EF Jr, Griffin MR. Initiation of rheumatoid arthritis treatments and the risk of serious infections. *Rheumatology (Oxford).* 2010;49:82–90.
16. Strangfeld A, Eveslage M, Schneider M et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis.* 2011;70:1914–1920.
17. Dixon WG, Kezouh A, Bernatsky S, Suissa S. The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study. *Ann Rheum Dis.* 2011;70:956–960.
18. Soh H, Chun J, Han K et al. Increased risk of herpes zoster in young and metabolically healthy patients with inflammatory bowel disease: a nationwide population-based study. *Gut Liver.* 2019;13:333–341.
19. Colombel JF. Herpes zoster in patients receiving JAK inhibitors for ulcerative colitis: mechanism, epidemiology, management, and prevention. *Inflamm Bowel Dis.* 2018;24:2172–2182.
20. Gupta G, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2006;4:1483–1490.
21. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2013;37:420–429.
22. Khan N, Patel D, Trivedi C et al. Overall and comparative risk of herpes zoster with pharmacotherapy for inflammatory bowel diseases: a nationwide cohort study. *Clin Gastroenterol Hepatol.* 2018;16:1919–1927.
23. Winthrop KL, Melmed GY, Vermeire S et al. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. *Inflamm Bowel Dis.* 2018;24:2258–2265.
24. Brenner EJ, Ungaro RC, Gearry RB et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology.* 2020;159:481–491.

Authors and Affiliations

Gary R. Lichtenstein[1] · Benjamin L. Cohen[2] · Leonardo Salese[3] · Irene Modesto[4] · Wenjin Wang[3] · Gary Chan[3] · Haytham Mohamed Ahmed[5] · Chinyu Su[3] · Laurent Peyrin-Biroulet[6]

Gary R. Lichtenstein
gary.lichtenstein@pennmedicine.upenn.edu

Benjamin L. Cohen
cohenb3@ccf.org

Leonardo Salese
ls7799@yahoo.com

Wenjin Wang
wenjin.wang@pfizer.com

Gary Chan
gary.chan@pfizer.com

Haytham Mohamed Ahmed
haitham.m.ahmed.mohamed@pfizer.com

Chinyu Su
chinyu.su@pfizer.com

Laurent Peyrin-Biroulet
peyrinbiroulet@gmail.com

1 Division of Gastroenterology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

2 Department of Gastroenterology, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

3 Pfizer Inc, Collegeville, PA, USA

4 Pfizer Inc, 235 East 42nd Street, New York, NY 10017, USA

5 Pfizer Inc, Dubai, UAE

6 Department of Gastroenterology, Inserm U1256 NGERE, Nancy University Hospital, University of Lorraine, Vandœuvre-lès-Nancy, France