Tofacitinib Induction Therapy Reduces Symptoms Within 3 Days for Patients With Ulcerative Colitis

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BACKGROUND & AIMS: **Tofacitinib is an oral, small molecule inhibitor of JAK for the treatment of ulcerative colitis (UC). We evaluated the onset of symptom improvement in post-hoc analyses of data from 2 phase 3 trials of induction therapy with tofacitinib in patients with UC (OCTAVE Induction 1 and 2).**

METHODS: **The studies comprised patients with moderate to severe active UC who were intolerant to, or failed by previous treatment with, corticosteroids, thiopurines, and/or tumor necrosis factor (TNF) antagonists. Patients received tofacitinib (10 mg twice daily, n = 905) or placebo (n = 234) for 8 weeks. Daily Mayo stool frequency and rectal bleeding subscores were calculated using diary data from the first 15 days of therapy. We analyzed data from subgroups including failure of prior anti-TNF therapy, baseline corticosteroid use, and baseline serum levels of C-reactive protein.**

RESULTS: **Mean changes were significantly greater in patients given tofacitinib vs placebo in reductions from baseline stool frequency subscore (tofacitinib: −0.27 vs placebo: −0.11; $P < .01$), total number of daily bowel movements (−1.06 vs −0.27; $P < .0001$), and rectal bleeding subscore (−0.30 vs −0.14; $P < .01$) by day 3. Compared with placebo, more tofacitinib-treated patients had reductions from baseline in stool frequency subscore (by ≥1 point for tofacitinib, 241/837, 28.8% vs placebo, 39/218, 17.9%) ($P < .01$) and rectal bleeding subscore (by ≥1 point for tofacitinib, 266/830, 32.0% vs placebo, 43/214, 20.1%) ($P < .01$) by day 3. A consistent effect of tofacitinib was observed in all subgroups.**

CONCLUSIONS: **In a post-hoc analysis of data from phase 3 trials of induction therapy with tofacitinib in patients with UC, we found significant improvements in symptoms among patients given tofacitinib compared with placebo within 3 days. These findings indicate the rapid onset of effect of this drug in patients with UC. ClinicalTrials.gov no: NCT01465763 and NCT01458951.**

Keywords: Inflammatory Bowel Disease; Efficacy; Onset of Action; IBD.

See editorial on page 34; and related article on page 130.

Ulcerative colitis is a chronic, disabling, inflammatory condition of the colon. The primary goals of therapy in ulcerative colitis are to induce and maintain remission.[1,2] Although corticosteroids are effective for ulcerative colitis induction therapy—with response expected within days[3]—they are not suitable for long-term use owing to an increased risk of side effects and loss of efficacy.[4] Conversely, thiopurines (azathioprine and 6-mercaptopurine) have limited use in the acute setting, as maximal clinical effect with these therapies may take at least 8 weeks.[3,5] Onset of efficacy with anti–tumor necrosis factor (TNF) therapies (infliximab, adalimumab, and golimumab) and anti-integrin therapy (vedolizumab;

Abbreviations used in this paper: CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value; TNF, tumor necrosis factor.

Most current article

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abstract presented at the American College of Gastroenterology Annual Scientific Meeting 2017) has been observed as early as week 2 in clinical trials.[6–10] While biologic therapies are effective for many patients, many fail to respond or lose response over time, which may be related to inadequate serum drug concentrations, the formation of antidrug antibodies, or an inadequate mechanistic response to anti-TNF therapy.[11] Furthermore, these agents require administration via injection or infusion. Accordingly, safe and effective oral treatment options with a new mechanism of action, rapid onset of induction efficacy, and durability of maintenance efficacy would represent a meaningful addition to the current ulcerative colitis treatment armamentarium, and address patients' preferences for treatments with rapid onset of efficacy.[12,13]

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis. In 2 identical phase 3, 8-week induction trials,[14] a significant improvement from baseline partial Mayo score (which includes Mayo rectal bleeding and stool frequency subscores) was observed with tofacitinib 10 mg twice daily vs placebo as early as week 2—the first time point at which partial Mayo score was assessed. The safety profile of tofacitinib during 8-week induction and 52-week maintenance trials was consistent with that observed with tofacitinib in other disease populations,[14] and long-term safety in ulcerative colitis is being evaluated in an ongoing open-label extension study (NCT01470612; the Oral Clinical Trials for tofAcitinib in ulceratiVE colitis [OCTAVE] Open trial).

In these post-hoc analyses we evaluated the rapidity of symptomatic improvement measured using daily telephone diary entry data collected during OCTAVE Induction 1 and 2 to evaluate daily treatment effect during the first 2 weeks (up to day 15) of tofacitinib induction therapy.

What You Need to Know

Background

Onset of action is an important attribute of therapies for patients with moderately to severely active ulcerative colitis. Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis.

Findings

In phase 3 induction studies, clinically relevant improvements in symptoms were observed within 3 days of initiating treatment with tofacitinib 10 mg BID. Early symptomatic improvement occurred irrespective of prior anti-tumor necrosis factor therapy failure, baseline corticosteroid use, or baseline C-reactive protein level and correlated with clinical response at week 8.

Implications for patient care

These observations support rapid onset of efficacy with tofacitinib 10 mg BID as induction therapy for ulcerative colitis.

Methods

Studies

The OCTAVE Induction 1 (NCT01465763) and 2 (NCT01458951) trials[14] were 2 identical, 8-week, phase 3 induction studies of patients with moderately to severely active ulcerative colitis who had inadequate response to, lost response to, or were intolerant to treatment with corticosteroids, azathioprine, and 6-mercaptopurine, and/or anti-TNF therapy (infliximab and adalimumab). Patients in the OCTAVE Induction 1 and 2 trials were aged $\geq$18 years, with moderately to severely active ulcerative colitis defined by total Mayo score $\geq$6, with rectal bleeding subscore of $\geq$1 and endoscopic subscore (centrally read) of $\geq$2. Detailed study design and patient inclusion criteria were reported previously.[14]

Study Treatments

Patients in the OCTAVE Induction 1 and 2 trials were randomized 1:4 to 8 weeks of therapy with placebo or tofacitinib 10 mg twice daily. Oral aminosalicylates and oral corticosteroids (maximum dose 25 mg/day, prednisone equivalence) were permitted during the studies provided they were stably dosed throughout the study. Prohibited concomitant therapies included: azathioprine, 6-mercaptopurine, and methotrexate (2 weeks' washout); cyclosporine, mycophenolate, and tacrolimus (4 weeks' washout); and anti-TNF therapies (8 weeks' washout).

Diary Assessments

Patients were instructed on the use of an interactive voice recording system to record their bowel movement data on a daily basis, including the number of bowel movements per day and blood in the stools (if any).

Statistical Analyses

In these post-hoc analyses, pooled data are presented for all patients who were randomized to placebo or tofacitinib 10 mg twice daily in OCTAVE Induction 1 and 2. Daily Mayo stool frequency and Mayo rectal bleeding subscores[15] were calculated based on the daily diary entry. Stool frequency and rectal bleeding subscores ranged between 0–3 (stool frequency: 0 = normal; 1 = 1–2 stools/day more than normal; 2 = 3–4 stools/day more than normal; 3 = more than 4 stools per day more than normal; rectal bleeding: 0 = no rectal bleeding, 1 = visible blood with stool less than half the time, 2 = visible blood with stool half of the time or more, and 3 = passing blood alone).[15] Baseline values were derived using the average of the daily diary data from the most recent 3 of 5 days before the day of the first dose.

Changes from baseline in stool frequency subscore, rectal bleeding subscore, and the total number of daily

bowel movements were evaluated during the first 15 days of therapy using a linear mixed effects model with baseline value, treatment group, prior treatment with anti-TNF therapy, corticosteroid use at baseline, geographic region, study, day, treatment group by day interaction, and patients as random effect.

The following binary endpoints based on diary data were evaluated for each day during the first 15 days of therapy: stool frequency subscore = 0, stool frequency subscore ≤1, reduction of ≥1 point from baseline in stool frequency subscore, rectal bleeding subscore = 0, rectal bleeding subscore ≤1, and reduction of ≥1 point from baseline in rectal bleeding subscore. Cochran-Mantel-Haenszel chi-square test was used to compare tofacitinib 10 mg twice daily vs placebo, stratified by prior treatment with anti-TNF therapies, study, corticosteroid use at baseline, and geographic region. In addition, the difference between treatment groups was calculated along with 95% confidence interval using the normal approximation for the difference in binomial proportions.

Positive predictive values (PPVs) for 1) reduction of ≥1 point from baseline in stool frequency subscore at day 15, 2) reduction of ≥1 point from baseline in rectal bleeding subscore at day 15, and 3) reduction of ≥1 point from baseline in both stool frequency and rectal bleeding subscores at day 15 were calculated based on patients achieving the respective efficacy response at day 3. PPVs for clinical response at week 8 (≥3-point and ≥30% reduction from baseline total Mayo score plus decrease ≥1 point in rectal bleeding subscore or absolute rectal bleeding subscore ≤1) were calculated based on patients achieving stool frequency and rectal bleeding efficacy responses at 1) day 3 and 2) day 7. Negative predictive values (NPVs) were defined as the proportions of patients without responses at day 3 or day 7 who did not have subsequent clinical response at week 8.

Subgroup analyses by prior anti-TNF treatment failure, corticosteroid use at baseline, and baseline C-reactive protein (CRP) (≤6 mg/L vs >6 mg/L) were conducted for reduction of ≥1 point from baseline in stool frequency subscore, reduction of ≥1 point from baseline in rectal bleeding subscore, and rectal bleeding subscore = 0.

Analyses were based on observed case data. For analyses of reduction from baseline of ≥1 point in stool frequency subscore and reduction from baseline of ≥1 point in rectal bleeding subscore, patients were excluded if the corresponding baseline subscore was 0.

Study Ethics and Patient Consent

All studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization 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 by a central institutional review board. All patients provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patients

Baseline demographics and disease characteristics of patients in the OCTAVE Induction 1 and 2 trials were similar across the placebo and tofacitinib 10 mg twice daily treatment groups (Table 1). At baseline, mean stool frequency subscore was 2.5 for both treatment groups, mean rectal bleeding subscore was 1.6 for both groups, and median total number of daily bowel movements was 7.0 for both groups.

Onset of Efficacy Based on Patient Diary Data

Improvements in stool frequency subscore. A significant improvement in stool frequency subscore was observed with tofacitinib 10 mg twice daily vs placebo within 3 days (Supplementary Figure 1). Mean change from baseline stool frequency subscore at day 3 was −0.27 with tofacitinib 10 mg twice daily vs −0.11 with placebo ($P < .01$). Thereafter, a significant effect of treatment was observed at each day through to day 15. Mean change from baseline stool frequency subscore at day 15 with tofacitinib 10 mg twice daily was −0.74 vs −0.35 with placebo ($P < .0001$).

The proportion of patients with stool frequency subscore = 0 over time is shown in Figure 1*A*. Significantly more patients had stool frequency subscore = 0 at day 7 with tofacitinib 10 mg twice daily (9.2%) vs placebo (2.3%; $P < .01$). At day 15, 14.6% of patients had stool frequency subscore = 0 with tofacitinib vs 8.0% with placebo ($P < .01$).

The proportion of patients with stool frequency subscore ≤1 was significantly greater with tofacitinib 10 mg twice daily within 4 days (tofacitinib 10 mg twice daily: 24.2%; placebo: 16.7%; $P < .05$) (Figure 1*B*), and at each day thereafter through to day 15. At day 15, 42.0% of patients receiving tofacitinib 10 mg twice daily had stool frequency subscore ≤1 vs 25.4% with placebo ($P < .0001$).

For the proportion of patients with reduction from baseline stool frequency subscore of ≥1 (Figure 1*C*), a significant effect of tofacitinib treatment was also seen within 3 days (tofacitinib 10 mg twice daily: 28.8%; placebo: 17.9%; $P < .01$), which was maintained through to day 15 (tofacitinib 10 mg twice daily: 53.8%; placebo: 32.1%; $P < .0001$).

Improvements in rectal bleeding subscore. For change from baseline in rectal bleeding subscore, improvement with tofacitinib 10 mg twice daily was statistically significant within 3 days (tofacitinib 10 mg twice daily: −0.30; placebo: −0.14; $P < .01$), and at each day

Table 1. Baseline Demographics and Disease Characteristics of Patients in the OCTAVE Induction 1 and 2 Trials

	Placebo (n = 234)	Tofacitinib 10 mg BID (n = 905)
Male	132 (56.4)	536 (59.2)
Age, y	41.1 ± 14.4	41.2 ± 13.8
Geographic region		
Europe	135 (57.7)	534 (59.0)
North America	53 (22.6)	187 (20.7)
Other	46 (19.7)	184 (20.3)
Duration of disease, y	8.1 ± 7.0	8.1 ± 7.0
Total Mayo score	9.0 ± 1.5	9.0 ± 1.4
Stool frequency subscore	2.5 ± 0.7	2.5 ± 0.7
0	0/233 (0.0)	14/903 (1.6)
≤1	26/233 (11.2)	109/903 (12.1)
Rectal bleeding subscore	1.6 ± 0.6	1.6 ± 0.6
0[a]	4/233 (1.7)	18/903 (2.0)
≤1	103/233 (44.2)	380/903 (42.1)
Daily bowel movements	7.9 ± 3.9	7.9 ± 4.1
Median (range)	7.0 (2.0–23.0)	7.0 (1.0–40.0)
CRP		
≤6 mg/L	127 (54.5)	510 (57.2)
>6 mg/L	106 (45.5)	381 (42.8)
Oral corticosteroid use at baseline	113 (48.3)	412 (45.5)
Mean dose[b]	16.5 ± 6.0	16.1 ± 6.4
Median dose (range)[b]	20.0 (5.0–25.0)	20.0 (2.0–30.0)
Prior anti-TNF treatment	130 (55.6)	488 (53.9)
Prior anti-TNF failure	124 (53.0)	465 (51.4)
Prior immunosuppressant failure[c]	158 (67.5)	661 (73.0)

NOTE. Values are n (%), mean ± SD, or n/N (%), unless otherwise indicated.
BID, twice daily; CRP, C-reactive protein; N, number of evaluable patients; n, number of patients; TNF, tumor necrosis factor.
[a]The 22 patients with rectal bleeding subscore = 0 at baseline were protocol deviations as patients were required to have a rectal bleeding subscore ≥1 at baseline.
[b]Mean and median corticosteroid doses are at day 1 of the studies and are expressed as prednisone equivalent dose, excluding patients taking budesonide or beclomethasone.
[c]Immunosuppressants included agents such as azathioprine and 6-mercaptopurine, and did not include biologic agents or corticosteroids.

thereafter through to day 15 (Supplementary Figure 2). Mean change from baseline rectal bleeding subscore at day 15 with tofacitinib 10 mg twice daily was −0.76 vs −0.44 with placebo ($P < .0001$).

The proportion of patients with rectal bleeding subscore = 0 was also significantly greater with tofacitinib 10 mg twice daily within 3 days (tofacitinib 10 mg twice daily: 14.4%; placebo: 8.2%; $P < .05$) (Figure 2*A*), and at each day thereafter through to day 15. The proportion of patients with rectal bleeding subscore = 0 at day 15 was 41.2% with tofacitinib 10 mg twice daily vs 21.1% with placebo ($P < .0001$).

For the proportion of patients with rectal bleeding subscore of ≤1 (Figure 2*B*), a significant effect of tofacitinib treatment was seen within 4 days (tofacitinib 10 mg twice daily: 64.2%; placebo: 51.5%; $P < .01$), and at each day thereafter (except for day 6) through to day 15 (tofacitinib 10 mg twice daily: 76.5%; placebo: 66.2%; $P < .01$).

A significantly greater proportion of patients receiving tofacitinib 10 mg twice daily (32.0%) also had improvement from baseline rectal bleeding subscore of ≥1 within 3 days vs placebo (20.1%; $P < .01$) (Figure 2*C*), maintained through to day 15 (tofacitinib 10 mg twice daily: 62.5%; placebo: 41.6%; $P < .0001$).

Improvement in total number of daily bowel movements. For change from baseline in the total number of daily bowel movements, a significant difference was observed within 3 days with tofacitinib 10 mg twice daily (−1.06) vs placebo (−0.27; $P < .0001$), maintained through to day 15 (Supplementary Figure 3). Mean change from baseline in total number of daily bowel movements at day 15 was −2.37 with tofacitinib 10 mg twice daily vs −0.94 with placebo ($P < .0001$).

Predictive Values of Day 3 and Day 7 Responses for Responses at Day 15 and Week 8

For reduction from baseline stool frequency subscore of ≥1 point, response at day 3 was associated with a PPV for response at day 15 of 79.3% (ie, 79.3% of patients who had response at day 3 had subsequent response at day 15) (Table 2). For reduction from baseline rectal bleeding subscore of ≥1 point, the PPV of response at day 3 to predict response at day 15 was 89.2%. For reduction from baseline stool frequency and rectal bleeding subscore of ≥1 point the PPV was 72.6%.

Table 3 shows PPVs of responses based on patient diary data at day 3 and day 7 to predict clinical response

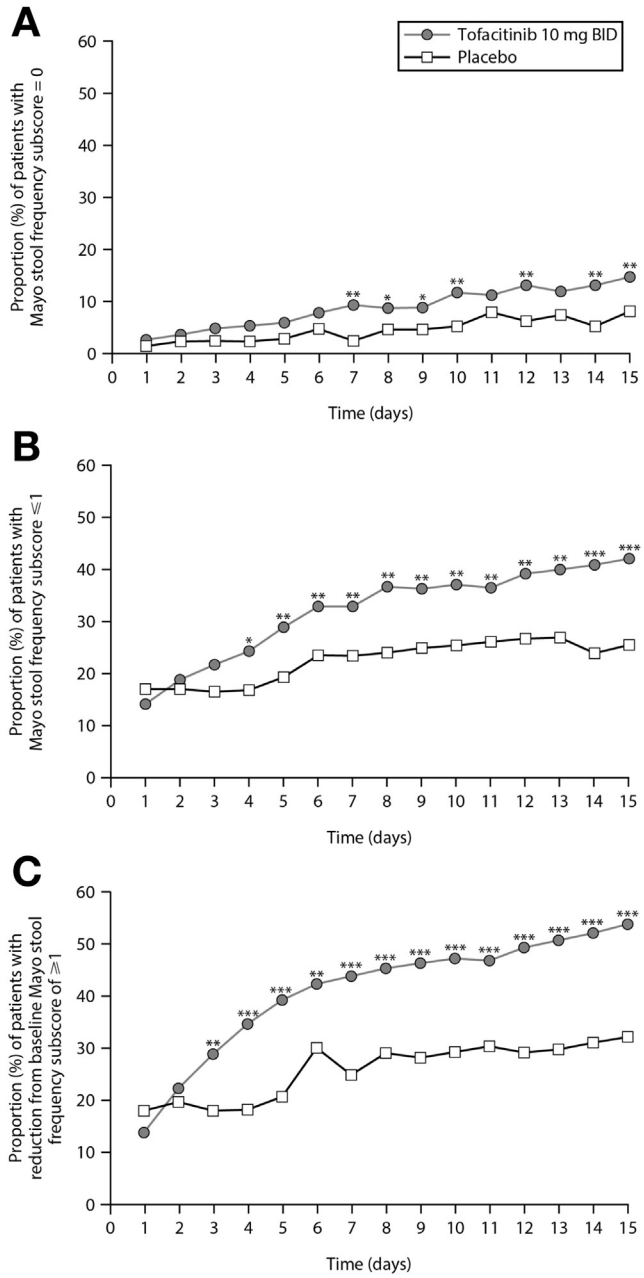


Figure 1. Proportion of patients with (*A*) Mayo stool frequency subscore = 0, (*B*) Mayo stool frequency subscore ≤1, and (*C*) reduction from baseline Mayo stool frequency subscore of ≥1 point, over time. Data are full analysis set, observed case. Day 0 represents data reported within 5 days before the baseline visit, and day 1 reflects the first dose of medication. Proportion of patients with reduction from baseline Mayo stool frequency subscore of ≥1 point excludes patients with baseline Mayo stool frequency subscore = 0. BID, twice daily. **P* < .05. ***P* < .01. ****P* < .0001 vs placebo.

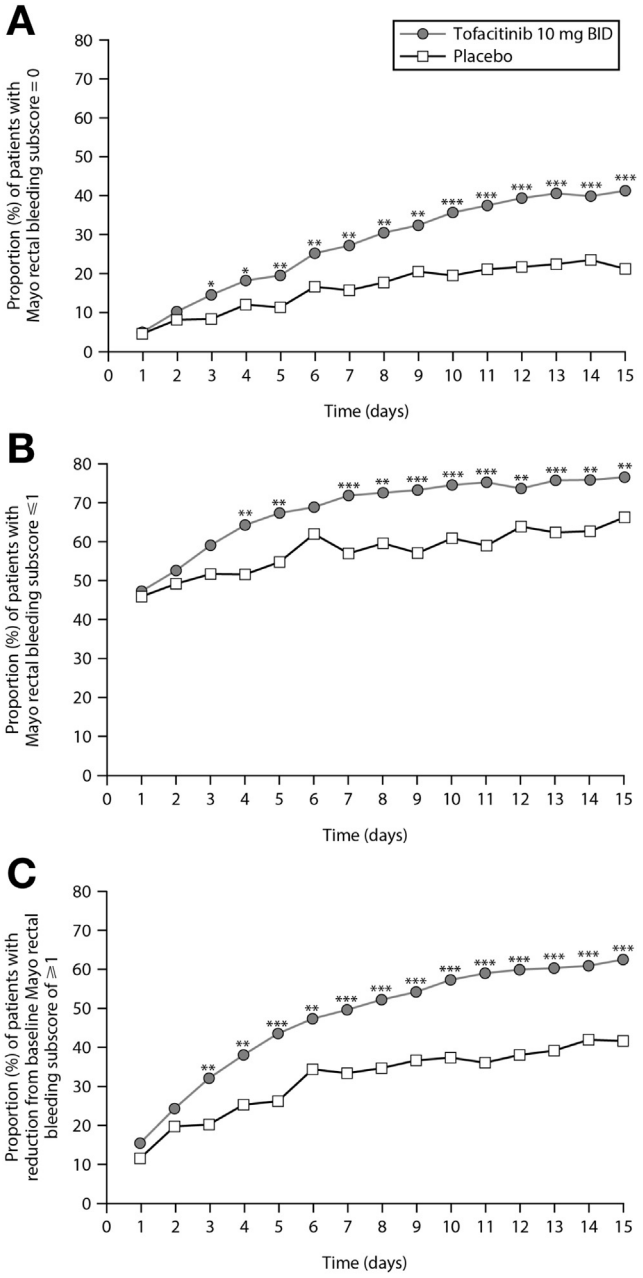


Figure 2. Proportions of patients with (*A*) Mayo rectal bleeding subscore = 0, (*B*) Mayo rectal bleeding subscore ≤1, and (*C*) reduction from baseline Mayo rectal bleeding subscore of ≥1 point, over time. Data are full analysis set, observed case. Day 0 represents data reported within 5 days before the baseline visit, and day 1 reflects the first dose of medication. Proportion of patients with reduction from baseline Mayo rectal bleeding subscore of ≥1 point excludes patients with baseline Mayo rectal bleeding subscore = 0. BID, twice daily. **P* < .05. ***P* < .01. ****P* < .0001 vs placebo.

at week 8. For reduction from baseline stool frequency subscore of ≥1 point, day 3 and day 7 PPVs for week 8 clinical response were 73.9% and 76.8%, respectively. Day 3 and day 7 NPVs (ie, the proportions of patients without day 3 or day 7 responses who did not have subsequent week 8 clinical response) were 48.2% and 55.7%, respectively. For reduction from baseline rectal bleeding subscore of ≥1 point, day 3 and day 7 PPVs were 65.0% and 69.9%, respectively. Respective NPVs were 44.0% and 51.4%. Day 3 and day 7 PPVs for reduction from baseline stool frequency and rectal bleeding subscore of ≥1 point were 77.1% and 82.8%, respectively. NPVs were 44.0% and 50.6%, respectively.

Table 2. PPVs of Subscore Responses Based on Patient Diary Data at Day 3 to Predict Respective Subscore Responses at Day 15

	PPV of Response at Day 3 to Predict Response at Day 15
Reduction from baseline stool frequency subscore of ≥1 point	79.3
Reduction from baseline rectal bleeding subscore of ≥1 point	89.2
Reduction from baseline stool frequency and rectal bleeding subscore of ≥1 point	72.6

NOTE. Values are %. Data are full analysis set, observed case. Positive predictive value (PPV) was defined as the proportion of patients with response at day 3 who subsequently had response at day 15. Proportion of patients with reduction from baseline Mayo stool frequency subscore of ≥1 point excludes patients with baseline Mayo stool frequency subscore = 0. Proportion of patients with reduction from baseline Mayo rectal bleeding subscore of ≥1 point excludes patients with baseline Mayo rectal bleeding subscore = 0.

Onset of Efficacy by Subgroups

Subgroup analyses of the proportion of patients with reduction from baseline stool frequency subscore of ≥1 point, the proportion of patients with rectal bleeding subscore = 0, and the proportion of patients with reduction from baseline rectal bleeding subscore of ≥1 point demonstrated the efficacy of tofacitinib regardless of prior anti-TNF treatment failure status (Figure 3), the use of corticosteroids at baseline (Supplementary Figure 4), or baseline CRP level (Supplementary Figure 5), with consistent treatment effects observed across all subgroups.

Discussion

In these post-hoc analyses of daily telephone diary data collected during the OCTAVE Induction 1 and 2 tofacitinib ulcerative colitis induction trials, significant symptomatic improvements were observed for patients receiving tofacitinib 10 mg twice daily vs those receiving placebo within 3 days of treatment initiation. Rapid onset of action was demonstrated based on improvement in Mayo stool frequency subscore, Mayo rectal bleeding subscore, and the total number of daily bowel movements. Differences were also clinically relevant as demonstrated by the significantly greater proportions of tofacitinib-treated patients with reduction of ≥1 point from baseline in stool frequency subscore and rectal bleeding subscore within 3 days. Early response, as measured by improvements in stool frequency and rectal bleeding subscores at day 3 and day 7, also correlated with better outcomes at day 15 and week 8 time points. Nevertheless, patients who did not achieve response by day 3 or day 7 were still able to achieve efficacy at week 8.

Subgroup analyses demonstrated a generally consistent effect of tofacitinib treatment for patients regardless of whether they had prior anti-TNF treatment failure or were receiving corticosteroids at baseline, and regardless of baseline CRP level. Of note, is our observation that baseline CRP may be a modulator of the magnitude of the effect. Nonetheless, our findings are supportive of the rapid onset of tofacitinib efficacy, previously reported based on significant improvement in partial Mayo score at week 2 with tofacitinib 10 mg twice daily vs placebo.[14]

For patients with moderately to severely active ulcerative colitis, onset of action is an important

Table 3. PPVs of Subscore Responses Based on Patient Diary Data at Day 3 and Day 7 to Predict Clinical Response at Week 8

	Response Rate at Day 3	PPV of Response at Day 3 to Predict Clinical Response at Week 8	Response Rate at Day 7	PPV of Response at Day 7 to Predict Clinical Response at Week 8
Reduction from baseline stool frequency subscore of ≥1 point	241/837 (28.8)	73.9	362/827 (43.8)	76.8
Reduction from baseline rectal bleeding subscore of ≥1 point	266/830 (32.0)	65.0	408/822 (49.6)	69.9
Reduction from baseline stool frequency and rectal bleeding subscore of ≥1 point	118/820 (14.4)	77.1	239/812 (29.4)	82.8

NOTE. Values are n/N (%) or %. Data are full analysis set, observed case. Positive predictive value (PPV) was defined as the proportion of patients with response at day 3/7 who subsequently had clinical response at week 8. Proportion of patients with reduction from baseline Mayo stool frequency subscore of ≥1 point excludes patients with baseline Mayo stool frequency subscore = 0. Proportion of patients with reduction from baseline Mayo rectal bleeding subscore of ≥1 point excludes patients with baseline Mayo rectal bleeding subscore = 0. N, number of evaluable patients with data available at day 3/7; n, number of patients who had response at day 3/7.

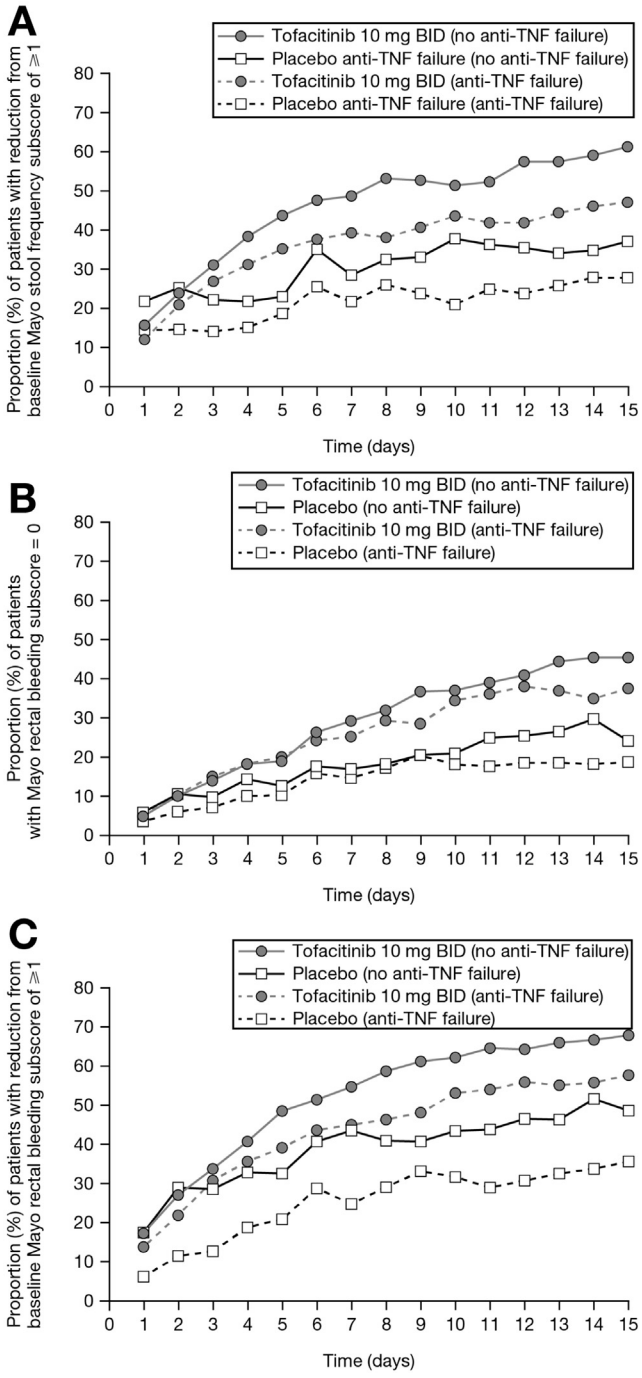


Figure 3. Proportion of patients with (*A*) reduction from baseline Mayo stool frequency subscore of ≥1 point over time, (*B*) Mayo rectal bleeding subscore = 0 over time, and (*C*) reduction from baseline Mayo rectal bleeding subscore of ≥1 point over time, by prior anti–tumor necrosis factor (TNF) failure (yes/no). Data are full analysis set, observed case. Day 0 represents data reported within 5 days before the baseline visit, and day 1 reflects the first dose of medication. Proportion of patients with reduction from baseline Mayo stool frequency subscore of ≥1 point excludes patients with baseline Mayo stool frequency subscore = 0. Proportion of patients with reduction from baseline Mayo rectal bleeding subscore of ≥1 point excludes patients with baseline Mayo rectal bleeding subscore = 0. BID, twice daily.

consideration when choosing appropriate therapy to provide timely symptomatic relief. Patients' preferences for therapies with rapid onset of action is evidenced by real-world and patient-survey data, where rapidity of action was rated among the most important attributes of ulcerative colitis therapy.[12,13] Tofacitinib is the first agent to demonstrate rapid onset of action, along with robust induction and maintenance efficacy, including robust efficacy in patients who have previously failed corticosteroids or anti-TNF.[14] Induction of remission with corticosteroids has been reported within 5 days; however, corticosteroids are associated with escalating side effects and lack maintenance benefits.[3] In these analyses, onset of tofacitinib efficacy occurred within 3 days irrespective of concomitant corticosteroid use or prior anti-TNF treatment failure status. In contrast, onset of effect with thiopurines (azathioprine and 6-mercaptopurine) may require at least 8 weeks to demonstrate steroid-sparing effects.[3,5]

Recent clinical trials of biologic therapy with anti-TNF and anti-integrin agents for moderately to severely active ulcerative colitis have reported measures of efficacy at week 2 following treatment initiation, but have not reported efficacy at earlier time points.[6–9] In studies of subcutaneous golimumab for ulcerative colitis induction therapy, onset of efficacy at week 2 was reported based on significant decrease in mean CRP and median decreases in partial Mayo score (results of significance testing for decrease in partial Mayo score were not reported) compared with placebo.[8] Numerical improvement vs placebo in partial Mayo score at week 2 has also been reported with infliximab therapy.[6] Infliximab has also been shown to be efficacious in an open-label study of hospitalized patients with severe colitis, which demonstrated an improvement in modified Truelove-Witts criteria (the Lichtiger index, which includes number of daily stools, nocturnal stools, visible blood in the stool, abdominal pain global assessment, general wellbeing, use of antidiarrheal agents, and urgency) within 3 days compared with cyclosporine, but this was not sustained beyond day 4.[16] A statistically significant effect of adalimumab therapy was observed from week 2 onward based on improvement in partial Mayo score vs placebo.[7] In a trial of vedolizumab therapy for patients with moderately to severely active ulcerative colitis, earlier improvement in partial Mayo score was not reported until reaching statistical significance vs placebo at week 6.[9] Post-hoc analyses from the vedolizumab induction trial demonstrated statistically significant improvements with vedolizumab vs placebo by week 4 for percent change from baseline in Mayo stool frequency subscore and Mayo rectal bleeding subscore in the overall population, with greater efficacy in anti-TNF-naïve patients (statistically significant reduction in Mayo stool frequency subscore at week 2, only in the

anti-TNF–naive population) than in the overall study population.[10]

The findings of these analyses are consistent with rapid onset of efficacy observed with tofacitinib in other disease populations. For patients with moderate to severe rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs, improvements from baseline were observed with tofacitinib as early as day 3 for Patient Global Assessment of Disease Activity and Patient Global Assessment of Pain.[17]

These analyses of onset of efficacy based on daily telephone diary entry data were post-hoc and should be interpreted with caution. *P* values reported were not corrected for multiplicity. In addition, these data reflect findings from clinical trial patient populations. Onset of tofacitinib efficacy in the wider population of patients with ulcerative colitis may differ, owing to different treatment regimens and different disease and demographic characteristics.

In conclusion, in phase 3 induction studies of tofacitinib for patients with moderately to severely active ulcerative colitis, clinically relevant symptomatic improvements were observed with tofacitinib 10 mg twice daily vs placebo within 3 days. These observations support rapid onset of efficacy with tofacitinib 10 mg twice daily as induction therapy for ulcerative colitis.

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.2018.07.009.

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