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Review article: guide to tofacitinib dosing in patients with ulcerative colitis

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Summary

Background: Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). The induction dose is 10 mg twice daily (b.d.), whilst for maintenance therapy, the lowest effective dose should be used.

Aim: To examine published evidence on the two tofacitinib dosing strategies used in UC treatment, including expert interpretation of the data and how they could inform clinical practice.

Methods: The use of tofacitinib 5 or 10 mg b.d. was assessed using data from the tofacitinib UC clinical programme in the context of different clinical scenarios. We include experts' opinions on the clinical implications of dose adjustment to inform the benefit/risk of using tofacitinib 5 or 10 mg b.d., based on clinical scenarios and real-world data.

Results: Factors to consider when adjusting the tofacitinib dose include disease severity, comorbidities and previous biological exposure. The endoscopic subscore can determine whether a patient is a good candidate for dose reduction. Following disease relapse, the response can be recaptured in a substantial number of patients with a dose increase. Furthermore, data are now published showing real-world use of tofacitinib and, so far, these are consistent with data from the clinical trials.

Conclusion: Clinicians must consider the benefit/risk balance of tofacitinib 10 versus 5 mg b.d. in terms of dose-related side effects, as well as the safety implications of undertreating active disease. All patients should be closely monitored for disease relapse following dose reduction or interruption for early recapture of response.

1 | INTRODUCTION

Tofacitinib is an oral small molecule Janus kinase (JAK) inhibitor for the treatment of ulcerative colitis (UC). The efficacy and safety of tofacitinib have been evaluated in patients with moderately to severely active UC in the tofacitinib UC clinical programme. Response to induction was assessed in two identical 8-week, Phase 3 studies (OCTAVE Induction 1 and 2; NCT01465763 and NCT01458951).[1] Patients were randomised to receive either tofacitinib 10 mg twice daily (b.d.), 15 mg b.d. (discontinued following a protocol amendment) or placebo for 8 weeks. The primary efficacy endpoint was remission at Week 8 (defined as a total Mayo score of ≤2, with no individual subscore >1, and a rectal bleeding subscore of 0). OCTAVE Induction 1 and 2 established the efficacy of induction therapy with tofacitinib 10 mg b.d. versus placebo.[1]

Patients with clinical response (defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, with a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1) during OCTAVE Induction 1 or 2 could enrol in OCTAVE Sustain (NCT01458574), a 52-week, Phase 3 maintenance study in which patients were randomised to receive tofacitinib 10 mg b.d., tofacitinib 5 mg b.d. or placebo.[1] In OCTAVE Sustain, both doses of tofacitinib demonstrated efficacy at maintaining remission at Week 52 versus placebo.[1]

Patients could join an open-label, long-term extension (OLE) study (OCTAVE Open; NCT01470612)[2] if they had completed or withdrawn early (after experiencing treatment failure) from OCTAVE Sustain or if they were non-responders after completing OCTAVE Induction 1 or 2. OCTAVE Open demonstrated a consistent safety profile for tofacitinib with up to 7.0 years of exposure, with infrequent occurrences of serious infections, malignancies and venous thromboembolic events. Further, OCTAVE Open demonstrated the efficacy of both doses of tofacitinib as a long-term therapy (up to 36 months).[2]

The Phase 3b/4, double-blind, randomised RIVETING (NCT03281304) study enrolled patients from OCTAVE Open who had been in stable remission (≥6 months) on tofacitinib 10 mg b.d. (≥2 consecutive years). In a 6-month primary completion analysis, the efficacy and safety of dose reduction to tofacitinib 5 mg b.d., compared with patients remaining on 10 mg b.d., were evaluated.[3]

Primary and post hoc analyses derived from these studies may inform clinical practice, potentially enabling clinicians to identify patients who might benefit from altering tofacitinib dose or duration, based on response to treatment, demographics or clinical characteristics, including prior exposure to UC therapies such as tumour necrosis factor inhibitors (TNFi). Furthermore, data are now published showing real-world use of tofacitinib and, so far, these are consistent with data from the clinical trials.[4-9] Here, we include experts' interpretation of these data and their opinion on the clinical implications to inform the benefit/risk of using tofacitinib 5 or 10 mg b.d. in UC, based on clinical scenarios and real-world data (Figure 1).[10-13]

Tofacitinib was first approved for the treatment of adults with moderately to severely active UC in 2018 by the United States (US) Food and Drug Administration (FDA).[14,15] ORAL Surveillance (NCT02092467) evaluated the risk of cardiovascular events and malignancies (excluding non-melanoma skin cancer [NMSC]) with tofacitinib 5 and 10 mg b.d. versus TNFi in patients with rheumatoid arthritis who were ≥50 years old with at least one additional cardiovascular risk factor, some of which are also known risk factors for malignancy.[16,17] Following ad hoc safety analyses from this study, the tofacitinib product label was updated to advise clinicians to use the lowest effective dose to maintain clinical response when treating patients with UC, which would suggest lowering the dose from 10 mg b.d. to 5 mg b.d. as soon as possible after 8 weeks of induction therapy.[14,18] However, some patients may need extended induction or dose increase to recapture efficacy (Figure 1). This review aimed to examine the available evidence published on the use of two doses of tofacitinib in UC, including expert interpretation of these data and how they may inform clinical practice, particularly in relation to dose adjustment.

2 | CLINICAL SCENARIOS

### 2.1 | What can be done if patients do not achieve therapeutic benefit after 8 weeks of induction?

2.1.1 | What is known from observations in the UC clinical programme?

In OCTAVE Open, tofacitinib induction non-responders continued to receive tofacitinib 10 mg b.d. for an additional 8 weeks of induction therapy (Figure 1A). Amongst patients who did not achieve clinical response after 8 weeks of treatment with tofacitinib 10 mg b.d. in the induction studies, 52.2% (154/295) achieved a clinical response following extended induction for a further 8 weeks (delayed responders).[10] Accordingly, extended induction resulted in a further 17.0% of patients achieving clinical response, resulting in a total of 74.6% of patients with overall clinical response to tofacitinib 10 mg b.d. induction therapy (Figure 2A).[10]

The majority of patients who achieved a clinical response following extended induction (ie 16 weeks of induction therapy) with tofacitinib 10 mg b.d. maintained this response following maintenance treatment with tofacitinib 10 mg b.d., with clinical response rates of 70.3% (104/148) and 56.1% (83/148) at Months 12 and 36, respectively.[10] Tofacitinib 10 mg b.d. for induction beyond 16 weeks is not recommended per product labelling.

2.1.2 | Real-world and registry database observations

Several real-world studies with populations ranging from 35–113 patients have reported the use of extended induction with tofacitinib in patients with UC, in which between approximately one-third and half of the patients received an additional 8 weeks of tofacitinib 10 mg b.d. induction therapy.[4,5,7] One such study was a prospective, observational analysis of 113 treatment-refractory patients with UC enrolled
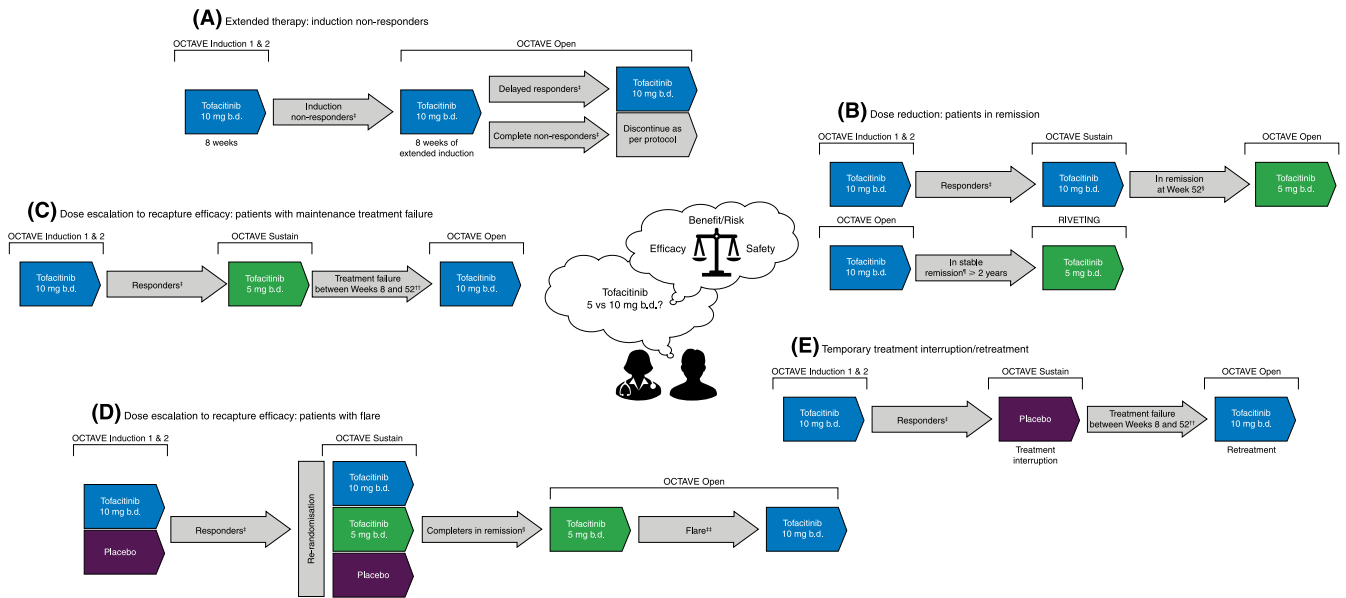
FIGURE 1 Clinical scenarios relating to tofacitinib dose in patients with UC: subgroups from the tofacitinib UC clinical programme.[10-13] †OCTAVE Induction 1 and 2 (NCT01465763 and NCT01458951); OCTAVE Sustain (NCT01458574); OCTAVE Open (NCT01470612); RIVETING (NCT03281304). ‡Clinical response was defined 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. §Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. ¶Stable remission included patients who were in remission on tofacitinib 10 mg b.d. for ≥6 months prior to enrolment in RIVETING. ††Treatment failure was defined as an increase from OCTAVE Sustain baseline total Mayo score of ≥3 points, plus an increase in rectal bleeding subscore and endoscopic subscore of ≥1 point and an absolute endoscopic subscore ≥2 points after ≥8 weeks of maintenance therapy. ‡‡Flare was defined as an increase in total Mayo score of ≥3 points from a baseline of OCTAVE Sustain, accompanied by an increase in rectal bleeding and endoscopic subscores of ≥1 point, after a minimum of 8 weeks of treatment. Adaptation permission requested. b.d., twice daily; N, number of patients in each treatment group; UC, ulcerative colitis.

in the ENEIDA registry (a Spanish database) who received treatment with tofacitinib 5, 10, or 15 mg b.d (not an approved dose) for a median duration of 44 weeks. Overall, tofacitinib treatment was shown to be effective in patients who had previously failed biological therapy, with 28/113 patients receiving 16 weeks of treatment with tofacitinib 10 mg b.d.[4] A small real-world study of patients with UC in Russia demonstrated that extended induction up to 16 weeks was required in more patients with prior TNFi exposure compared with those without.[7] Patients with prior TNFi exposure may represent a more refractory group of patients, and the proportion of patients receiving extended induction needs to be considered in the context of real-world cohorts describing early use of tofacitinib which tend to have a high proportion of patients failing at least one TNFi. Whilst the use of extended induction with tofacitinib 10 mg b.d. in these studies is reported, they do not report outcomes at Week 16 in a way that differentiates between those patients who received extended induction therapy and those who reduced to tofacitinib 5 mg b.d. after Week 8.[4,5,7]

2.1.3 | Interpretation and conclusions

Data from both the UC clinical programme and real-world evidence support the use of tofacitinib 10 mg b.d. for a further 8 weeks in patients who do not achieve a clinical response after 8 weeks of

tofacitinib induction therapy.[4,5,7,10] Up to half of the patients without a clinical response at Week 8 may benefit from another 8 weeks of induction therapy.[10] In clinical practice, the decision to extend a patient's treatment with tofacitinib for a further 8 weeks is generally dependent on individual circumstances. For instance, patients showing no sign of clinical response following 8 weeks of tofacitinib induction therapy who, for example, still require high doses of corticosteroids, may not be suitable candidates for extended induction therapy. However, patients who have been able to reduce their corticosteroid dose during the initial 8 weeks of tofacitinib induction therapy and show some clinical improvement may benefit from an additional 8 weeks of tofacitinib 10 mg b.d. This may be particularly relevant when considering patients who are refractory to multiple UC therapies. Assessment of clinical symptoms and relevant biomarkers may also help guide decision-making in this scenario as decreased levels of biomarkers, such as C-reactive protein and faecal calprotectin, have been shown to correlate with clinical outcomes in patients receiving tofacitinib 10 mg b.d.[19]

2.2 | What are the outcomes for patients who undergo dose reduction?

For patients with UC, reducing the dose of tofacitinib may be desirable for several reasons, including reducing the risk of potential
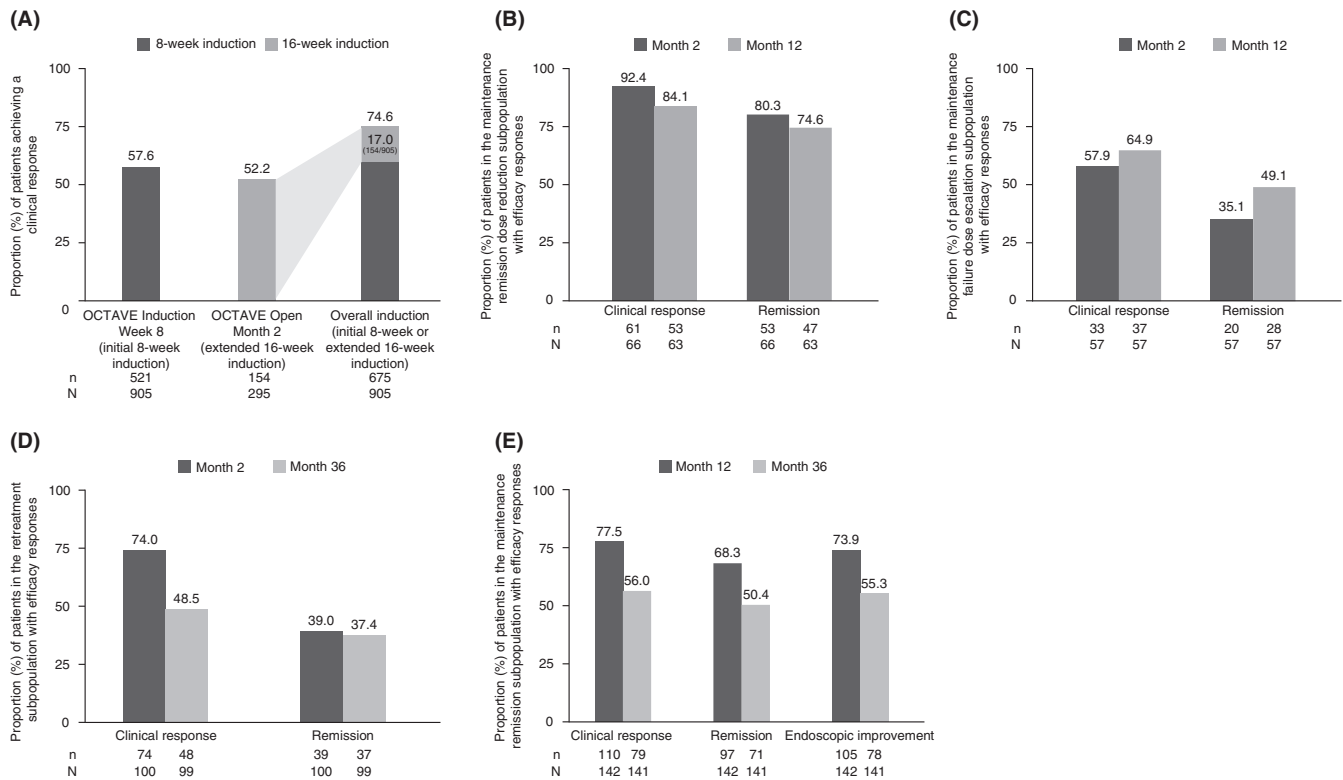
FIGURE 2 Key efficacy outcomes in subpopulations of the tofacitinib UC clinical programme. (A) Efficacy of extended induction with tofacitinib 10 mg b.d.[10] (B) Efficacy amongst patients who had a clinical response to tofacitinib 10 mg b.d. induction therapy who were in remission following 52 weeks of tofacitinib 10 mg b.d. maintenance therapy, and subsequently dose-reduced to 5 mg b.d. in OCTAVE Open.[11] (C) Efficacy amongst patients who had a clinical response to tofacitinib 10 mg b.d. induction therapy, subsequently experienced treatment failure after being re-randomised to receive tofacitinib 5 mg b.d. maintenance therapy and then had their dose increased to tofacitinib 10 mg b.d. in OCTAVE Open.[11] (D) Efficacy amongst patients who experienced treatment failure whilst receiving placebo in OCTAVE Sustain and who were retreated with tofacitinib 10 mg b.d. in OCTAVE Open.[13] (E) Efficacy amongst patients who were in remission following 52 weeks of tofacitinib treatment in OCTAVE Sustain and received 5 mg b.d. during OCTAVE Open.[12] b.d., twice daily; N, number of patients in subpopulation; n, number of patients achieving endpoint; UC, ulcerative colitis.

dose-dependent side effects associated with long-term immunosuppression (including management of illnesses, such as infections, whereby immunosuppressive therapies might delay recovery, and malignancy) and decreasing treatment-related costs.[20,21] Currently, tofacitinib product labels and clinical guidelines state that the lowest effective dose needed to maintain response should be used,[14,18,22,23] and clinicians should carefully consider the benefits and risks for the individual patient.

2.2.1 | What is known from observations in the UC clinical programme?

The effect of dose reduction on the efficacy of tofacitinib was evaluated throughout the UC clinical programme (Figure 1B). Amongst patients who received tofacitinib 15 mg b.d. (n = 22) or 10 mg b.d. (n = 905) during OCTAVE Induction 1 and 2 and were re-randomised to receive tofacitinib 5 mg b.d. in OCTAVE Sustain, 32.4% (57/176) of patients were in remission at Week 52 of OCTAVE Sustain.[1] A post hoc analysis assessed dose reduction amongst patients with clinical

response to tofacitinib induction therapy who were in remission following 52 weeks of tofacitinib 10 mg b.d. maintenance therapy and subsequently dose-reduced to 5 mg b.d. in OCTAVE Open. After tofacitinib dose reduction, clinical response was maintained in 92.4% (61/66) and 84.1% (53/63) of patients at Months 2 and 12, respectively.[11] In OCTAVE Sustain, higher rates of remission were observed at Week 52 amongst patients with prior TNFi failure who received tofacitinib 10 mg b.d. compared with patients who received 5 mg b.d. (36.6% vs. 24.1%).[24]

The effect of dose reduction on efficacy outcomes was also evaluated in the 6-month primary completion analysis of the RIVETING study, which assessed the efficacy and safety of tofacitinib in patients with UC in stable remission (≥6 months) on tofacitinib 10 mg b.d. (≥2 consecutive years) who dose reduced to tofacitinib 5 mg b.d., compared with patients who remained on tofacitinib 10 mg b.d. This analysis reported that, of the 70 patients re-randomised to tofacitinib 5 mg b.d. in the study, 77.1% (54/70) of patients were in modified Mayo score remission at Month 6 (defined as an endoscopic subscore of ≤1, a stool frequency subscore of ≤1 and a rectal bleeding subscore of 0).[3] Of note, patients in deep remission at baseline

(an endoscopic subscore of 0; 82.4% [42/51]) were more likely to maintain remission following dose reduction than those not in deep remission at baseline (endoscopic subscore of 1; 63.2% [12/19]). Moreover, patients without prior TNFi failure (79.1% [34/43]) were more likely to maintain remission following dose reduction than those with prior TNFi failure (74.1% [20/27]).[3]

2.2.2 | Real-world and registry database observations

A retrospective, observational study of 30 Japanese patients with UC showed that response and remission rates were maintained up to 52 weeks following dose reduction from tofacitinib 20 mg/day to tofacitinib 10 mg/day after the 8-week induction period (47% and 40% of patients had clinical response and remission, respectively, at Week 8; corresponding values at Week 52 were 45% and 41%, respectively).[9]

In another retrospective observational study of 134 patients with UC in the UK, 78% (81/104) of patients who received tofacitinib 10 mg b.d. induction therapy reduced their dose to 5 mg b.d. after a median of 73 days (interquartile range 56–99). Following dose reduction, 32% (24/74) of patients relapsed after a median of 41 days (interquartile range 26–91).[6]

2.2.3 | Interpretation and conclusions

Overall, the clinical data suggest that the majority of patients are able to maintain tofacitinib-induced remission on the lower dose, at least up to 52 weeks.[9,11] However, data published from the OCTAVE Sustain and RIVETING studies suggest that patients with prior TNFi failure may be more likely to relapse following dose reduction than patients without prior TNFi failure.[3,24] Due to the high risk of relapse for these patients (i.e. patients with prior biological failure), dose reduction may present a challenging clinical scenario. Conversely, patients without prior TNFi failure are more likely to maintain remission after dose reduction and may be less likely to require subsequent dose increase.[3]

Clinical guidance and the product label state that the lowest effective dose of tofacitinib for maintenance treatment should be used[14,18,22,23]; therefore, the clinician must carefully consider the patient's overall disease severity, including endoscopic disease activity, history of prior biological therapy and potential dose-dependent adverse events, when making decisions around benefits and risks with regards to dosing. Patients who reduce their dose of tofacitinib should be monitored closely for symptoms and signs of disease relapse, as some patients may be at high risk of loss of response after dose reduction.

Thus far, outcomes in the RIVETING study are from a 6-month primary completion analysis, and the planned longer-term analyses may better determine patients at risk of relapse following dose reduction. The US prescribing information states that tofacitinib is indicated for patients who had an inadequate response or are

intolerant to TNFi,[14] therefore additional real-world data will be key to understanding the long-term implications of dose reduction in refractory patients.

2.3 | Can loss of clinical response with tofacitinib be recaptured with dose increase?

2.3.1 | What is known from observations in the UC clinical programme?

Dose increase to recapture response was explored in the OCTAVE Open study amongst patients with maintenance treatment failure (Figure 1C). A post hoc analysis evaluated a group of patients who had a clinical response to tofacitinib 10 mg b.d. induction therapy, subsequently experienced treatment failure after being re-randomised to receive tofacitinib 5 mg b.d. maintenance therapy and then had their dose increased to tofacitinib 10 mg b.d. in OCTAVE Open.[11] Following dose increase, 57.9% (33/57) and 64.9% (37/57) of patients recaptured clinical response at Months 2 and 12, respectively.[11]

Patients who had their dose increased following a flare during OCTAVE Open were also assessed (Figure 1D). Flare was defined as an increase in total Mayo score of ≥3 points from a baseline of OCTAVE Sustain, accompanied by an increase in rectal bleeding and endoscopic subscores of ≥1 point, after a minimum of 8 weeks of treatment. Amongst the maintenance remission subpopulation (163 patients who were in remission at Week 52 following tofacitinib treatment in OCTAVE Sustain who received 5 mg b.d. during OCTAVE Open), the tofacitinib dose was increased from 5 to 10 mg b.d. due to flare in 25.2% (41/163) of patients. Following dose increase, 73.2% (30/41), 58.5% (24/41), 64.1% (25/39) and 48.7% (19/39) of patients achieved partial Mayo score remission at Months 3, 6, 9 and 12, respectively (non-responder imputation).[12]

2.3.2 | Real-world and registry database observations

Whilst real-world data that comment specifically on dose increase following tofacitinib treatment failure are limited, results from a retrospective observational cohort study of 134 patients with UC in the UK support the clinical trial data. In this study, efficacy outcomes were assessed with tofacitinib for up to 26 weeks, with dose increase successfully recapturing response in approximately half (47% [9/19]) of patients who had lost response.[6]

2.3.3 | Interpretation and conclusions

Patients who relapse after dose reduction may be able to recapture response after increasing to tofacitinib 10 mg b.d.[6,11] However, as

not all patients respond to dose increases, clinicians should carefully consider factors that could be used to guide dose reduction of tofacitinib, to minimise the risk of failing to recapture response (discussed in Section 2.2.3).

2.4 | What is the expectation for patients after temporary treatment interruption and subsequent retreatment?

Interruption of UC treatment may be necessary for a variety of reasons, including illness, pregnancy, adverse events, comorbidities, infection, surgery, or funding.[25] It is, therefore, important for physicians managing patients with UC to understand the possible clinical consequences of temporarily discontinuing a therapy, such as relapse rates and time to relapse.

The potential to recapture response following retreatment with UC therapy is an important consideration when interrupting treatment. Retreatment with biologics can be challenging due to the risk of neutralising anti-drug antibody formation leading to secondary loss of response.[25] However, as tofacitinib is a small molecule, the risk of it inducing an immunogenic response that might limit retreatment is extremely low.[26]

2.4.1 | Temporary treatment interruption: what is known from observations in the UC clinical programme?

In the OCTAVE studies, the effect of treatment interruption was evaluated in 174 patients who had a clinical response at the end of OCTAVE Induction 1 and 2 and were re-randomised to receive a placebo for 52 weeks in OCTAVE Sustain (the 'temporary treatment interruption' subpopulation; Figure 1E). Following treatment interruption, the proportion of patients with clinical response in the temporary treatment interruption subpopulation declined from 98.9% (172/174) at OCTAVE Sustain baseline (end of OCTAVE Induction 1 and 2) to 19.0% (33/174) at Week 52 of OCTAVE Sustain.[13]

Median time to treatment failure following interruption of tofacitinib treatment was 169 (95% confidence interval [CI], 94.0–179.0) and 123 (95% CI, 91.0–168.0) days for patients who achieved remission following tofacitinib induction therapy, and patients who achieved clinical response but not remission, respectively.[13] Treatment failure was defined as an increase from OCTAVE Sustain baseline total Mayo score of ≥3 points, plus an increase in rectal bleeding subscore and endoscopic subscore of ≥1 point, and an absolute endoscopic subscore ≥2 points after ≥8 weeks of maintenance therapy.[13] At Week 8 in OCTAVE Sustain, rates of treatment failure following treatment interruption were 21.7% (95% CI, 11.2–34.5) in patients who achieved remission following induction therapy, versus 29.0% (95% CI, 20.9–37.4) in patients who had a clinical response but were not in remission. Corresponding rates of treatment failure

at Week 52 were 81.8% (95% CI, 67.0–90.4) versus 72.4% (95% CI, 62.7–80.0).[13]

2.4.2 | Recapture of response with retreatment: what is known from observations in the UC clinical programme?

In the OCTAVE studies, the 'retreatment' subpopulation consisted of patients from the 'treatment interruption' subpopulation who experienced treatment failure between Week 8 (first post-baseline assessment) and Week 52 of OCTAVE Sustain (whilst receiving placebo), and subsequently entered OCTAVE Open and received tofacitinib 10 mg b.d.

Following retreatment with tofacitinib, rates of clinical response and remission were 74.0% (74/100) and 39.0% (39/100) of patients, respectively, at Month 2 (non-responder imputation); in OCTAVE Open, non-responder imputation was used for missing data before discontinuation. Corresponding values at Month 36 were 48.5% (48/99) and 37.4 (37/99) (Figure 2D).[13] Amongst patients in remission following tofacitinib induction therapy and patients with a clinical response but not in remission, rates of clinical response at Month 36 were 60.6% (20/33) and 42.4% (28/66; non-responder imputation), respectively.[13] Response to retreatment was similar in those who had not previously failed TNFi treatment.[13]

2.4.3 | Real-world and registry database observations

There are currently no published real-world studies directly relating to outcomes following temporary interruption or retreatment with tofacitinib therapy of which the authors are aware.

2.4.4 | Interpretation and conclusions

Loss of response to tofacitinib following treatment interruption may occur within 6 months or less amongst patients not in remission at the time of cessation of therapy.[13] However, in patients with UC who had interrupted treatment with tofacitinib, retreatment with tofacitinib 10 mg b.d. was demonstrated to be safe and successful in a substantial proportion of patients within 2 months,[13] although not all patients recaptured response following retreatment with tofacitinib 10 mg b.d. Therefore, we suggest that any temporary interruption of tofacitinib treatment should be carefully considered on an individual basis and, if required, patients should be closely monitored for symptoms and signs of relapse. Whilst situations such as pregnancy may dictate the need for dose interruption, assessment of biomarkers (which have been shown to correlate with clinical outcomes in patients with UC)[19] and mucosa via endoscopy (as an indicator of clinical disease activity) may be useful in the decision to interrupt or restart tofacitinib treatment.

2.5 | What is the long-term efficacy of tofacitinib for patients who initially respond?

2.5.1 | What is known from observations in the UC clinical programme?

Of the 142 patients who were in remission following 52 weeks of tofacitinib treatment in OCTAVE Sustain and received 5 mg b.d. during OCTAVE Open, 68.3% (97/142) were in remission and 77.5% (110/142) had clinical response at Month 12 (non-responder imputation). Corresponding values at Month 36 were 50.4% (71/141) and 56.0% (79/141), respectively (Figure 2E).[12] Efficacy rates were sustained over 36 months of treatment, regardless of whether patients had previously received tofacitinib 5 or 10 mg b.d. during maintenance treatment and regardless of their prior TNFi failure status.[12] Steroid tapering was mandatory in OCTAVE Open; therefore, patients who remained in the study were steroid-free.[27]

2.5.2 | Real-world and registry database observations

As it is too early for long-term analysis of tofacitinib effectiveness in real-world populations, there is an opportunity for future studies to examine this area.

2.5.3 | Interpretation and conclusions

Whilst there is currently limited long-term efficacy data for tofacitinib from patients in the real world, published results from the tofacitinib UC clinical programme suggest that rates of remission, endoscopic improvement and clinical response were maintained over 36 months of treatment.[12] This highlights the importance of deep remission, not just response, when considering the success of any UC treatment in inducing a durable remission in patients.

3 | CLINICAL SAFETY CONSIDERATIONS

Patients with inflammatory bowel disease (IBD) are known to have a higher risk of certain health complications, including infection, malignancy, NMSC, venous thromboembolism and cardiovascular morbidity.[28–32] JAK inhibitors, such as tofacitinib, have an immunomodulatory mechanism of action, blocking the JAK-signal transducer and activator of the transcription pathway and, in turn, inhibiting multiple cytokine signalling pathways.[33] It is therefore important to consider the safety profile of tofacitinib over time and to establish whether any adverse safety outcomes are related to the tofacitinib dose.

Adverse events of special interest have been evaluated amongst patients throughout the tofacitinib UC clinical programme. Adverse events were assessed in three cohorts: Induction Cohort (patients receiving placebo or tofacitinib 10 mg b.d. for 8 weeks in the induction studies), Maintenance Cohort (patients receiving placebo or tofacitinib 5 or 10 mg b.d. in the 52-week maintenance study) and Overall Cohort (patients receiving ≥1 dose of tofacitinib 5 or 10 mg b.d. in Phase 2, Phase 3 and OLE studies; analysis in the Overall Cohort was by predominant dose [5 or 10 mg b.d. based on average daily dose <15 mg or ≥ 15 mg, respectively]).[27] Incidence rates (IRs, calculated as the number of unique patients with events per 100 patient-years) of adverse events of special interest in the Overall Cohort are summarised in Table 1.

3.1 | Risk of infection

Compared with the general population, patients with IBD are at higher risk of infections including opportunistic infections and herpes zoster, likely due to the use of immunosuppressive therapies.[28,34] Corticosteroids, thiopurines and TNFi have all been shown to be significantly associated with the risk of opportunistic infection amongst patients with IBD (univariate analysis; odds ratio [OR] 3.4 [95% CI, 1.8–6.2]; OR 3.1 [95% CI, 1.7–5.5] and OR 4.4 [95% CI, 1.2–17.1], respectively). The risk of opportunistic infection was further increased when any of these therapies were used in combination (multivariate analysis; 1 therapy, OR 2.9 [95% CI, 1.5–5.3] vs 2 or 3 therapies, OR 14.5 [95% CI 4.9–43]).[34]

The risk of herpes zoster has also been reported to be significantly associated with corticosteroids (OR 1.73 [95% CI, 1.51–1.99]), thiopurines (OR 1.85 [95% CI, 1.61–2.13]) and TNFi (OR 1.81 [95% CI, 1.48–2.21]) therapies amongst patients with IBD in a multivariate analysis.[35]

3.1.1 | What is known from observations in the UC clinical programme?

A recent post hoc analysis of data from the tofacitinib UC clinical programme demonstrated that IRs for adverse events of special interest remained stable over an extended period (up to 7.8 years of treatment).[36] There were no significant changes from the previous data cut which found that serious infections were more frequent with tofacitinib 10 mg b.d. versus placebo during induction, whereas rates were comparable between placebo and tofacitinib 5 and 10 mg b.d. groups during maintenance. Overall, serious infections were generally infrequent (Overall Cohort IR 1.70 [95% CI 1.24–2.27]) in patients treated with tofacitinib 5 or 10 mg b.d., regardless of dose or duration of treatment.[37]

Herpes zoster IR was numerically higher with tofacitinib 10 mg b.d. versus placebo during induction; in the Maintenance Cohort, herpes zoster IR was numerically higher in the tofacitinib 10 mg b.d. group versus the tofacitinib 5 mg b.d. group. However, over time in the Overall Cohort, IRs were similar between doses and remained stable.[37] Non-herpes zoster opportunistic infections occurred infrequently (Overall Cohort IR 0.15 [95% CI 0.04–0.38]) in the tofacitinib

TABLE 1 Proportions and IRs[a] of adverse events of special interest in the tofacitinib UC clinical programme, up to 7.8 years of exposure[36]

	Maintenance Cohort (52 weeks)			Overall Cohort (≤7.8 years)		
	Placebo (N = 198; 100.4 PY)	Tofacitinib 5 mg b.d. (N = 198; 146.2 PY)	Tofacitinib 10 mg b.d. (N = 196; 154.3 PY)	PD tofacitinib 5 mg b.d. (N = 201; 776.4 PY)	PD tofacitinib 10 mg b.d. (N = 956; 2038.0 PY)	Tofacitinib All (N = 1157; 2814.4 PY)
Serious infections[b]						
n (%)	2 (1.0)	2 (1.0)	1 (0.5)	10 (5.0)	40 (4.2)	50 (4.3)
IR [95% CI]	1.94 [0.23–7.00]	1.35 [0.16–4.87]	0.64 [0.02–3.54]	1.26 [0.60–2.31]	1.90 [1.36–2.59]	1.72 [1.28–2.27]
Herpes zoster (non-serious and serious)[b]						
n (%)	1 (0.5)	3 (1.5)	10 (5.1)	22 (10.9)	70 (7.3)	92 (8.0)
IR [95% CI]	0.97 [0.02–5.42]	2.05 [0.42–6.00]	6.64 [3.19–12.22]	3.02 [1.89–4.58]	3.51 [2.74–4.44]	3.38 [2.73–4.15]
Opportunistic infections[b,c,d]						
n (%)	1 (0.5)	2 (1.0)	4 (2.0)	8 (4.0)	22 (2.4)	30 (2.7)
IR [95% CI]	0.97 [0.02–5.42]	1.36 [0.16–4.92]	2.60 [0.71–6.65]	1.04 [0.45–2.05]	1.05 [0.66–1.60]	1.05 [0.71–1.50]
Malignancies excluding NMSC[c,d,e]						
n (%)	1 (0.5)	0 (0.0)	0 (0.0)	5 (2.5)	20 (2.2)	25 (2.2)
IR [95% CI]	0.97 [0.02–5.39]	0.00 [0.00–2.48]	0.00 [0.00–2.35]	0.63 [0.20–1.47]	0.95 [0.58–1.46]	0.86 [0.56–1.27]
NMSC[c,d,e]						
n (%)	1 (0.5)	0 (0.0)	3 (1.5)	5 (2.5)	16 (1.7)	21 (1.9)
IR [95% CI]	0.97 [0.02–5.40]	0.00 [0.00–2.48]	1.91 [0.39–5.59]	0.63 [0.21–1.48]	0.77 [0.44–1.25]	0.73 [0.45–1.12]
MACE[c,d,e]						
n (%)	0 (0.0)	1 (0.5)	1 (0.5)	4 (2.0)	4 (0.4)	8 (0.7)
IR [95% CI]	0.00 [0.00–3.57]	0.68 [0.02–3.77]	0.64 [0.02–3.54]	0.51 [0.14–1.30]	0.19 [0.05–0.48]	0.28 [0.12–0.54]
Deep vein thrombosis[b]						
n (%)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
IR [95% CI]	0.97 [0.02–5.39]	0.00 [0.00–2.48]	0.00 [0.00–2.35]	0.00 [0.00–0.46]	0.05 [0.00–0.26]	0.03 [0.00–0.19]
Pulmonary embolism[b]						
n (%)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)	5 (0.4)
IR [95% CI]	0.98 [0.02–5.44]	0.00 [0.00–2.48]	0.00 [0.00–2.35]	0.00 [0.00–0.46]	0.24 [0.08–0.55]	0.17 [0.06–0.40]
Gastrointestinal perforations[b,c,f]						
n (%)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.2)	3 (0.3)
IR [95% CI]	0.97 [0.02–5.39]	0.00 [0.00–2.48]	0.00 [0.00–2.35]	0.13 [0.00–0.70]	0.09 [0.01–0.34]	0.10 [0.02–0.30]

TABLE 1 (Continued)

	Maintenance Cohort (52 weeks)			Overall Cohort (≤7.8 years)		
	Placebo (N = 198; 100.4 PY)	Tofacitinib 5 mg b.d. (N = 198; 146.2 PY)	Tofacitinib 10 mg b.d. (N = 196; 154.3 PY)	PD tofacitinib 5 mg b.d. (N = 201; 776.4 PY)	PD tofacitinib 10 mg b.d. (N = 956; 2038.0 PY)	Tofacitinib All (N = 1157; 2814.4 PY)
Death[e]						
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.7)	7 (0.6)
IR [95% CI]	0.00 [0.00–3.57]	0.00 [0.00–2.48]	0.00 [0.00–2.35]	0.00 [0.00–0.46]	0.33 [0.13–0.68]	0.24 [0.10–0.49]

Abbreviations: b.d., twice daily; CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular events; N, number of patients who received at least one dose of the study drug; n, number of patients with the specified event within the given category; NMSC, non-melanoma skin cancer; PD, predominant dose; PY, patient-years; UC, ulcerative colitis.

[a]IRs were calculated as the number of unique patients with events per 100 PY.

[b]Events that occurred >28 days after the last dose of the study drug were excluded.

[c]Adjudicated events.

[d]For adjudicated events, N = 923 and N = 1124 for PD tofacitinib 10 mg b.d. and Tofacitinib All, respectively, in the Overall Cohort (excludes Phase 2).

[e]For the Maintenance Cohort, events that occurred >28 days after the last dose of the study drug were excluded; for the Overall Cohort, all events, including those outside the 28-day risk period, were included.

[f]Gastrointestinal perforation excludes preferred terms of pilonidal cyst, perirectal abscess, rectal abscess, anal abscess, perineal abscess and any preferred terms containing the term fistula.

UC clinical programme.[37] Other than herpes zoster, there was no specific clustering of viral infections or viral opportunistic infections in the tofacitinib UC clinical programme.[37]

3.2 | Risk of venous thromboembolism

Patients with IBD have a higher risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) compared with the general population.[38] A recent international consensus on the prevention of venous and arterial thrombotic events recommends that deep remission should be the goal for treating patients as an active disease is a significant risk factor.[38]

3.2.1 | What is known from observations in the UC clinical programme?

In the tofacitinib UC clinical programme, the incidence of venous thromboembolic events was evaluated in a post hoc analysis of 1157 patients with up to 6.1 years of tofacitinib treatment. In the Induction Cohort, one patient had DVT and one had PE; the same was true in the Maintenance Cohort. All four of these patients received placebo, highlighting the risk of venous thromboembolism in patients with untreated UC.[39]

In the Overall Cohort, one patient had DVT and four had PE. All events occurred during the OLE study amongst patients who received a predominant dose of 10 mg b.d. throughout the tofacitinib UC clinical programme. Of note, the majority of patients (83%) in the Overall Cohort received a predominant dose of 10 mg b.d., and all patients with DVT or PE events had venous thromboembolism risk factors (e.g., a history of smoking, history of oral contraceptive use or history of DVT/PE) in addition to UC.[39]

The ORAL Surveillance study evaluated patients with rheumatoid arthritis and cardiovascular risk factors with the primary objective of demonstrating the noninferiority of tofacitinib compared to TNFi for MACE and malignancies (excluding NMSC).[17,40] During the study, the Rheumatology Data Safety Monitoring Board observed that treatment with tofacitinib 10 mg b.d. was associated with an increase in PE relative to TNFi.[17] Importantly, the study also found that the risk of VTE was highest in patients with a history of VTE irrespective of the treatment received.[41] Subsequently, in 2019, the tofacitinib 10 mg b.d. arm of the study was stopped, and this resulted in revisions to the product label, including the US Prescribing Information and Boxed Warning for thrombosis.[14] These revisions included the movement of the position of tofacitinib treatment to after TNFi failure in the US and recommendations to use the lowest effective dose of tofacitinib and to screen for VTE risk prior to tofacitinib treatment.[14] An international consensus on the prevention of venous and arterial thrombotic events in patients with IBD involving 14 IBD experts and 3 thrombosis experts was recently published in which it was concluded that further evidence is needed regarding the

drug-related risk of thrombosis with newer therapies in patients with IBD.[38]

3.3 | Risk of cardiovascular morbidity

Although patients with IBD generally have a lower body mass index and lower prevalence of diabetes and hypertension than the general population[42–44]; conversely, they have a higher risk of cardiovascular morbidity.[32,42]

3.3.1 | What is known from observations in the UC clinical programme?

A recent review of data from OCTAVE Open on lipid levels and major adverse cardiovascular events (MACE) in patients with UC receiving tofacitinib showed that tofacitinib treatment was not associated with major changes from baseline in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, total cholesterol: high-density lipoprotein cholesterol ratio and low-density lipoprotein cholesterol: high-density lipoprotein cholesterol ratio. Furthermore, lipid levels and ratios remained generally stable over time. In this analysis of the Phase 3 OLE study, MACE were infrequent (IR 0.26).[45] A previous analysis of data from the Phase 2 and OCTAVE studies found reversible increases in lipid levels with tofacitinib treatment with no meaningful changes in lipid ratios or Reynolds Risk Score.[46]

ORAL Surveillance was a large, randomised, post-marketing safety study in patients with rheumatoid arthritis ≥50 years old with at least one additional cardiovascular risk factor evaluating the safety of tofacitinib at two doses (5 and 10 mg b.d.) vs TNFi.[16,17] Initial co-primary endpoint results showed that patients treated with tofacitinib had a higher rate of MACE and malignancies relative to TNFi, regardless of tofacitinib dose received.[16] Study findings have resulted in revisions to the product label, including the US Prescribing Information Boxed Warning which has been updated to include MACE and revised for mortality, malignancies, and thrombosis; the warning describes that rheumatoid arthritis patients treated with tofacitinib in the ORAL Surveillance study had higher rates of these events compared to those treated with TNFi.[14] Clinicians are advised to carefully consider the benefits and risks of tofacitinib therapy, particularly in patients who are current or ex-smokers and patients with other cardiovascular risk factors.[14]

Table 2 shows baseline demographics of the ORAL Surveillance rheumatoid arthritis study and the tofacitinib UC clinical programme populations, respectively. ORAL Surveillance specifically enrolled a cardiovascular risk-enriched patient population (patients were ≥50 years with at least one cardiovascular risk factor and had to have been receiving methotrexate to be eligible for enrolment).[17] Patients enrolled in the tofacitinib UC clinical programme were generally younger and healthier in the context of cardiovascular risk (amongst patients receiving ≥1 dose of tofacitinib in the Overall Cohort of the tofacitinib UC clinical programme, the mean age was 41.3 years (standard deviation 13.9 years); 13.8% of patients had a

TABLE 2 Baseline demographics of the ORAL Surveillance tofacitinib rheumatoid arthritis study population and the tofacitinib UC clinical programme population

	ORAL Surveillance[17]		Tofacitinib UC clinical programme Overall Cohort[27,45]
	Tofacitinib 5 mg b.d. (*N* = 1455)	Tofacitinib 10 mg b.d. (*N* = 1456)	Tofacitinib All[a] (*N* = 1157)
Age			
Mean, years	60.8 ± 6.8	61.4 ± 7.1	41.3 ± 13.9
Age ≥ 65 years, *n* (%)	413 (28.4)	478 (32.8)	77 (6.7)
Female, *n* (%)	1169 (80.3)	1124 (77.2)	478 (41.3)
Race			
White	1128 (77.5)	1126 (77.3)	927 (80.1)
Black	63 (4.3)	65 (4.5)	10 (0.9)
Asian	65 (4.5)	56 (3.8)	144 (12.4)
Other	199 (13.7)	209 (14.4)	42 (3.6)
Smoking status, *n* (%)			
Never smoked	735 (50.5)	752 (51.6)	716 (63.7)[b,c]
Ever smoked	720 (49.5)	704 (48.4)	408 (36.3)[b,c]

Abbreviations: b.d., twice daily; *N*, number of patients in the treatment group; *n*, number of unique patients with characteristics; OLE, open label, long-term extension; *SD*, standard deviation; UC, ulcerative colitis.

[a]Tofacitinib All: all patients receiving 5 or 10 mg b.d. in Phase 2/Phase 3/OLE studies.

[b]Based on data collected at the start of the phase 3 induction studies.

[c]*N* = 1124.

body mass index ≥30 kg/m^2, and 94.8% of patients were either non-smokers or ex-smokers).[27,45]

3.4 | Risk of malignancy (excluding NMSC)

Patients with UC have a higher risk of developing a malignancy compared with the general population.[30] This may be due to the disease itself, the use of immunosuppressive therapies or a combination of both factors.[29]

3.4.1 | What is known from observations in the UC clinical programme?

A recent analysis in the tofacitinib UC clinical programme of treatment durations up to 6.8 years demonstrated that malignancies occurred infrequently and that the risk did not increase over time. Furthermore, there did not appear to be any apparent clustering of type of malignancy.[47] The IR of malignancy (excluding NMSC) with tofacitinib was similar to that in patients with UC treated with biologics, as reported from claims data (IR 0.75 vs IR 0.63, respectively).[47,48]

Similar to the risk of MACE, results from the ORAL Surveillance study showed that patients treated with tofacitinib had a higher rate of malignancies (excluding NMSC), including lung cancer and lymphoma, relative to TNFi, regardless of tofacitinib dose received,[16,17] resulting in revisions to the product label including the US Prescribing Information and Boxed Warning for malignancies.[14] Subgroup analyses from ORAL Surveillance have shown that differences in the risk of MACE and malignancies between tofacitinib and TNFi were more pronounced in patients aged ≥65 years versus younger patients. Even though patients enrolled in the tofacitinib UC clinical programme were generally younger, the risk of malignancies in patients with UC remains an important consideration.

3.5 | Risk of NMSC

Patients with UC have an increased risk of developing NMSC,[31] attributed to treatment with immunosuppressive therapies, particularly thiopurines.[49,50] Patients with UC who are naïve to thiopurines have the same risk of NMSC as the general population.[49]

3.5.1 | What is known from observations in the UC clinical programme?

Rates of NMSC in the tofacitinib UC clinical programme have remained stable over time (up to 6.8 years of treatment).[51] Furthermore, IRs with tofacitinib were similar to those in patients with UC treated with TNFi.[48,51] A review of risk factors identified in the Overall Cohort demonstrated that NMSC was more likely to occur in patients with the recognised risk factors of prior NMSC and increasing age.[52]

3.6 | Real-world and registry database observations on tofacitinib safety

A recent meta-analysis looking at the real-world safety of tofacitinib in patients with UC found that tofacitinib had a real-world safety profile similar to the profile reported in the tofacitinib UC clinical programme.[8] The authors acknowledged that, although herpes zoster risk appeared to be dose-dependent, it was not possible to fully evaluate the risk associated with the different doses from the available data.[8]

3.7 | Interpretation and conclusions in relation to tofacitinib safety

The safety profile of tofacitinib in patients with UC from the tofacitinib UC clinical programme was generally consistent with that of other UC therapies, including biologics, with the exception of herpes zoster.[48] Tofacitinib treatment is a known risk for herpes zoster[37]; however, clinicians should remember that other UC therapies, including corticosteroids, thiopurines, and TNFi, have also long been associated with a significantly increased risk of herpes zoster.[35] Furthermore, the use of vaccines may protect against herpes zoster infections in patients with IBD.[53] IRs for adverse events of special interest have remained stable over an extended period of time (up to 7.8 years).[36] Safety of tofacitinib in a real-world setting supports the results from the tofacitinib UC clinical programme; however, it is worth noting that the studies included in this real-world meta-analysis were generally small cohorts with short follow-up and a lack of protocolised reporting of adverse events.[8]

The tofacitinib UC clinical programme was not of sufficient size and duration to evaluate long-latency or rare safety events of interest including cardiovascular adverse events, opportunistic infections, and malignancy. As mentioned previously, findings from ORAL Surveillance have resulted in revisions to the tofacitinib product label including the US Prescribing Information Boxed Warning which has been updated to include MACE and revised for mortality, malignancies, and thrombosis.[14]

A recent meta-analysis of 26 studies reporting the efficacy or safety of tofacitinib in UC found a dose-dependent increase in adverse events with tofacitinib.[54] Due to the study design, the Overall Cohort included patients who had switched tofacitinib doses.[27] As >80% of patients received a predominant dose of tofacitinib 10 mg b.d., it is difficult to give a clear evaluation of tofacitinib dose dependency in relation to adverse events of special interest.[36]

As with discussion around other UC medications such as biologics, the risks of treatment should be discussed in the context of risks of untreated disease, which may also increase risks of infection due to the need for steroid dosing and risks of thromboembolic events
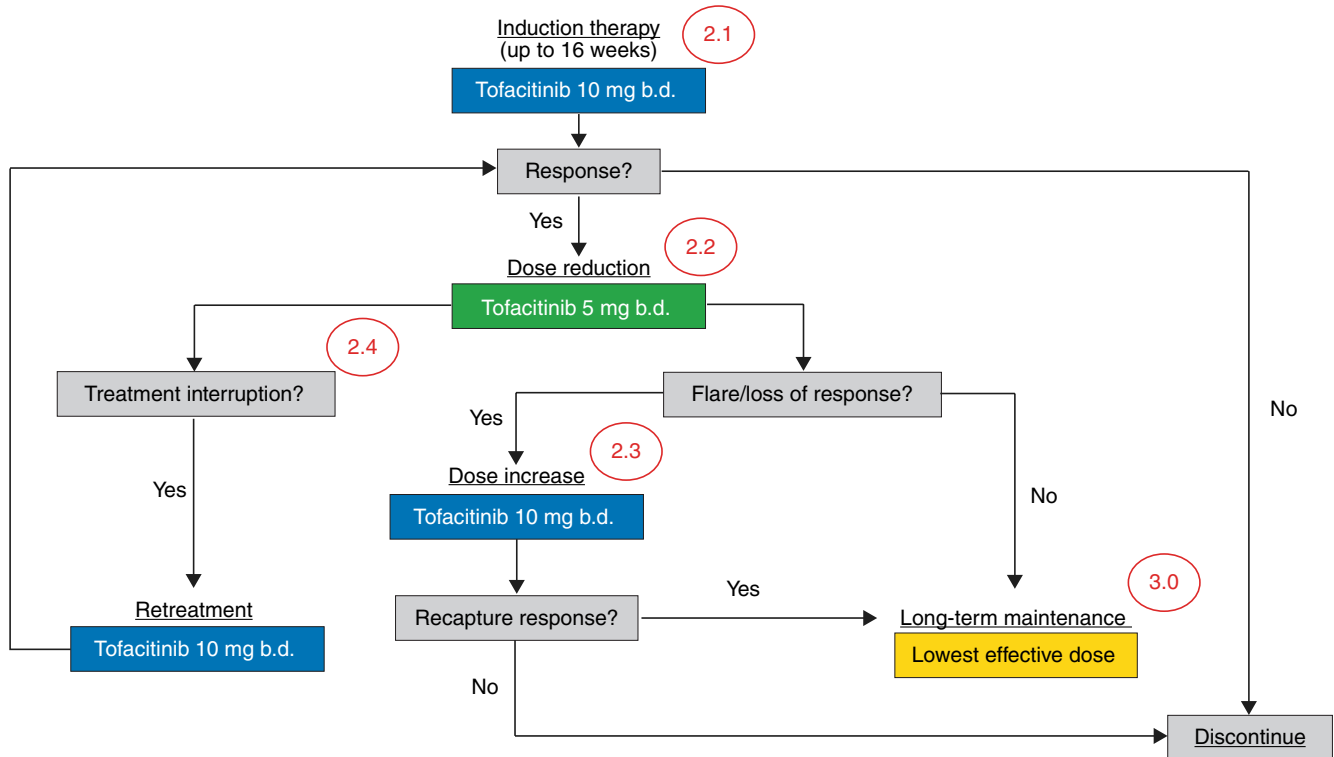
Key considerations

Extended induction (Section 2.1)
- When considering if extended induction with tofacitinib 10 mg b.d. will be of benefit in patients who do not achieve a clinical response after 8 weeks induction therapy, consider if the patient has been able to reduce their corticosteroid dose during the initial 8 weeks of tofacitinib induction therapy and shown some clinical improvement.
- Assessment of clinical symptoms and biomarkers, such as C-reactive protein or faecal calprotectin during induction therapy, may also help to guide decision-making.

Dose reduction (Section 2.2)
- When considering dose reduction from tofacitinib 10 mg b.d. to 5 mg b.d. in patients who previously had a flare/loss of response, consider the patient's overall disease severity, history of prior biological therapy and potential dose-dependent adverse events when making decisions around benefits and risks with regard to dosing.
- Patients who reduce their dose of tofacitinib should be monitored closely for symptoms and signs of disease relapse as some patients may be at high risk of loss of response after dose reduction.

Dose increase (Section 2.3)
- For patients with loss of response during maintenance treatment, the higher dose may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient.

Temporary treatment interruption and subsequent retreatment (Section 2.4)
- Patients should be carefully considered on an individual basis if temporary interruption of tofacitinib treatment is required. If tofacitinib treatment interruption is required, patients should be closely monitored for symptoms and signs of relapse.
- Assessment of biomarkers and mucosa via endoscopy may be useful in the decision to interrupt or restart tofacitinib therapy.

Safety and risk/benefit assessment (Section 3.0)
- For all patients, the risks of treatment should be discussed in the context of risks of untreated disease, which may also increase risks of infection due to the need for steroid dosing and risks of thromboembolic events due to active inflammation.
- A patient's individual risks for adverse events, particularly infection, malignancies, MACE and venous thromboembolic events, should be carefully assessed and, where possible, risks should be mitigated (eg herpes zoster vaccination).

FIGURE 3 Summary of tofacitinib dosing pathways in patients with UC. For each consideration, the relevant section of the article is shown in parentheses. Red numbers in the flow diagram correspond to the relevant section in the article. b.d., twice daily; UC, ulcerative colitis; MACE, major adverse cardiovascular events.

due to active inflammation. We recommend that a patient's individual risks for adverse events, particularly infection, malignancies, MACE and venous thromboembolic events, are carefully assessed and, where possible, risks are mitigated (e.g. varicella vaccination for herpes zoster).

4 | FUTURE PERSPECTIVES

Tofacitinib offers an oral alternative to patients with moderate to severe UC. Studies have highlighted other advantages of tofacitinib as a treatment option, including a lack of immunogenicity and its utility following TNFi failure in the treatment sequence for UC.[23,24,26] It also provides an opportunity for flexible dosing, which therefore raises questions about which patients should be maintained on 10 versus 5 mg b.d. Figure 3 presents a summary of the potential dosing pathways for patients with UC. Factors to consider include severity of disease, comorbidities, and previous exposure and response to other biologics. In the real world, clinicians must consider the balance of benefit and risk of tofacitinib 10 versus 5 mg b.d. in terms of dose-related side effects, as well as the safety implications of undertreating active disease. Patients in deep remission have been shown to be more likely to maintain remission than those with an endoscopic subscore of >0.

Clinicians should be reassured that long-term efficacy can be maintained with tofacitinib 5 mg b.d. in patients in remission. Furthermore, in patients whose dose reduce from tofacitinib 10 to 5 mg b.d., there are data to support that in the event of disease relapse, the response can be recaptured in a substantial number of patients. The data evaluated in this review are relevant to different clinical scenarios in practice. We recommend that all patients are closely monitored for disease relapse when dose reduction or interruption occurs, to maximise the chance of early recapture of response.

AUTHORSHIP
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Peter Irving: Conceptualization (equal); writing – review and editing (equal). **Yvette Leung:** Conceptualization (equal); writing – review and editing (equal). **Marla C Dubinsky:** Conceptualization (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT
Not applicable - this manuscript is a review of published articles all referenced (x54) in the draft.

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