Efficacy of JAK inhibitors in Ulcerative Colitis

Marc Ferrante and João Sabino

Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Corresponding author: Marc Ferrante, MD PhD, Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Herestraat 49, B3000 Leuven, Belgium. Email: marc.ferrante@uzleuven.be

Abstract

Janus kinase [JAK] inhibitors are a completely novel therapy for the treatment of patients with immune-mediated inflammatory disorders. The oral formulation of tofacitinib has recently been approved for the treatment of moderate-to-severe ulcerative colitis. In the placebo-controlled OCTAVE programme, tofacitinib proved to be efficacious for both inducing and maintaining clinical remission, and this both in anti-tumour necrosis factor-naïve and exposed patients. Several other anti-JAK inhibitors are currently explored. This review summarises the available efficacy data from all anti-JAK inhibitors in ulcerative colitis.

Key Words: JAK inhibition; tofacitinib; upadacitinib; ulcerative colitis; efficacy

1. Introduction

Ulcerative colitis [UC] is characterised by recurring episodes of inflammation limited to the mucosal layer of the colon. Inflammatory episodes give rise to rectal bleeding, diarrhoea, and abdominal pain. Most patients with UC can be treated successfully with a symptom-focused step-up approach comprising 5-aminosalicylates, sulphasalazine, corticosteroids, thiopurines, and calcineurin inhibitors. However, a population-based cohort study in 1994 showed that throughout follow-up with this treatment arsenal, UC remained active in up to 50% of patients and approximately 20% required colectomy. In the past 15 years, several new molecules have been introduced for the treatment of patients with moderate-to-severe UC. Biologic therapies include: the anti-tumour necrosis factor [anti-TNF] agents adalimumab, golimumab, and infliximab; the anti-α4β7 integrin vedolizumab; and the anti-interleukin 12/23 [anti-IL12/23] agent ustekinumab. As first-in-class, the JAK1/3 inhibitor tofacitinib [CP-690,550; Pfizer] has shown efficacy in patients with moderate-to-severe UC, and is currently approved by both the Food and Drug Administration [FDA] and the European Medicines Agency [EMA] for patients who previously had an inadequate response, loss of response, or were intolerant to either conventional therapy [mesalamine plus steroids or thiopurines] or a biologic agent.

Janus kinase [JAK] inhibitors are a completely novel type of therapy for the treatment of immune-mediated inflammatory diseases, including UC. These small molecules act intracellularly and—in contrast to the available biologic agents—can modulate the response of a variety of pro-inflammatory cytokines implicated in the pathogenesis of UC. The latter is probably resulting in a wider effect on [gastrointestinal] inflammation. As first-in-class, the JAK1/3 inhibitor tofacitinib [CP-690,550; Pfizer] has shown efficacy in patients with moderate-to-severe UC, and is currently approved by both the Food and Drug Administration [FDA] and the European Medicines Agency [EMA] for patients who previously had an inadequate response, loss of response, or were intolerant to either conventional therapy [mesalamine plus steroids or thiopurines] or a biologic agent. As shown in Table 1, several other anti-JAK inhibitors are currently under investigation, including: another anti-JAK1/3 inhibitor peficitinib [ASP015K, INJ-54781532; Astellas Pharma, Johnson & Johnson]; the anti-JAK1 inhibitors filgotinib [GLPG0634, Galapagos, Gilead Sciences], upadacitinib [ABT-494, Abbvie], itacitinib [INCB039110, Incyte Corporation], and SHR0302 [Jiangsu Hengrui Medicine Co, Reistone Biopharma]; the gut-selective pan-JAK inhibitor TD-1473 [Theravance Biopharma]; the anti-JAK1 inhibitor PF-06651600 [Pfizer]; and the anti-TYK2/JAK1 inhibitor PF-06700841 [Pfizer].

In this review, we will focus on the efficacy data available with tofacitinib and other anti-JAK inhibitors in the treatment of moderate-to-severe UC. We will discuss the clinical trial data as well as the limited real-world experience that is currently available.
evaluated in 194 adult patients with moderate-to-severe UC [total Mayo score 6–12, Mayo endoscopic sub-score 2–3]. Patients were randomly assigned to receive placebo \([n = 48]\) or tofacitinib at a dose of \(0.5 \text{ mg} [n = 31], 3 \text{ mg} [n = 33], 10 \text{ mg} [n = 33], \text{ or } 15 \text{ mg} [n = 49]\) twice daily \([\text{BID}]\) and this during an 8-week study period. Overall, 70% of patients were previously exposed to anti-TNF agents, 63% were on mesalamine, and 34% on oral prednisone at baseline. Concomitant immunomodulators or biologic therapies were not allowed.

The primary outcome was clinical response at Week 8, defined as an absolute decrease in total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding sub-score of at least 1 point or an absolute rectal bleeding sub-score of 0 or 1. As shown in Table 2, the primary endpoint was achieved by 42% of patients randomised to placebo, compared with 32\% \([p = 0.39]\), 48\% \([p = 0.55]\), 61\% \([p = 0.10]\), and 78\% \([p < 0.001]\) of patients randomised to tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg twice daily.

### Table 1. JAK inhibitors in IBD.

| Compound | Selectivity | Developmental stage in UC | Main results from trials | Pharmaceutical company |
|----------|-------------|----------------------------|--------------------------|------------------------|
| BMS-986165 | TYK2 | Phase 2 ongoing | No data yet | Bristol-Myers Squibb |
| Filgotinib [GLPG0634] | JAK1 | Phase 2/3 ongoing [NCT02914522] | No published data in UC yet | Galapagos, Gilead Sciences |
| Itacitinib [INC039110] | JAK1 | Phase 2 ongoing [NCT03627052] | No published data in UC yet | Incyte Corporation |
| Peficitinib [NJ-54781532, ASP015K] | JAK1/3 | Phase 2 completed [NCT01959282] | No dose-response was observed in the dose ranging trial. The high dose of 150 mg QD was associated with higher rates of clinical remission and mucosal healing | Astellas Pharma, Johnson & Johnson |
| PF-06651600 | JAK3 | Phase 2 ongoing [NCT02958865] | No published data in UC yet | Pfizer |
| PF-06700841 | TYK2/ JAK1 | Phase 2/3 ongoing [NCT02958865] | No published data in UC yet | Pfizer |
| SHR0302 | JAK1 | Phase 2 ongoing [NCT03675477] | No published data in UC yet | Jiangsu Hengrui Medicine Co., Reistone Biopharma |
| TD-1473 | JAK1/2/3 intestinally restricted | Phase 1b completed [NCT02818686] | Trend for higher rates of clinical response and endoscopic improvement | Theravance Biopharma |
| Tofacitinib [CP-690,550] | JAK1/3 | Approved | Two phase 3 RCTs confirmed the efficacy of tofacitinib in inducing remission after 8 weeks of treatment. Another phase 3 RCT showed efficacy of tofacitinib in maintaining remission | Pfizer |
| Upadacitinib [ABT-494] | JAK1 | Phase 2 completed [NCT02819635] Phase 3 ongoing [NCT03653026] | Higher rates of clinical remission and endoscopic improvement | Abbvie |

IBD, inflammatory bowel disease; UC, ulcerative colitis; RCT, randomised controlled trial; QD, once daily.

### Table 2. Efficacy endpoints in the phase 2 trial with tofacitinib.

|                     | Placebo \([n = 48]\) | Tofacitinib \(0.5 \text{ mg} [n = 31]\) | 3 mg \([n = 33]\) | 10 mg \([n = 33]\) | 15 mg \([n = 49]\) |
|---------------------|-----------------------|---------------------------------|-----------------|-----------------|-----------------|
| Clinical response   | 42\%                  | 32\% \(p = 0.39\)               | 48\% \(p = 0.55\) | 61\% \(p = 0.10\) | 78\% \(p < 0.001\) |
| Clinical remission  | 10\%                  | 13\% \(p = 0.76\)               | 33\% \(p = 0.01\) | 48\% \(p < 0.001\) | 41\% \(p < 0.001\) |
| Endoscopic response | 46\%                  | 52\% \(p = 0.64\)               | 58\% \(p = 0.30\) | 67\% \(p = 0.07\) | 78\% \(p = 0.001\) |
| Endoscopic remission| 2\%                   | 10\% \(p = 0.14\)               | 18\% \(p = 0.01\) | 30\% \(p < 0.001\) | 27\% \(p < 0.001\) |
| Mean \(\pm SD\) change in IBDQ from baseline | 27.8 \(\pm 29.8\) | 27.7 \(\pm 33.4\) | 30.3 \(\pm 27.3\) | 30.4 \(\pm 39.8\) | 50.7 \(\pm 35.6\) |

Clinical response: decrease in the total Mayo score with ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding sub-score of ≥1 point or absolute rectal bleeding sub-score of 0 or 1. Clinical remission: total Mayo score of ≤2, with no individual sub-score >1 point. Endoscopic response: a decrease in the endoscopy sub-score with ≥1. Endoscopic remission: endoscopic sub-score of 0.

IBDQ: Inflammatory Bowel Disease Questionnaire; SD: standard deviation.
2.2. Phase 3 programme with tofacitinib

The phase 3 OCTAVE programme consisted of two randomised, double-blind, placebo-controlled, 8-week induction trials [OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951], one randomised, double-blind, placebo-controlled 52-week maintenance trial [OCTAVE Sustain, NCT01458574], and an open label extension trial [OCTAVE Open, NCT01470612]. An overall flowchart of the OCTAVE study programme is shown in Figure 1. In the induction trials, patients were randomised 1:4 towards placebo or tofacitinib 10 mg BID, and for the maintenance trial patients who had responded after 8 weeks in the induction trials were re-randomised 1:1:1:1 towards placebo, tofacitinib 5 mg, or 10 mg, BID. Of note, the induction trials initially included groups who received tofacitinib at a dose of 15 mg BID, but the sponsor decided to discontinue further exploration of this dose after feedback of the regulatory authorities on their rheumatoid arthritis programme. In total, 22 patients with UC have been treated with this high induction dose of 15 mg tofacitinib BID. Eligible patients of OCTAVE Induction 1 and 2 had moderate-to-severe UC with a total Mayo score of 6 to 12, a rectal bleeding sub-score of at least 1, and a centrally read endoscopic sub-score of at least 2. Overall, 54% of patients were previously exposed to anti-TNF agents, and 46% were on oral prednisone at baseline. During the entire OCTAVE programme, concomitant immunomodulators or biologic therapies were not allowed.

As shown in Table 3, in both OCTAVE Induction 1 and Induction 2, the primary endpoint of clinical remission at Week 8 occurred more frequently in the tofacitinib 10 mg BID group compared with placebo [18.5% vs 8.2%, p = 0.007 for Induction 1; 16.6% vs 3.6%, p <0.001 for Induction 2]. In the OCTAVE Sustain trial, clinical remission at Week 52 occurred more frequently in both tofacitinib groups compared with placebo [34.3% in the 5 mg BID group, 40.6% in the 10 mg BID group, and 11.1% in the placebo group, p <0.001 for both comparisons]. For all secondary endpoints [clinical response, mucosal healing, endoscopic remission, Inflammatory Bowel Disease Questionnaire [IBDQ] remission], tofacitinib was significantly more efficacious than placebo [Table 3]. Of note, tofacitinib 10 mg BID significantly improved health-related quality of life during induction therapy, and improvements were maintained through the 52 weeks’ maintenance therapy. Among patients who were in clinical remission at entry into OCTAVE Sustain, sustained glucocorticoid-free remission occurred in 35.4% [23 of 65] in the 5 mg BID group, in 47.3% [26 of 55] in the 10 mg BID group, versus 5.1% [3 of 59] in the placebo group [p <0.001 for both comparisons].

Interestingly, in both induction trials, the effects on clinical remission and mucosal healing rates were similar between anti-TNF naïve and anti-TNF exposed patients. Similarly, concomitant therapy with corticosteroids in OCTAVE Induction 1 and 2 did not influence efficacy rates at Week 8. Furthermore, a post-hoc analysis of the OCTAVE induction trials showed already by Day 3 a significantly greater reduction in baseline stool frequency [-0.27 vs -0.11,
Clinical remission: total Mayo score of ≤2, with no individual sub-score >1 point and a rectal bleeding sub-score of 0. Clinical response: decrease from induction study baseline in Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding sub-score of ≥1 point or absolute rectal bleeding sub-score of 0 or 1. Mucosal healing: endoscopic sub-score of 0 or 1. Endoscopic remission: endoscopic sub-score of 0. IBDQ remission: an IBDQ score of ≥170.

### Table 3. Efficacy endpoints in the phase 3 program with tofacitinib.

|                        | OCTAVE Induction 1 | OCTAVE Induction 2 | OCTAVE Sustain |
|------------------------|--------------------|--------------------|----------------|
|                        | Placebo [n = 122] | 10 mg [n = 476]    | Placebo [n = 112] | 10 mg [n = 429] | Placebo [n = 198] | 5 mg [n = 198] | 10 mg [n = 197] |
| Clinical remission     | 8.2%               | 18.5%              | 3.6%           | 16.6% | 11.1% | 34.3% | 40.6% |
| p = 0.007             |                    |                    |                |       | p < 0.001 | p < 0.001 |               |
| Clinical response      | 32.8%              | 59.9%              | 28.6%          | 55.0% | 20.2% | 51.5% | 61.9% |
| p < 0.001             |                    |                    |                |       | p < 0.001 | p < 0.001 |               |
| Mucosal healing        | 15.6%              | 31.3%              | 11.6%          | 28.4% | 13.1% | 37.4% | 45.7% |
| p < 0.001             |                    |                    |                |       | p < 0.001 | p < 0.001 |               |
| Endoscopic remission   | 1.6%               | 6.7%               | 1.8%           | 7.0%  |       |       |       |
| p = 0.04              |                    |                    |                |       |       |       |       |
| IBDQ remission        | 37.7%              | 52.5%              | 25.9%          | 49.4% | 20.2% | 48.0% | 57.4% |
| p = 0.004             |                    |                    |                |       | p < 0.001 | p < 0.001 |               |

Clinical remission: total Mayo score of ≤2, with no individual sub-score >1 point and a rectal bleeding sub-score of 0. Clinical response: decrease from induction study baseline in Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding sub-score of ≥1 point or absolute rectal bleeding sub-score of 0 or 1. Mucosal healing: endoscopic sub-score of 0 or 1. Endoscopic remission: endoscopic sub-score of 0. IBDQ remission: an IBDQ score of ≥170.

IBDQ: Inflammatory Bowel Disease Questionnaire.

p < 0.01, total number of daily bowel movements [-1.06 vs -0.27, p < 0.0001] and rectal bleeding sub-score [-0.30 vs -0.14, p < 0.01] with tofacitinib 10 mg BID compared with placebo.10 This rapid onset of tofacitinib was regardless of previous anti-TNF failure status.

Patients who did not achieve clinical response at Week 8 in the OCTAVE induction trials could enter the open-label, long-term extension study [OCTAVE Open] with tofacitinib 10 mg BID. At Week 8 of the extension study [after a total of 16 weeks of induction therapy with tofacitinib 10 mg BID], 51.2% of patients had achieved clinical response.11 The total number of patients achieving clinical response with tofacitinib 10 mg BID after either 8 weeks of induction therapy [in OCTAVE Induction 1 and 2] or a total of 16 weeks of induction therapy [for non-responders to initial 8-week induction] was 74.0% [compared with 57.6% after OCTAVE Induction 1 and 2]. Of the patients who achieved clinical response after 16 weeks of induction therapy, 72.9% maintained clinical response throughout Week 52, and 45.1%, 45.1%, and 54.4%, achieved clinical remission, clinical steroid-free remission, and mucosal healing, respectively, at Week 52. Of note, patients who were still non-responders at Week 8 in the open-label extension [OLE] study were obligated to discontinue the trial.

A recent interim analysis, on the long-term efficacy of tofacitinib in the OCTAVE Open study, supported the long-term efficacy of tofacitinib.12 Patients who were in remission at Week 52 of OCTAVE Sustain continued tofacitinib at a dose of 5 mg BID. Clinical response, clinical remission, and mucosal healing rates at Month 36 in OCTAVE Open were 65.8%, 55.9%, and 62.5% [non-responder imputation], respectively. Patients who were not in remission when they entered OCTAVE Open received tofacitinib at a dose of 10 mg BID. In this more refractory population, clinical response, clinical remission, and mucosal healing rates at Month 36 in OCTAVE Open were 38.9%, 32.2%, and 35.8% [non-responder imputation], respectively.

In OCTAVE SUSTAIN, 174 patients who initially responded to 8 weeks of tofacitinib 10 mg BID were re-randomised to placebo, including 52 patients who were in clinical remission.13 Using non-responder imputation, clinical response, clinical remission, and mucosal healing rates at Week 52 were 19.0%, 10.3%, and 12.6%, respectively. During OCTAVE Sustain, treatment failure was defined as an increase with at least 3 points from OCTAVE Sustain baseline total Mayo score, with an increase in rectal bleeding sub-score and endoscopic sub-score of at least 1 point and an absolute endoscopic sub-score of 2 points or more after at least 8 weeks of maintenance therapy. Estimated cumulative rates of treatment failure were 26.6% at Week 8, 46.3% at Week 16, 65.3% at Week 24 and 75.3% at Week 52. The median time to treatment failure was 135 days after tofacitinib interruption; 101 patients who experienced treatment failure during OCTAVE Sustain under placebo therapy entered OCTAVE Open and received rescue therapy with tofacitinib 10 mg BID.14 Clinical response, clinical remission, and mucosal healing rates after 2 months were 75.5%, 40.4%, and 55.4%, respectively. At 12 months, the proportions were 67.5%, 43.4%, and 53.6%, respectively.

In addition, patients who were randomised to tofacitinib 5 mg BID during OCTAVE Sustain could be escalated to tofacitinib 10 mg BID in case of loss of response. Twelve months after dose escalation, 64.9% of patients recaptured clinical response, 49.1% were in clinical remission, and 57.9% showed mucosal healing. These proportions decreased to 54.7%, 39.6% and 47.2%, respectively, after 24 months.

### 2.3. Real-world evidence with tofacitinib

Since 2018, the results of seven cohort studies with tofacitinib for UC have been presented [Table 4]. These retrospective studies are, however, hampered by a low sample size, unclear definitions of outcome measures, and missing data.

A mixed retrospective refractory cohort from the University of Chicago included 53 patients with UC, four patients with Crohn’s disease, and one patient with pouchitis.16 Patients were treated with at least 8 weeks of tofacitinib 5 mg or 10 mg BID, and one patient received a daily dose of 11 mg of an extended release formulation. At Week 8, 21 patients [36%] achieved a clinical response defined as symptomatic improvement but not resolution, and an additional 19 patients [33%] achieved clinical remission defined as complete resolution of clinical symptoms. Steroid-free clinical remission at 8 weeks was achieved in 15 patients [26%]. Indication and drug dosing were not predictive of efficacy at Week 8.

In a French multicentre cohort study, 37 multirefractory UC patients were treated with tofacitinib 10 mg BID.17 The primary endpoint [survival without colectomy at Week 24] was achieved by 76.9% of the patients, and 62.6% of the patients were still on
tofacitinib at Week 24. Clinical response at Week 24 occurred in 40.5% of patients, including 12 patients [32.4%] who were in steroid-free clinical remission.

In a multicentre American cohort study, the investigators reported partial results of their cohort of 123 UC patients treated with tofacitinib 10 mg BID.18 Of note, only 96 patients completed treatment until Week 8. At Week 8, 60.8% [non-responder imputation: 48.0%] had clinical response and 13.5% [non-responder imputation: 10.6%] had clinical remission. At Month 6, 64.9% of 57 patients showed mucosal healing [non-responder imputation: 30.1%]. In multivariate analysis, bio-naïve status (odds ratio 5.50 [95% confidence interval 1.71–17.65], p = 0.004), female gender (4.00 [1.20–14.29], p = 0.02), and absence of baseline steroids (4.00 [1.20–12.50], p = 0.02) were associated with clinical response at Week 8.

In a separate retrospective trial from Seattle, 24 patients with moderate-to-severe UC were treated with tofacitinib 5 or 10 mg BID for at least 4 weeks.19 Mean [±standard deviation, SD] Simple Clinical Colitis Activity Index [SCCAI] dropped significantly from 7.18 [±2.97] to 4.53 [±3.44] [p = 0.009], and a numerical but not significant drop was observed for the Mayo endoscopic sub-score from 2.21 [±1.18] to 1.25 [±0.36] [p = 0.36].

A retrospective cohort study from Prague included 24 patients with UC, including 25% patients who were bio-naïve.20 After 8 weeks of tofacitinib 10 mg BID, mucosal healing [endoscopic Mayo sub-score ≤1] was demonstrated in 52.9% of the patients. In responders, the mean [±SD] total Mayo score decreased from 5.9 [±3.5] to 1.1 [±1.3] [p = 0.01], the mean endoscopic sub-score decreased from 2.0 [±1.0] to 0.6 [±0.7] [p = 0.02], the mean CRP dropped from 6.7 [±6.2] to 2.0 [±2.2] mg/L [p = 0.04], and the mean faecal calprotectin level dropped from 1195 [±1189] to 578 [±654] µg/g [p = 0.05]. These variables did not change significantly in non-responders.

### Table 4. Real-world evidence with tofacitinib for ulcerative colitis.

| Publication | Population | Treatment with tofacitinib | Outcome in the UC population | Result |
|-------------|------------|----------------------------|-------------------------------|--------|
| Weisshof16  | 53 UC, 4 CD, 1 pouchitis 93% previously failing anti-TNF 81% previously failed VDZ 47% concomitant steroids | 5 or 10 mg BID for ≥8 weeks | Clinical response at Week 8: symptomatic improvement but not resolution | 36% |
| Lair-Mehiri17 | 37 UC 100% previously failed anti-TNF 97% previously failed VDZ | 10 mg BID | Clinical remission at Week 8: complete resolution of clinical symptoms | 33% |
| Patel18     | 123 UC 29% bio-naïve 41% previously failed anti-TNF and VDZ | 10 mg BID for ≥8 weeks | Clinical response at Week 8: >50% reduction in symptoms | 48% [61%]* |
| Clark-Snustad19 | 24 UC | 5 or 10 mg BID for ≥4 weeks | Median drop in SCCAI by Week 4 | 7.18 to 4.53 [p = 0.009] |
| Kolar20     | 24 UC 75% bio-exposed 41% concomitant steroids | 10 mg BID for ≥8 weeks | Mucosal healing at Week 8: Mayo endoscopic sub-score ≤1 | 53% |
| Honap21     | 25 UC 96% previously failing anti-TNF 56% previously failing VDZ | Not available | Median drop in SCCAI by Week 8 [in 15 patients] | 8 to 2 [p <0.0001] |
| Berinstein22 | 4 acute severe UC | 10 mg TID for 3 days In combination with methylprednisolone [n = 3] or budesonide [n = 1] | Median drop in faecal calprotectin by Week 8 [in 15 patients] | 451 to 95 µg/g [p <0.0001] |

BID, twice daily; CD, Crohn’s disease; SCCAI, Simple Clinical Colitis Activity Index; TID, three times daily; TNF, tumour necrosis factor; UC, ulcerative colitis; VDZ, vedolizumab.

* Non-responder imputation [as observed].

---

**Efficacy of JAK inhibitors in Ulcerative Colitis**

S741
The St Thomas’ Hospital in London reported their experience with 25 patients with UC treated with 8 weeks of tofacitinib. Median [range] baseline SCCAI fell from 8 [2–14] to 2 [0–6] at Week 8 [n = 15, p < 0.0001], and median [range] baseline faecal calprotectin fell from 451 [63–6020] to 95 [5–1420] at Week 8 [n = 15, p <0.0001]. The proportions of patients achieving clinical response/remission were not reported.

Finally, Bernstein et al. reported on the efficacy of tofacitinib 10 mg three times daily in four patients with acute severe UC. On top of tofacitinib, three patients received intravenous [IV] methylprednisolone and one patient received budesonide. After receiving tofacitinib and steroids, all four patients had a rapid improvement in clinical symptoms and CRP. Only one patient was unable to achieve clinical remission. Although more prospective data are required to conclude on the efficacy of tofacitinib in this setting, the combination of high doses of steroids and tofacitinib seems contra-indicated due to the high risk of [viral] infections and venous thromboembolism.

2.4. Practical considerations with tofacitinib
Tofacitinib is a valid treatment option for patients with moderate-to-severe UC, and this for both biologic-exposed and biologic-naive patients. However, in many jurisdictions tofacitinib is only reimbursed as a second-line therapy, limited to patients who previously failed biologic therapy.

As in the pivotal trials, one should stop all concomitant immunosuppressive agents [thiopurines, methotrexate, calcineurin inhibitors, biologic therapy] when initiating tofacitinib. Topical steroids or a low dose of systemic steroids [maximum 20 mg of prednisolone or equivalent] could be associated, but these should be tapered as soon as possible. Due to the increased risk of [opportunistic] infections, one should adopt a good vaccination policy and consider Pneumocystis jiroveci prophylaxis when combining tofacitinib and systemic steroids.

The induction schedule consists of 8 weeks of tofacitinib 10 mg BID. After these 8 weeks, a clinical and endoscopic evaluation should be performed. Based on the safety profile of the high dose of tofacitinib, it is suggested to taper the dose to tofacitinib 5 mg BID in case of a clinical benefit at Week 8. In patients without both clinical and endoscopic improvement at Week 8, one could consider a prolonged induction with another 8 weeks of tofacitinib 10 mg BID. However, if a patient does not show response to 16 consecutive weeks of tofacitinib 10 mg BID, one should discontinue the therapy as the patient can be regarded as a primary non-responder.

In case of a flare during maintenance therapy, one could consider a temporary dose optimisation to tofacitinib 10 mg BID, after a thorough and repeated discussion with the patient on potential safety issues [including infections and venous thromboembolism].

3. Peficitinib
Peficitinib is an oral JAK inhibitor with moderate selectivity for JAK3 over JAK1, JAK2, and TYK2. The phase 2b dose-ranging, double-blind, placebo-controlled, randomised trial included 219 patients with moderate-to-severe UC [NCT01959282]. Patients were randomised to receive either placebo [n = 43] or peficitinib 25 mg once daily [QD] [n = 44], peficitinib 75 mg QD [n = 44], peficitinib 75 mg BID [n = 44], or peficitinib 150 mg QD [n = 44]. The efficacy and safety of the different doses of peficitinib was compared with the efficacy and safety of placebo. The primary endpoint was efficacy, evaluated as a change from baseline in the total Mayo score [including centrally read endoscopy] after 8 weeks of treatment.

Secondary endpoints included clinical response, clinical remission, and mucosal healing. Although a trend toward increased clinical response, clinical remission, and endoscopic remission was observed at doses of 75 mg or higher per day, no significant dose–response relationship was observed in the patients taking peficitinib. Patients taking peficitinib 150 mg QD were significantly more likely to be in clinical remission [27.3% vs 7.0% for placebo, p <0.05] or have mucosal healing [45.5% vs 18.6% for placebo, p <0.05]. However, CRP and faecal calprotectin were not consistently reduced after treatment with peficitinib.

4. Upadacitinib
The U-Achieve trial [NCT02819635] was a phase 2, double-blind, placebo-controlled, dose-ranging, randomised trial including patients with moderate-to-severe therapy-refractory UC. Patients were randomly assigned to take placebo [n = 46] or upadacitinib 7.5 mg QD [n = 47], 15 mg QD [n = 49], 30 mg QD [n = 52], or 45 mg QD [n = 56]. The primary endpoint was clinical remission per adapted Mayo score [stool frequency, rectal bleeding, and endoscopic sub-scores] at Week 8. The primary endpoint was met for doses of 15 mg QD or higher. None of the patients taking placebo achieved the primary endpoint; however, clinical remission per adapted Mayo was observed in 8.5% of patients taking 7.5 mg upadacitinib QD [p-value >0.05], 14.3% of patients taking 15 mg QD [p-value <0.05], 13.5% of patients taking 30 mg QD [p-value <0.05], and 19.6% of patients taking 45 mg QD [p-value <0.01]. Patients exposed to upadacitinib had significantly higher endoscopic improvement [endoscopic sub-score ≤1] and clinical response per adapted Mayo score rates than patients randomised to placebo. At doses of 15 mg QD or higher, upadacitinib was associated with significantly higher rates of clinical remission per full Mayo score. Histological improvement, defined as any decrease from baseline in the Geboes score, and histological remission, defined as a Geboes score less than 2, were significantly more frequent in patients taking 8 weeks of upadacitinib than in patients taking placebo. Table 5 summarises the main outcomes of the upadacitinib studies.

5. TD-1473
Contrary to the tendency of more selective JAK inhibition, TD-1473 was developed as an oral pan-JAK inhibitor. According to the manufacturer, TD-1473 is gut-selective and has no significant systemic exposure upon oral dosing. In mouse experiments, the systemic levels of TD-1473 were 1000-fold lower than those of tofacitinib. In a phase 1b study, patients with moderately-to-severely active UC were given placebo [n = 9] or TD-1473 20 mg QD [n = 10], 80 mg QD [n = 10], or 270 mg QD [n = 11] for 4 weeks. Patients receiving TD-1473 were more prone to experience clinical response [11% vs 20%, 20%, and 50%, respectively] and endoscopic improvement [0% vs 20%, 30%, and 18%, respectively] than patients receiving placebo. The plasma concentration of TD-1473 was 10-fold lower than the expected concentration after exposure to tofacitinib 10 mg BID. Phase 2 and 3 trials in Crohn’s disease and UC have been initiated [NCT03758443 and NCT03635112].

6. Other JAK inhibitors in development for UC
Filgotinib, an oral JAK1-selective inhibitor, has been shown to induce clinical remission in patients with moderate-to-severe Crohn’s disease. The SELECTION trial [NCT02914522] is a Phase 2b/3 in patients with moderate-to-severe UC. An interim futility analysis was performed after 350 patients completed the induction period in the Phase 2b. The independent Data Monitoring Committee
conducting the analysis recommended to proceed the study into Phase 3.31

PF-06651600 [JAK3 inhibitor] and PF-06700841 [TYK2/JAK1] are being developed by Pfizer. A double-blind, placebo-controlled, parallel group, randomised trial including patients with moderate-to-severe UC is ongoing and will compare the efficacy and safety of these compounds and placebo [NCT02958865]. Phase 2 trials are also ongoing with SHR0302 [JAK1 inhibitor, NCT03675477] and itacitinib [JAK1 inhibitor, NCT03627052].

BMS-986165 is a potent oral TYK2 allosteric inhibitor that has been studied in psoriasis with promising results.32 This molecule blocks IL-12, IL-23, and type I interferon, and has been successfully applied in preclinical models of IBD.33 Phase 2 trials in UC and CD are ongoing [NCT03934216 and NCT03599622].

7. Discussion

JAK inhibition is a valuable new therapeutic strategy to treat immune-mediated inflammatory disorders,34 including UC,35 rheumatoid arthritis,36 and psoriatic arthritis.36 This new mode of action substantially differs from that of other available therapies for UC, by targeting a wide range of JAK-dependent cytokines. The oral route of administration, the short half-life, and the fast onset of action are key advantages of JAK inhibitors. Tofacitinib, the first-in-class molecule, has been approved to treat patients with UC. This rapidly acting orally administered agent has a very short half-life [3.3 h] and a high level of intestinal bioavailability37 which allows a fast and effective anti-inflammatory effect.

Although the oral route of administration of the JAK inhibitors is perceived as an advantage, it might result in lower treatment adherence.38 Direct comparison between different routes of administration [e.g. subcutaneous, intravenous, or oral drugs] in patients with IBD is lacking; however, less frequent dosing seems to be associated with higher adherence.39 Some of the new JAK inhibitors are administered once daily, which might result in higher adherence rates without loss of efficacy, as it was seen with oral mesalasine.40

Several JAK inhibitors are currently being tested in UC. Head-to-head randomised trials are needed to directly compare the efficacy, safety, and adherence of the different JAK inhibitors and biologic therapies. One direct comparison between two different JAK inhibitors is ongoing, with a head-to-head phase 2 trial comparing PF-06651600, PF-06700841, and placebo [NCT02958865]. In the absence of head-to-head trials including tofacitinib, one network meta-analysis suggested no significant superiority or inferiority of tofacitinib compared with biologic therapies.41 In another network meta-analysis, tofacitinib was associated with the highest rate of clinical remission in maintenance phases, whereas infliximab was most efficacious in the induction phase.42 There is also indirect evidence that tofacitinib is the best option for induction of clinical remission in patients with previous anti-TNF exposure.43 In the OCTAVE trials, tofacitinib was as efficacious in anti-TNF naïve as in anti-TNF exposed patients.44 Although the absolute values of clinical response/remission and endoscopic response were higher in anti-TNF naïve patients, the delta between placebo and tofacitinib was similar in anti-TNF naïve and anti-TNF exposed patients.

The efficacy of tofacitinib and upadacitinib showed to be dose-dependent, with higher doses being associated with higher remission rates.45,46 Interestingly, the dose and exposure [plasma concentrations] of tofacitinib were both linked to the observed outcomes.44 Patients who do not respond to the induction phase [8 weeks] of tofacitinib may benefit from an extended induction period [another 8 weeks]. However, the rates of adverse events are also observed to be dose-dependent,47 precluding the widespread use of higher doses of tofacitinib and extended induction periods.

The idea of aiming for histological remission in patients with UC is gaining traction.48,49 Upadacitinib was associated with higher rates of histological improvement and remission.50 This effect was not observed with TD-147351, implying that the histological effect of upadacitinib is not a class effect that can be expected from all JAK inhibitors.

In conclusion, tofacitinib has shown efficacy in patients with moderate-to-severe UC, in randomised placebo-controlled trials as in retrospective cohort studies. Several other anti-JAK inhibitors are currently under investigation to evaluate their efficacy not only on clinical and endoscopic, but also on histological endpoints. Besides the need for good predictors of response to more advanced therapies, prospective head-to-head trials including anti-JAK inhibitors and biologics are eagerly awaited.

Funding

No specific funding has been received for this manuscript.

Conflict of Interest

MF: research grants: Abbvie, Biogen, Janssen, Pfizer, Takeda; consultancy: Abbvie, Boehringer-Ingelheim, Janssen, MSD, Pfizer, Sandoz, Takeda; speaker’s fees: Abbvie, Amgen, Biogen, Boehringer-Ingelheim, Falk, Ferring, Janssen, Lampevo, MSD, Mylan, Pfizer, Takeda. JS: speaker’s fees: Abbvie and Nestle Health Sciences.

Table 5. Results from the U-ACHIEVE trial with upadacitinib.

| Treatment                        | Week 8 | Week 12 | Week 16 | Week 24 | Week 48 |
|---------------------------------|--------|---------|---------|---------|---------|
| Placebo [n = 46]                | 0.0%   | 8.5%    | 14.3%   | 13.5%   | 19.6%   |
| Clinical response               | 13.0%  | 29.8%   | 44.9%   | 44.2%   | 50.0%   |
| Endoscopic improvement          | 2.2%   | 14.9%   | 30.6%   | 26.9%   | 17.9%   |
| Histological improvement       | 6.5%   | 31.9%   | 51.0%   | 44.2%   | 48.2%   |
| Clinical remission              | 0.0%   | 8.5%    | 14.3%   | 13.5%   | 19.6%   |
| Histological remission         | 2.2%   | 12.8%   | 22.4%   | 30.8%   | 41.1%   |

Clinical remission: clinical remission per adapted Mayo score at Week 8 [stoel frequency sub-score ≤1, rectal bleeding sub-score ≤1, and endoscopic sub-score ≤1]. Clinical response: clinical response per adapted Mayo score at Week 8 [decrease from baseline in the adapted Mayo score ≥2 points and ≥50% from baseline, plus a decrease in rectal bleeding score ≥1 or an absolute rectal bleeding score ≤1]. Endoscopic remission: endoscopic sub-score ≤0. Histological improvement: any decrease from baseline in the Geboes score. Histological remission: a Geboes score <2.

QD: once daily.

*p <0.05; **p <0.01; ***p <0.001.
Acknowledgements
MF holds a basic-clinical research position at the Flemish Foundation for Scientific Research [FWO Vlaanderen].

Author Contributions
MF and JS both wrote the manuscript.

References
1. Magro F, Gionchetti P, Eliakim R, et al.; European Crohn’s and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis 2017;11:649–70.
2. Harbord M, Eliakim R, Bettenworth D, et al.; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367:616–24.
3. Panés J, Su C, Bushmakín AG, Cappelleri JC, Mamolo C, Healey P. Randomised trial of tofacitinib in active ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology 1994;107:3–11.
4. Sandborn WJ, Ghosh S, Panes J, et al.; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367:616–24.
5. Panés J, Su C, Bushmakín AG, Cappelleri JC, Mamolo C, Healey P. Randomised trial of tofacitinib in active ulcerative colitis: analysis of efficacy based on patient-reported outcomes. BMC Gastroenterology 2015;15:14.
6. Sandborn WJ, Su C, Sands BE, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–36.
7. Rubin DT MS, Schreiber S, Quirk D, et al. Tofacitinib 15 milligrams twice daily for patients with moderate to severe ulcerative colitis: results from 8-week induction studies OCTAVE induction 1 & 2. Paper presented at: American College of Gastroenterology Annual Scientific Meeting; October 9, 2018; Philadelphia, PA.
8. Panés J, Vermeire S, Lindsay JO, et al. Tofacitinib in patients with ulcerative colitis: health-related quality of life in phase 3 randomised controlled induction and maintenance studies. J Crohns Colitis 2018;12:145–56.
9. Lichtenstein GRCBL, Salese I, SooNarla A, Modesto I, et al. Impact of baseline corticosteroid use on tofacitinib induction efficacy and infection risk in patients with ulcerative colitis: data from global clinical trials. Paper presented at: United European Gastroenterology Week; Oct 19–23, 2019; Barcelona, Spain.
10. Hanauer SB, Sandborn WJ, Feagan BG, et al.; Peficitinib-UC Study Group. Peficitinib, an oral Janus kinase inhibitor, in moderate-to-severe ulcerative colitis: results from a randomised, phase 2 study. J Crohns Colitis 2018;12:1158–69.
11. Sandborn WJ, Panés J, Schreiber S, et al. Efficacy and safety of upadacitinib as an induction therapy for patients with moderately-to-severely active ulcerative colitis: data from the phase 2b study U-AChieve. Paper presented at: UEG Week; Oct 20–24, 2018; Vienna.
12. Beattie DTP, Shen F, Brasili P, et al; A novel, potent, and orally administered, GIT-targeted, pan-Janus kinase [JAK] inhibitor. Paper presented at: European Crohn’s and Colitis Organisation Congress; Mar 16–19 2016; Amsterdam.
13. W. Sandborn DN, Ferslew B, Hao L-Y, et al. Clinical, endoscopic, histological and biomarker activity following treatment with the gut-selective, pan-JAK inhibitor TD-1473 in moderately to severely active ulcerative colitis. Paper presented at: ECCO Congress; Mar 6–9, 2019; Copenhagen.
14. Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn’s disease treated with filgotinib [the FITZROY study]: results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet 2017;389:266–75.
15. Sands BE, Armuzzi A, Marshall JK, et al. Efficacy and safety of tofacitinib dose de-escalation and dose escalation for patients with ulcerative colitis: results from OCTAVE Open. Aliment Pharmacol Ther 2020;S1:271–80.
16. Weishoff R, Aharoni Golan M, Sossenheimer PH, et al. Real-world experience with tofacitinib in IBD at a tertiary center. Dig Dis Sci 2019;64:1945–51.
17. Lai-Mehiri CS, Vassye T, Laharie D, et al.; P715 Real-world tofacitinib effectiveness and safety in patients with refractory ulcerative colitis. Paper presented at: ECCO Congress; Mar 6, 2019; Copenhagen.
18. Patel A, Fenster M, Bader G, et al. Real-world effectiveness of tofacitinib in ulcerative colitis; a multi-center study. Gastroenterology 2019;156:S-168–9.
19. Clark-Smutstad KD, Sngla A, Lee SD. Tofacitinib improves clinical disease activity in a real-world population of patients with moderate-severe ulcerative colitis and Crohn’s disease. Gastroenterology 2019;156:S-644.
20. Kolur LM, Malickova K, Bortlik M, et al. Tofacitinib induction efficiency and intracellular cytokine dynamics in ulcerative colitis: results from clinical practice. Paper presented at: UEG Week; Oct 19–23 2019; Barcelona, Spain.
21. Konap S, Sharma E, Ray S, et al. Early ‘Real World’ experience with tofacitinib for moderate to severe ulcerative colitis. Gut 2019;68:A78–9.
22. Bernstein JA, Steiner CA, Regal RE, et al. Efficacy of induction therapy with high-intensity tofacitinib in 4 patients with acute severe ulcerative colitis. Clin Gastroenterol Hepatol 2019;17:988–90.e1.
23. Konap SE, Ray S, Begum Y, et al. Early ‘Real World’ experience with tofacitinib for moderate to severe ulcerative colitis. Paper presented at: UEG Week; Oct 19–23 2019; Barcelona, Spain.
24. Hamaguchi H, Amano Y, Morimoto A, et al. Discovery and structural characterization of peficitinib [ASP015K] as a novel and potent JAK inhibitor. Bioorg Med Chem 2018;26:4977–83.
25. Sands BE, Sandborn WJ, Feagan BG, et al.; Peficitinib-UC Study Group. Peficitinib, an oral Janus kinase inhibitor, in moderate-to-severe ulcerative colitis: results from a randomised, phase 2 study. J Crohns Colitis 2018;12:1158–69.
26. Sandborn WJ, Panés J, Schreiber S, et al. Efficacy and safety of upadacitinib as an induction therapy for patients with moderately-to-severely active ulcerative colitis: data from the phase 2b study U-AChieve. Paper presented at: UEG Week; Oct 20–24, 2018; Vienna.
27. Sandborn WJ, Lee SD, Lindsay JO, et al. Improved endoscopic outcomes and mucosal healing of upadacitinib as an induction therapy in adults with moderately to severely active ulcerative colitis: data from the U-AChieve study. Paper presented at: ECCO Congress; Mar 6–9, 2019; Copenhagen.
28. Gilead. Gilead and Galapagos Announce Results With Filgotinib in the Phase 2 Equator Study in Psoriatic Arthritis and Progression Into Phase 3 for the Selectivity Study in Ulcerative Colitis. 2019. https://www.gilead.com/news-and-press/press-room/press-releases/2018/5/gilead-and-galapagos-announce-results-with-filgotinib-in-the-phase-2-equator-study-in-psoriatic-arthritis-and-progression-into-phase-3-for-the-selecti Accessed November 08, 2019.
29. Papp K, Gordon K, Thaçi D, et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. N Engl J Med 2018;379:1313–21.
30. Xie JH, Gillooly K, Zhang Y, et al. BMS-986165 is a highly potent and selective allosteric inhibitor of TYK2, Blocks II-12, IL-23 and type I interferon signaling and provides for robust efficacy in preclinical models of inflammatory bowel disease. Gastroenterology 2018;154:S-137.
34. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O’Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov* 2017;16:843–62.

35. van Vollenhoven RF, Fleischmann R, Cohen S, et al.; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508–19.

36. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med* 2017;377:1525–36.

37. Dowty ME, Lin J, Ryder TF, et al. The pharmacokinetics, metabolism, and clearance mechanisms of tofacitinib, a janus kinase inhibitor, in humans. *Drug Metab Dispos* 2014;42:759–73.

38. Moran K, Null K, Huang Z, Lissoos T, Kane S. Retrospective claims analysis indirectly comparing medication adherence and persistence between intravenous biologics and oral small-molecule therapies in inflammatory bowel diseases. *Adv Ther* 2019;36:2260–72.

39. Vangeli E, Bakhshi S, Baker A, et al. A systematic review of factors associated with non-adherence to treatment for immune-mediated inflammatory diseases. *Adv Ther* 2015;32:983–1028.

40. Sandborn WJ, Korzenik J, Lashner B, et al. Once-daily dosing of delayed-release oral mesalamine [400-mg tablet] is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology* 2010;138:1286–96, 1296.e1–3.

41. Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018;47:454–65.

42. Trigo-Vicente C, Gimeno-Ballester V, García-López S, López-Del Val A. Systematic review and network meta-analysis of treatment for moderate-to-severe ulcerative colitis. *Int J Clin Pharm* 2018;40:1411–9.

43. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018;47:162–73.

44. Mukherjee A, Hazra A, Smith MK, et al. Exposure-response characterization of tofacitinib efficacy in moderate to severe ulcerative colitis: results from a dose-ranging phase 2 trial. *Br J Clin Pharmacol* 2018;84:1136–45.

45. Sandborn WJ, Panés J, D’Haens GR, et al. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. *Clin Gastroenterol Hepatol* 2019;17:1541–50.

46. Danese S, Roda G, Peyrin-Biroulet L. Evolving therapeutic goals in ulcerative colitis: towards disease clearance. *Nat Rev Gastroenterol Hepatol* 2020;17:1–2.

47. Pai RK, Jairath V, Vande Casteele N, Rieder F, Parker CE, Lauwers GY. The emerging role of histologic disease activity assessment in ulcerative colitis. *Gastrointest Endosc* 2018;88:887–98.