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Efficacy of JAK inhibitors in Ulcerative Colitis

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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.[1] Most patients with UC can be treated successfully with a symptom-focused step-up approach comprising 5-aminosalicylates, sulphasalazine, corticosteroids, thiopurines, and calcineurin inhibitors.[2] 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.[3] 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.[2] Although the introduction of these biologic agents led to more ambitious treatment goals in both clinical trials and daily clinical practice, major limitations include the mode of administration [subcutaneous and/or intravenous] and the development of immunogenicity towards these large monoclonal antibodies.

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, JNJ-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-JAK3 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.

2. Tofacitinib

2.1. Phase 2 study with tofacitinib

In a dose-finding, double-blind, placebo-controlled, phase 2 trial [clinicaltrials.gov NCT00787202] the efficacy of oral tofacitinib was

evaluated in 194 adult patients with moderate-to-severe UC [total Mayo score 6–12, Mayo endoscopic sub-score 2–3].[4] Patients were randomly assigned to receive placebo [$n = 48$] or tofacitinib at a dose of 0.5 mg [$n = 31$], 3 mg [$n = 33$], 10 mg [$n = 33$], or 15 mg [$n = 49$] twice daily [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

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 [INCB039110]	JAK1	Phase 2 ongoing [NCT03627052]	No published data in UC yet	Incyte Corporation
Peficitinib [JNJ-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	Ph2 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] Phase 2/3 ongoing [NCT03758443, NCT03920254]	Trend for higher rates of clinical response and endoscopic improvement	Theravance Biopharma
Tofacitinib [CP-690,550]	JAK1/3	Approved [NCT01465763, NCT01458951, and NCT01458574]	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 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 [±SD] change in IBDQ from baseline	27.8 [±29.8]	27.7 [±33.4] $p = 0.94$	30.3 [±27.3] $p = 0.28$	30.4 [±39.8] $p = 0.16$	50.7 [±35.6] $p < 0.001$

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.

BID, respectively. Endoscopic response, defined as a decrease from baseline in the endoscopy sub-score of at least 1 point, was more frequently observed in the 15-mg BID group only. Clinical remission at Week 8, defined as a total Mayo score of 2 or lower, with no individual sub-score exceeding 1 point, and endoscopic remission, defined as an endoscopic sub-score of 0, were observed significantly more frequently in the 3-mg, 10-mg, and 15-mg BID groups, but not in the 0.5-mg BID group. The mean C-reactive protein [CRP] concentrations, and mean faecal calprotectin concentrations improved significantly in the 15-mg BID group. A dose-dependent improvement in health-related quality of life and patient preferences for tofacitinib could be observed.[5]

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 towards placebo, or tofacitinib 5 mg, or 10 mg, BID.[6] 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.[7] 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].[6] 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.[8] 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].[6]

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.[6] Similarly, concomitant therapy with corticosteroids in OCTAVE Induction 1 and 2 did not influence efficacy rates at Week 8.[9] 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,

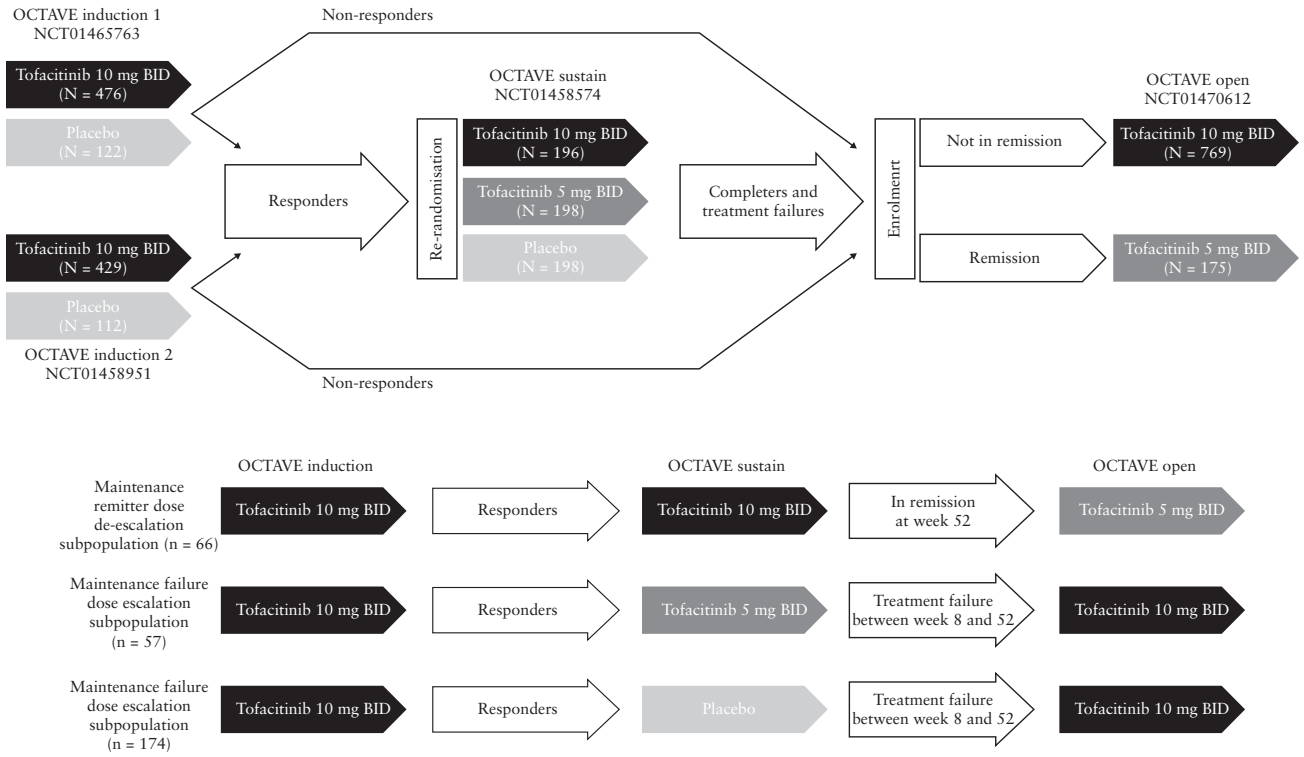

Figure 1. Phase 3 OCTAVE Programme.

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% *p* = 0.007	3.6%	16.6% *p* <0.001	11.1%	34.3% *p* <0.001	40.6% *p* <0.001
Clinical response	32.8%	59.9% *p* <0.001	28.6%	55.0% *p* <0.001	20.2%	51.5% *p* <0.001	61.9% *p* <0.001
Mucosal healing	15.6%	31.3% *p* <0.001	11.6%	28.4% *p* <0.001	13.1%	37.4% *p* <0.001	45.7% *p* <0.001
Endoscopic remission	1.6%	6.7% *p* = 0.04	1.8%	7.0% *p* = 0.04			
IBDQ remission	37.7%	52.5% *p* = 0.004	25.9%	49.4% *p* <0.001	20.2%	48.0% *p* <0.001	57.4% *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 trough at 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 of 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; 101patients 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.[15] 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

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

Publication	Population	Treatment with tofacitinib	Outcome in the UC population	Result
Weisshof[16]	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%
			Clinical remission at Week 8: complete resolution of clinical symptoms	33%
Lair-Mehiri[17]	37 UC 100% previously failed anti-TNF 97% previously failed VDZ	10 mg BID	Steroid-free clinical remission at Week 24: total Mayo score ≤2 without any sub-score >1	32%
			Clinical response at Week 24: decrease in the total Mayo score with ≥3 points and ≥30%, and decrease in rectal bleeding sub-score ≥1 point or absolute rectal bleeding sub-score ≤1	41%
			Survival without colectomy at Week 24	77%
Patel[18]	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%]*
			Clinical remission at Week 8: not further defined	11% [14%]*
			Endoscopic healing within 6 months: Mayo endoscopic sub-score ≤1 or absence of erosions/ulcerations	30% [65%]*
Clark-Snustad[19]	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]
			Median drop in endoscopic sub-score by Week 4	2.21 to 1.25 [p = 0.36]
Kolar[20]	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%
Honap[21]	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]
			Median drop in faecal calprotectin by Week 8 [in 15 patients]	451 to 95 µg/g [p <0.0001]
Berinstein[22]	4 acute severe UC	10 mg TID for 3 days In combination with methylprednisolone [n = 3] or budesonide [n = 1]	Clinical remission: not further specified	75%

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].

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 [±1.49] [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.

The St Thomas' Hospital in London reported their experience with 25 patients with UC treated with 8 weeks of tofacitinib.[23] 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, Berinstein *et al.* reported on the efficacy of tofacitinib 10 mg three times daily in four patients with acute severe UC.[22] 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-naïve 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.[24] 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.[25]

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.[26] 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.[27] 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.[28] 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.[29] 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.[30] 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

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

	Placebo [*n* = 46]	7.5 mg QD [*n* = 47]	15 mg QD [*n* = 49]	30 mg QD [*n* = 52]	45 mg QD [*n* = 56]
Clinical remission	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%***	35.7%***
Endoscopic remission	0.0%	6.4%	4.1%	9.6%*	17.9%**
Histological improvement	6.5%	31.9%**	51.0%***	44.2%***	48.2%***
Histological remission	2.2%	12.8%*	22.4%**	30.8%***	41.1%***

Clinical remission: clinical remission per adapted Mayo score at Week 8 [stool frequency sub-score ≤1, rectal bleeding sub-score = 0, 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 ≥30% from baseline, plus a decrease in rectal bleeding score ≥1 or an absolute rectal bleeding score ≤1]. Endoscopic improvement: endoscopic sub-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.

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,[6] rheumatoid arthritis,[35] 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 bioavailability[37] 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 mesalamine.[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 phase, 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.[6] 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.[4,26] 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,[45] 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.[46,47] Upadacitinib was associated with higher rates of histological improvement and remission.[27] This effect was not observed with TD-1473[29], 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.

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Conflict of Interest

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

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Author Contributions

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