

## REVIEW

# Tofacitinib and newer JAK inhibitors in inflammatory bowel disease—where we are and where we are going

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## Abstract

Inflammatory bowel diseases, comprising ulcerative colitis (UC) and Crohn's disease, are chronic, immune-mediated and progressive inflammatory disorders affecting the gastrointestinal tract. Tofacitinib is the first oral small-molecule Janus kinase (JAK) inhibitor licensed and approved by the National Institute for Health and Care Excellence (NICE) for use in moderately-to-severely active UC after intolerance, inadequate response, or loss of response to conventional treatment or biologic therapy. The pivotal OCTAVE studies demonstrated the efficacy and safety of tofacitinib for the induction and maintenance of remission in UC. A growing body of evidence from real-world data supports the positive clinical and endoscopic benefits observed with tofacitinib treatment in the OCTAVE trials. This narrative review summarizes the current literature regarding the mechanism of action of tofacitinib, data

from registrational trials, emerging real-world evidence, and an overview of the most recent safety evidence. We explore evolving treatment paradigms, including the use of tofacitinib in the COVID-19 era, pregnancy and extraintestinal manifestations, as well as the emerging concept of combining tofacitinib with biological therapy. We will also present a brief overview of the next generation of JAK inhibitors in the pipeline.

**Keywords:** Crohn's disease, effectiveness, efficacy, inflammatory bowel diseases, Janus kinase inhibitors, ulcerative colitis, safety, tofacitinib.

## Citation

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## Introduction

Inflammatory bowel diseases (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic, immune-mediated and progressive inflammatory disorders of the gastrointestinal tract.<sup>1</sup> Evolution in our understanding of the immunopathogenesis of IBD is reflected by the increase in our therapeutic armamentarium but is arguably still limited in comparison to other immune-mediated diseases.<sup>2</sup> The era of biological treatment was spearheaded by the introduction of anti-TNF agents but novel therapeutic agents targeting distinct aspects of the immune cascade, namely IL-12/IL-23 inhibitors (ustekinumab (UST)) and anti-integrin agents (vedolizumab (VDZ)) are available, with others in development.<sup>3</sup>

Biologics have gradually transformed the treatment landscape,<sup>4</sup> albeit with significant limitations such as

primary and secondary loss of response, mechanistic failure, immunogenicity, associated economic costs with drug administration and increased infection risk.<sup>5</sup> Furthermore, there are in fact several cytokine-driven inflammatory pathways that trigger and perpetuate the inflammatory cascade in IBD, underpinning the need to develop further therapeutic targets that overcome these associated drawbacks.<sup>6</sup>

The development of new molecules with the potential to target a myriad of cytokine targets, such as the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, has been shown to be effective in IBD.<sup>7,8</sup> Tofacitinib is a first-in-class JAK inhibitor with demonstrated efficacy in the treatment of rheumatoid arthritis (RA)<sup>9</sup> and psoriatic arthritis<sup>10</sup> and is now licensed for the treatment of UC.<sup>11</sup>

## Methods

The aim of this narrative review is to summarize the current knowledge regarding tofacitinib in UC, for the practising clinician and to present a brief overview of next-generation JAK inhibitors in the pipeline.

An extensive review of literature available on PubMed, EMBASE, Medline and conference abstracts was conducted up to 31 October 2021. We used the following keywords in our search strategy: “inflammatory bowel disease”, “ulcerative colitis”, “Crohn’s disease”, “JAK inhibitors”, “JAK/STAT”, “tofacitinib”, “small molecules”, “filgotinib”, “upadacitinib”, “OCTAVE”, “real world” and “safety”.

## Review

### Mechanism of action

Many of the current biological options target the extracellular components of the immune cascade, namely cytokines and their associated cell-surface receptors.<sup>12</sup> Tofacitinib differs from conventional biologics in that it is an oral targeted synthetic small molecule and operates at an intracellular level by reversibly and competitively inhibiting JAK.<sup>13</sup>

JAK pathways are involved in several key functions. They play a role in cell growth, survival, differentiation and migration as well as in modulating the innate and adaptive immune response and haemopoiesis.<sup>14,15</sup>

Being able to modulate JAK ultimately impacts the JAK–STAT signalling pathway, which has downstream effects on the above mentioned functions. There are four tyrosine kinase proteins: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), with each being activated by cytokines such as interleukins and interferons, as well as hormones such as thrombopoietin, growth hormone and erythropoietin.<sup>15</sup>

Each tyrosine kinase protein has specificity for certain cytokine receptors. Following the binding of a cytokine to a cytokine receptor, this leads to activation of the receptor-associated JAKs<sup>16</sup> (Figure 1). The associated JAK receptor proteins are then involved in phosphorylating the associated intracellular receptor, turning them effectively into binding sites for STAT1–7 proteins.<sup>17</sup> Once the STAT proteins bind to their associated receptor, they are phosphorylated by receptor-associated JAK proteins. The phosphorylated STAT proteins undergo dimerization after un-docking from the receptor subunit. Subsequently, they translocate into the nucleus of the cell and influence gene transcription, promoting further inflammation.<sup>14</sup>

Tofacitinib is the first-in-class, reversible competitive JAK inhibitor, selectively inhibiting JAK1 and JAK 3 (Figure 1). Its structure mimics that of adenosine triphosphate (ATP) without the associated triphosphate group. This prevents the phosphorylation of JAK proteins, which prevents the triggering of the STAT pathway and downstream signalling of  $\gamma$ -chain cytokines IL-2, IL-4, IL-7, IL-15 and IL-21 and the synthesis of

pro-inflammatory proteins that are implicated in mucosal inflammation.<sup>13</sup>

Tofacitinib is both rapidly absorbed after oral intake and rapidly eliminated due to a short half-life of 3 hours, thus has the potential dual benefit of quick effective onset of action and elimination.<sup>14</sup> Furthermore, tofacitinib is not a monoclonal antibody and therefore has the additional advantage of no immunogenicity risk.<sup>14</sup>

Tofacitinib was approved by US Food and Drug Administration (FDA), the European Medical Agency (EMA) and National Institute for Health and Care Excellence (NICE) for use in moderately-to-severely active UC.<sup>11</sup> Meanwhile, several selective JAK inhibitors are being developed that target specific JAK proteins.<sup>18</sup>

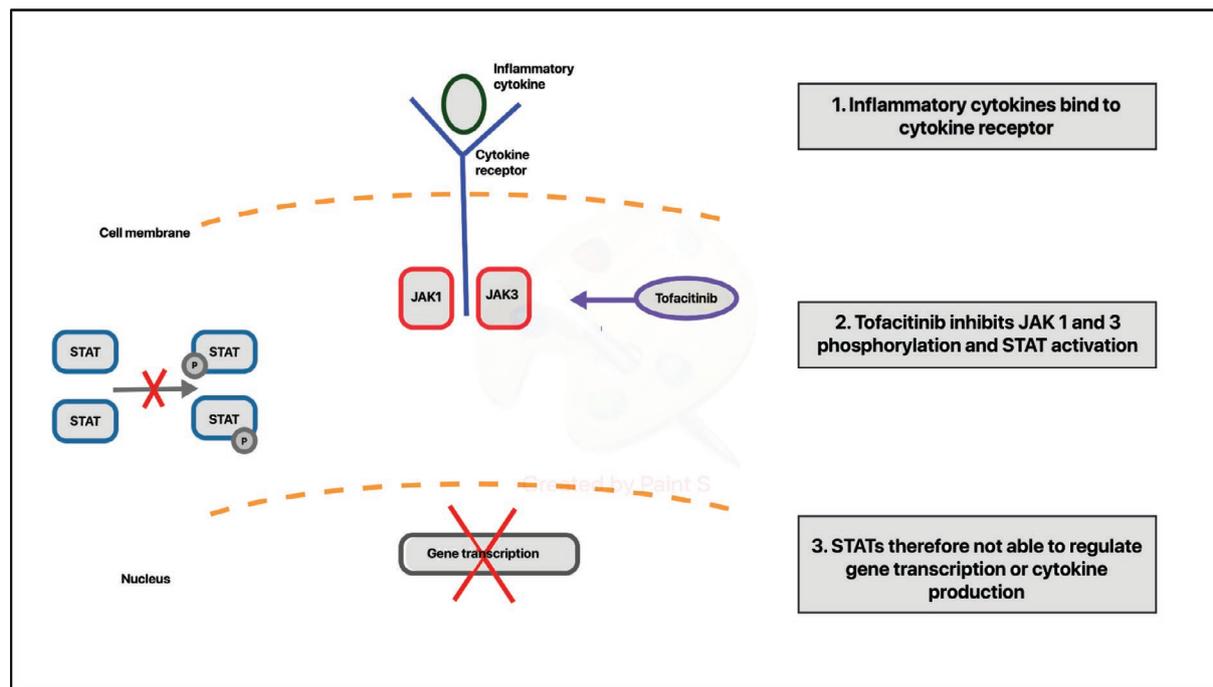
### Tofacitinib in UC

The approval for tofacitinib was based on the efficacy data from initial phase II trials and three subsequent distinct phase III trials.<sup>19,20</sup> In the phase II trial, 194 patients with moderately-to-severely active UC (Mayo score (MCS) 6–12, rectal bleeding subscore (RBS) 1–3 and Mayo endoscopic subscore (MES) 2–3) were assigned to receive placebo or oral tofacitinib 0.5, 3, 10 or 15 mg twice daily (BD) for 8 weeks. The primary endpoint of clinical response at 8 weeks was defined as  $\geq 3$  points absolute reduction from baseline MCS and a relative decrease of  $\geq 30\%$  from baseline along with a reduction of  $\geq 1$  point of the RBS, or an absolute RBS of 0 or 1. Clinical remission was defined as MCS  $\leq 2$ , with no subscore of  $>1$  at 8 weeks. The respective clinical response and remission rates at 8 weeks were 32% ( $p=0.39$ ) and 13% ( $p=0.76$ ) for the 0.5 mg arm, 48% ( $p=0.55$ ) and 33% ( $p=0.01$ ) for the 3 mg arm, 61% ( $p=0.10$ ) and 48% ( $p<0.001$ ) for the 10 mg arm, and 78% ( $p<0.001$ ) and 41% ( $p<0.001$ ) for the 15 mg arm as compared with 42% and 10% for patients receiving placebo. Furthermore, a dose–response relationship was noted for endoscopic response in the treatment group (higher for the 10 and 15 mg BD dose) compared to placebo or tofacitinib 5 mg BD.<sup>19</sup>

Three distinct phase III randomized controlled trials evaluated the efficacy and safety of tofacitinib: the identical OCTAVE 1 and 2 trials for induction therapy and OCTAVE Sustain for maintenance therapy in patients with moderately-to-severely active UC despite previous conventional therapy or treatment with an anti-TNF agent.<sup>20</sup> Oral aminosalicylates and/or oral glucocorticoids ( $\leq 25$  mg per day of prednisolone or equivalent) were permitted as concurrent medications provided they were continued at a stable dose throughout the induction trials and glucocorticoids were mandatorily tapered during maintenance.

The induction trials (to week 8) included 598 and 541 patients for OCTAVE 1 and 2, respectively, who were randomly assigned, in a 4:1 ratio, to receive induction therapy with oral tofacitinib (10 mg BD) or placebo for 8 weeks. The primary endpoint of clinical remission at 8 weeks (MCS  $\leq 2$ , with no

Figure 1. Schematic illustration of the mechanism of action of tofacitinib.



individual subscore >1) was noted more frequently in the active treatment arm compared to placebo (in OCTAVE 1: 18.2% versus 8.2% ( $p=0.007$ ); OCTAVE 2: 16.6% versus 3.6% ( $p<0.001$ )). A key secondary endpoint of mucosal healing was noted more frequently in the active treatment arm compared to the placebo arm (OCTAVE 1: 31.3% versus 15.6% ( $p<0.001$ ); OCTAVE 2: 28.4% versus 11.6% ( $p<0.001$ )). The treatment effects for both primary and secondary endpoints were similar in both TNF-naïve and TNF-exposed patients.<sup>19</sup> The dose selection was based on the dose-response data from the earlier phase II trial showing better treatment effects from the 10 and 15 mg doses. Originally, 16 and 6 patients were randomized to receive 15 mg doses of tofacitinib in the OCTAVE 1 and 2 trials, respectively. However, based on feedback received from regulatory authorities for RA, Pfizer discontinued further exploration of this dose in the trial. Limited analyses on the 15 mg dosing arm demonstrated clinical remission rates of 43.8% (7/16) in OCTAVE 1 and 50% (3/6) in OCTAVE 2 trials, providing avenues for further investigation of the 15 mg dose for induction therapy.<sup>19</sup>

A post hoc analysis of the OCTAVE 1 and 2 induction data showed a rapid onset of treatment effect. Significantly greater improvements in Mayo stool frequency subscore and RBS were noted in the tofacitinib arm compared to placebo by day 3 (9.2% versus 2.3% ( $p<0.01$ ) and 14.4% versus 8.2% ( $p<0.05$ ), respectively) with consistent effects thereafter until day 15. These effects were uniformly observed in all subgroups.<sup>21</sup>

Patients who had a clinical response to induction therapy ( $n=593$ ) were rerandomized 1:1:1 to receive oral 5 mg tofacitinib BD, 10 mg tofacitinib BD or placebo in the maintenance trial

for OCTAVE Sustain trial with a follow-up period of 52 weeks.<sup>20</sup> Significantly higher clinical remission rates were noted in patients receiving tofacitinib 5 mg BD (34.3%) and tofacitinib 10 mg BD (40.6%) when compared with the placebo arm (11.1%) ( $p<0.001$  for both comparisons with placebo). Similarly, for the key secondary endpoint of mucosal healing, significantly higher rates were noted in patients receiving tofacitinib 5 mg BD (37.4%) and tofacitinib 10 mg BD (45.7%) compared to placebo (13.1%) ( $p<0.001$  for both comparisons with placebo). Sustained and corticosteroid-free clinical remission (CFCR) rates were also significantly higher in patients receiving tofacitinib 5 mg BD (35.4%) and tofacitinib 10 mg BD (47.3%) when compared with the placebo arm (5.1%) ( $p<0.001$  for both comparisons with placebo).<sup>20</sup>

Statistically significant improvements in health-related quality of life were noted with tofacitinib in OCTAVE 1 and 2 compared with placebo and these improvements were maintained in the tofacitinib treatment arm for at least 52 weeks, irrespective of sex, baseline glucocorticoid use and previous anti-TNF exposure.<sup>22</sup>

Patients who completed OCTAVE Sustain were eligible to enrol into the long-term extension follow-on study (OCTAVE Open). Of the 142 patients in remission (defined as a total MCS  $\leq 2$ , no individual subscore >1, and RBS of 0 at week 52) at the end of OCTAVE Sustain, efficacy endpoints were maintained with ongoing tofacitinib 5 mg BD dosing in OCTAVE Open, with 68.3% achieving remission, 77.5% clinical response and 73.9% endoscopic improvement at 12 months, and 50.4%, 56.0% and 55.3%, respectively, at 36 months.<sup>23</sup>

The final analysis of OCTAVE Open was recently published, demonstrating long-term efficacy of tofacitinib use for up to 7 years.<sup>24</sup> A total of 944 patients entered OCTAVE Open; eligible patients were OCTAVE 1 or 2 non-responders, or OCTAVE Sustain completers or treatment failures. Patients in remission at baseline (81.5%) received 5 mg BD dosing and the remaining 18.5% received 10 mg BD dosing. At month 36 of OCTAVE Open (beyond week 52 of OCTAVE Sustain), 58.9% and 33.7% achieved or maintained clinical remission, 66.9% and 40.3% clinical response, and 64.6% and 37.1% endoscopic improvement, with tofacitinib 5 and 10 mg BD dosing, respectively.<sup>24</sup>

### Outcomes of dose reduction and escalation

Efficacy increases with higher tofacitinib exposure, as demonstrated in OCTAVE, with average drug concentration during maintenance proportionately increasing with higher dosage in OCTAVE Sustain.<sup>20</sup> However, adverse events (AEs) are also dose dependent, and manufacturer guidance is to use the lowest effective dose to maintain response where possible.<sup>25</sup>

In OCTAVE Open, patients in remission after 52 weeks of 10 mg BD dosing ( $n=66$ ) were de-escalated to 5 mg BD dosing.<sup>26</sup> After de-escalation, clinical response was maintained in 92.4% and 84.1%, and remission maintained in 80.3% and 74.6% at 2 months and 12 months, respectively. Tofacitinib induction responders who lost response on 5 mg maintenance dosing ( $n=57$ ) were escalated to 10 mg BD; 57.9% and 64.9% recaptured clinical response, and 35.1% and 49.1% achieved remission again at months 2 and 12, respectively.<sup>26</sup> OCTAVE Open data thus support the effectiveness of a dose-escalating strategy to recapture response in patients losing response on 5 mg BD maintenance. NICE also advocates dose escalation in cases of loss of response.<sup>11</sup>

The recently published primary analysis from RIVETING aimed to assess the outcomes of dose de-escalation in patients in stable remission.<sup>27</sup> Patients on 10 mg BD dosing for  $\geq 2$  years were randomized 1:1 to de-escalate to 5 mg BD or continue 10 mg BD. Remission at 6 months (MES  $\leq 1$ , Mayo stool frequency subscore  $\leq 1$ , RBS 0) was 77.1% and 90.0% in the 5 and 10 mg BD subgroups, respectively, with an adjusted treatment difference between the two groups of 12.9% (95% CI 0.5–25.0).<sup>27</sup> Deep endoscopic remission and no previous anti-TNF failure were factors predictive of maintenance of remission after de-escalation. Thus, endoscopic assessment and consideration of a patient's prior treatment history should be considered before dose reduction. AEs were similar across both dosage groups and consistent with previously reported safety profiles.<sup>27</sup>

## 'Real-world' experience of tofacitinib in UC

A growing body of evidence from real-world data for tofacitinib supports the effectiveness of tofacitinib in the more complex and diverse patient populations seen in the OCTAVE studies (Table 1).

In the largest real-world cohort to date, Honap et al. evaluated the efficacy of tofacitinib in 134 patients with UC from four centres in the United Kingdom.<sup>28</sup> In contrast to the relatively lower rates of prior anti-TNF exposure included in the OCTAVE 1 and 2 cohorts (53% and 55%, respectively),<sup>20</sup> the majority in the Honap et al. study cohort (80%) were previously treated with anti-TNF,<sup>27</sup> reflecting the more complex and treatment refractory patients typically included in real-world data. By week 8, 74% achieved clinical response, and by week 26, 44% patients achieved CFCR.<sup>27</sup> Younger age at initiation of tofacitinib treatment ( $p=0.014$ ) and higher baseline C-reactive protein (CRP; median 9 mg/L ( $p=0.004$ )) were independently associated with primary non-response. Clinical remission or response was not affected by prior anti-TNF exposure.<sup>28</sup> Even patients with prior first-line or second-line VDZ exposure had comparable response rates to tofacitinib.<sup>28</sup> Dose escalation was successful in recapturing response in 47% of patients.<sup>28</sup>

A multicentre US study reported on 123 patients with UC treated with tofacitinib with clinical response observed in 55%, clinical remission in 49% and endoscopic healing in 65% at week 16.<sup>29</sup> Bio-naive status was associated with an increased likelihood of week 16 clinical response (81%). No difference was noted between the prior anti-TNF group (36%) and the group with prior exposure to both anti-TNF and anti-integrin (35%;  $p<0.001$ ). Conversely, endoscopic healing at 6 months was lower in the group with prior exposure to two biologic classes (17%), compared to exposure to one biologic class (57%) or bio-naive status (87%). Other variables associated with week 8 response included concomitant steroids at tofacitinib initiation ( $p=0.002$ ) and male sex ( $p=0.007$ ).<sup>29</sup>

In a systematic review of 17 real-world studies including 1162 patients with UC, the clinical response rate at week 8 was 62% (95% CI 55–69%) with similar week 12–16 response rates (64%; 95% CI 56–73%).<sup>30</sup> Clinical remission was achieved by 35% (95% CI 24–45%) at week 8, and 47% (95% CI 40–54%) at weeks 12–16. Five studies assessed CFCR with 38% (95% CI 32–45%) achieving CFCR by week 8, and 31% (95% CI 20–42%) at 12 months, demonstrating sustained treatment efficacy.<sup>30</sup> The results were comparable with the outcomes from OCTAVE, though notably, the real-world cohort analysed in the meta-analysis was a more refractory cohort, with 88% biologic-experienced and two-thirds failing both anti-TNF and VDZ, as compared to 51% of OCTAVE participants being anti-TNF experienced and none with prior VDZ exposure.<sup>20,30</sup>

Rates of mucosal healing reported in separate real-world studies show varying results (Table 1). Systematic review analysis from six studies ( $n=252$ ) noted mucosal healing rates at week 8 of 42%, higher than those seen during OCTAVE 1 and 2 (31% and 28%).<sup>20,30</sup> However, this mucosal healing data should be treated with caution given the small numbers as well as the lack of systematically scheduled endoscopic evaluations in a real-life cohort, with endoscopic assessments more likely to be performed for patients showing non-response.

**Table 1. Real-world studies for tofacitinib.**

Study	n	Endpoint	Week 4	Week 8	Week 16	Week 26	Week 52
Taxonera et al. <sup>30</sup>	1162 (UC)	Clinical response		62%	64% (week 12–16)	51%	42%
Systematic review and meta-analysis		Clinical remission		<b>35%<sup>a</sup></b>	<b>47%<sup>a</sup></b> (week 12–16)	<b>38%<sup>a</sup></b>	
		CFCR		38%	44% (week 12–16)	34%	31%
		Mucosal healing		42%	35% (week 12–16)		
Honap et al. <sup>28</sup>	134 (118 UC, 5 IBD-U)	Clinical response		74%	66%	53%	
<b>LEO IBD Research Consortium:</b> Retrospective multicentre study		Clinical remission		57%	51%	45%	
		CFCR		48%	49%	44%	
Ungaro et al. <sup>29</sup>	123 (UC)	Clinical response		<b>61%<sup>a</sup></b>	55% <sup>b</sup>		
Multicentre retrospective study	40.7% prior anti-TNF and VDZ, 28.5% biologic naive	Clinical remission		14% <sup>b</sup>	49% <sup>b</sup>		
		Mucosal healing				65% <sup>b</sup> (within 6/12 of tofacitinib initiation)	
Takada et al. <sup>31</sup>	66 (UC) (38 TOF, 28 VDZ)	Clinical response	50% TOF versus 36% VDZ (ns) (week 2)	63% TOF versus 36% VDZ (week 6)			
Retrospective study		Clinical remission	24% TOF versus 29% VDZ (ns) (week 2)	39% TOF versus 32% VDZ (ns) (week 6)			
Biemans et al. <sup>32</sup>	123 (UC)  95% prior anti-TNF, 62% prior VDZ, 59% prior VDZ and anti-TNF	CFCR		35% (week 12)		<b>29%<sup>a</sup></b> (week 24)	
<b>ICC registry:</b> Prospective multicentre study		Clinical response		56% (week 12)		46% (week 24)	
		Clinical remission		41% (week 12)		33% (week 24)	
		Endoscopic response		36% (week 12)			
		Endoscopic remission		21% (week 12)			
Chaparro et al. <sup>33</sup>	113 (UC)	Clinical response	40%	60%	57%		
<b>ENEIDA Registry:</b> Prospective multicentre study	100% prior anti-TNF, 89% VDZ	Clinical remission	16%	31%	32%		

<sup>a</sup>Study primary endpoint (in bold text); <sup>b</sup>Study secondary endpoint.

CFCR, corticosteroid-free clinical remission; ENEIDA, Spanish Team for Intercultural Studies on Academic Disclosure; LEO IBD, London, Exeter, Oxford IBD; IBD-U, IBD-unclassified; ICC registry, Dutch Initiative on Crohn and Colitis Registry; TOF, tofacitinib; TROPIC, Tofacitinib Real-world Outcomes in Patients with ulcerative colitis and Crohn's disease.

A Japanese group carried out a real-world comparison of short-term efficacy and safety of tofacitinib and VDZ in UC.<sup>31</sup> Clinical response rates at week 6 were 63% with tofacitinib *versus* 36% with VDZ and clinical remission rates at week 6 of 39% for tofacitinib *versus* 32% for VDZ. The authors also noted significantly higher response rates amongst the prior biologic failure tofacitinib group (59%) compared with VDZ (21%) ( $p=0.038$ ), though the numbers included were small for firm conclusions to be drawn.<sup>31</sup>

The majority of real-world tofacitinib data have been limited by a retrospective design. The Dutch Initiative on Crohn and Colitis (ICC) Registry was the first prospective study of 123 patients with UC refractory to anti-TNF and VDZ treatment.<sup>32</sup> Inclusion criteria were combined clinical criteria (short clinical colitis activity index (SCCAI) >2) and objective criteria (MES  $\geq 1$ , CRP >5 mg/L, faecal calprotectin >250  $\mu\text{g/g}$ ). The primary endpoint was CFCR at week 24 (SCCAI  $\leq 2$ ), which was achieved by 29% of patients.<sup>32</sup> Clinical response declined over time from 56% at week 12 to 33% at week 24. Furthermore, in contrast to Honap *et al.*,<sup>28</sup> prior VDZ was associated with a significantly reduced week 24 clinical remission rate (OR 0.33, 95% CI 0.11–0.94;  $p=0.038$ ).<sup>32</sup> Association with prior anti-TNF could not be assessed due to the very low number of anti-TNF naive patients included.

The recently published prospective ENEIDA (Spanish Team for Intercultural Studies on Academic Discourse) registry reported data from 113 patients with highly refractory UC; 100% of patients had previously failed anti-TNF therapy, 89% failed VDZ, and 4% of patients had failed UST. Clinical response was achieved in 60% and clinical remission in 31% of patients by week 8.<sup>33</sup> During follow-up, 38% of patients subsequently relapsed at a median of 44 weeks; however, response was successfully recaptured with dose escalation in about 50% of cases.<sup>33</sup> Prior biologic exposure, baseline CRP levels and baseline corticosteroid use were not associated with likelihood of week 8 remission in line with OCTAVE results.<sup>33</sup>

TOUR (tofacitinib response in ulcerative colitis) is an ongoing real-world prospective multicentre study using an electronic system to capture SCCAI and patient-reported outcomes (PROs), including anxiety, depression and social satisfaction from patients commenced on tofacitinib therapy.<sup>34</sup> Preliminary data from 65 patients published in abstract form showed that tofacitinib was associated with rapid clinical response. Over half of the study patients met criteria for clinical response at day 14 (54.2%) and 52.2% at week 6; overall mean disease activity reduced from baseline SCCAI 5.6 to SCCAI 3.1 on day 14, and 2.7 on week 14.<sup>34</sup> Improvement in all PRO measures was also observed through week 14.

## Tofacitinib in CD

Tofacitinib failed to show significant clinical benefit in patients with CD. The primary endpoint of clinical remission was not achieved in the induction and maintenance phase II trials.<sup>35,36</sup>

The initial 4-week multicentre phase II trial randomized 139 patients with moderately-to-severely active CD (Crohn's Disease Activity Index (CDAI) score 220–450), 1:1:1 to receive oral tofacitinib 1 mg BD, 5 mg BD, 15 mg BD or placebo BD. The primary endpoint was the clinical response ( $\geq 70$  points reduction in CDAI score from baseline) at week 4, and secondary endpoints included clinical remission (CDAI <150 points) at week 4. No statistically significant differences were noted in the proportion of patients achieving clinical response or remission between the tofacitinib and the placebo arms;<sup>35</sup> of note, induction therapy was only for 4 weeks. This study was followed by two multicentre phase IIb studies (induction and maintenance) enrolling 280 patients with moderately-to-severely active CD. The results concluded minor treatment effects but did not demonstrate a statistically significant difference in primary endpoints between the treatment and placebo arms.<sup>36</sup>

A 48-week open-label extension study, investigating long-term safety in CD, reported worsening of CD in the treatment arm as the most frequent AE. This highlighted a lack of clinical efficacy of tofacitinib in CD, and further development of tofacitinib for CD was therefore discontinued.<sup>37</sup> It is plausible that the failure to meet the primary endpoint in the phase II trial and the high placebo response and remission rates may be a result of the concomitant use of corticosteroids in a high proportion of patients, the slow and arguably prolonged taper during maintenance, the absence of blinded central endoscopy reading at recruitment, and the absence of PRO and objective biomarkers as markers of disease activity.

## Safety profile

### Adverse events

In the OCTAVE studies, nasopharyngitis, arthralgia and headache were the most commonly reported AEs in any treatment group during the maintenance phase of the trial.<sup>20</sup> In the OCTAVE 1 trial, AEs were reported in 56.5% of patients receiving 10 mg BD tofacitinib and 59.8% receiving placebo; in OCTAVE 2, the corresponding figures were 54.1% and 52.7%, respectively. In OCTAVE Sustain, AEs were reported more frequently, with 72.2% of patients in the 5 mg group and 79.6% in the 10 mg group reporting AEs. The frequency of AEs reported in the placebo group was 75.3%.<sup>20</sup>

Serious AEs (SAEs) occurred at similar rates in treatment and placebo groups with the proportion of patients discontinuing treatment being similar in OCTAVE 1 and 2. A higher proportion of patients discontinued treatment due to AEs in the placebo group in OCTAVE Sustain (18.7% *versus* 9.1% in the 5 mg BD group, and 9.7% in the 10 mg group).<sup>20</sup>

The most recent safety data from 7.8 years of data from global clinical trials from 1157 patients reported that the incidence of AEs was comparable to placebo with worsening of UC (24%), nasopharyngitis (22%) and arthralgias (13%) being most frequently reported in both groups.<sup>38</sup> The safety profile

was generally consistent with other UC therapies, with the exception of herpes zoster discussed in the following.

### Infections

The incidence of serious infections from the OCTAVE studies was higher in the induction group (0.9% for tofacitinib) *versus* none for placebo. Serious infections are those that meet the definition for a SAE, including infections that result in death, are considered life threatening, or result in significant disability or hospitalization. This trend seemed to be dose dependent with the highest risk noted in patients treated with 10 mg BD. Similar low infection rates were noted in the maintenance and overall cohorts irrespective of dosing schedules when compared to placebo (incidence rate (IR) 1.94 for placebo and 1.35 and 0.64 for tofacitinib 5 and 10 mg BD, respectively).<sup>39</sup>

#### *Herpes zoster infection*

Herpes zoster infection has been reported as the most common serious infection in patients with RA treated with tofacitinib.<sup>40</sup> In the OCTAVE Sustain trial, the incidence of herpes zoster was higher in those patients treated with tofacitinib 10 mg ( $n=10$ , 5.1%) and 5 mg ( $n=3$ , 1.5%) than in the placebo group ( $n=1$ , 0.5%). None of the cases of herpes zoster seen were classed as severe AEs and treatment did not need to be discontinued. Furthermore, most cases were confined to only one or two adjacent dermatomes with none classed as severe or needing treatment discontinuation.<sup>20</sup>

When extrapolating and including all phase II/III/open-label extension studies involving patients receiving tofacitinib for UC, 65 (5.6%) patients were identified as having herpes zoster infection, 11 of whom had multidermatomal involvement with one patient developing herpes encephalitis.<sup>41</sup> In the overall cohort, herpes zoster risk was generally similar between doses, mostly limited to 1–2 dermatomes, non-serious and resolved without the need to discontinue tofacitinib.<sup>42</sup> Multivariate modelling identified older age, lower body weight, North American origin and prior anti-TNF failure as significant risk factors for herpes zoster infection. Patients of Asian origin had a higher herpes zoster risk on univariate but not in multivariate modelling.<sup>42</sup>

### Thromboembolic risk

The FDA<sup>43</sup> and EMA<sup>44</sup> have raised concerns regarding the thromboembolic risk associated with tofacitinib use based on early data from an ongoing study (study A3921133) exploring tofacitinib use in patients over the age of 50 with RA and with at least one known cardiovascular risk factor. The study demonstrated a venous thromboembolism (VTE) risk fivefold that associated with anti-TNFs<sup>43</sup> and highlighted an increased risk of thromboembolic events (deep vein thrombosis/pulmonary embolism) and an increase in all-cause mortality in patients receiving tofacitinib 10 mg BD dosing schedules compared to anti-TNFs and 5 mg tofacitinib.<sup>43</sup>

Accordingly, the Medicines and Healthcare products Regulatory Agency advised caution when considering tofacitinib in patients with known risk factors for thromboembolic disease, in addition to their underlying disease, adding that maintenance treatment at 10 mg BD is not recommended in patients with known risk factors for thromboembolic disease unless there is no suitable alternative.<sup>45</sup>

In contrast, a recently published population-based cohort study has found the occurrence of VTE in patients initiating both tofacitinib and a TNF inhibitor to be  $<1/100$  person-years, with no increased risk of thromboembolic events in those taking tofacitinib in comparison to a TNF inhibitor.<sup>46</sup> Furthermore, a 2020 systematic review and indirect meta-analysis has suggested that tofacitinib may have a protective effect against VTE.<sup>47</sup> Further trial data are required to define this paradigm.

### Cardiovascular risk and lipid profiles

IBD appears to be an independent risk factor for ischaemic heart disease and cerebrovascular disease.<sup>48</sup> Tofacitinib has been shown to reversibly increase serum lipid levels; however, this has not been shown to correlate with an increase in cardiovascular risk in the RA or psoriasis cohort.<sup>49,50</sup> An ongoing study (A3921133) is exploring the safety of tofacitinib in comparison to anti-TNFs in patients over the age of 50 with known cardiovascular risk factors.<sup>51</sup>

Amongst 1124 patients with UC receiving tofacitinib across the phase III/open-label extension tofacitinib UC clinical programme, LDL, HDL, total cholesterol and triglyceride elevation were noted. LDL to HDL ratios and total cholesterol to HDL ratios are strongly implicated in cardiovascular risk but these were relatively unchanged. Major adverse cardiovascular events were found to be infrequent.<sup>52</sup>

Whilst the exact mechanism for tofacitinib impacting lipid levels is not fully known, tofacitinib has been associated with decreasing the rate of cholesterol ester catabolism in patients with active RA.<sup>53</sup> Current recommendations advise monitoring lipids levels 4–8 weeks after initiation of tofacitinib, with guidelines followed for the management of hyperlipidaemia contextualizing cardiovascular risk.<sup>54</sup>

### Malignancy

The assessment of malignancy risk with tofacitinib in patients with UC is challenging given the heterogenous patient population and that many patients have previously received treatments which themselves are implicated in malignancy risk.<sup>55</sup>

In the tofacitinib UC clinical development programme, which includes trial data from 1124 patients with a tofacitinib treatment duration of up to 6.8 years, 20 patients developed malignancies (excluding non-melanoma skin cancer (NMSC)), with 17 of these occurring in patients receiving 10 mg BD. There was no clustering of malignancy type. Furthermore, the IR of malignancies was similar to that observed in the cohort of

patients with RA and psoriasis.<sup>55</sup> The authors also commented that the risk of malignancy was comparable to that of patients with UC on biologics and not on tofacitinib.<sup>55</sup>

Across the OCTAVE studies, NMSC occurred in 5 patients receiving tofacitinib and 1 patient receiving placebo.<sup>20</sup> NMSC occurred infrequently, being more likely to occur in patients with pre-existing risk factors for NMSC such as prior TNF failure, increasing age and prior NMSC.<sup>56</sup> Furthermore, the risk of NMSC was higher in patients receiving 10 mg BD dosing.<sup>55</sup>

In the absence of more data on cancer risk with tofacitinib, extreme caution is advised in patients with a previous history of malignancy. We recommend discussion in multidisciplinary team panels with appropriate conversations regarding the associated risks from trial data at the time. This statement would need to be reviewed as more data become available over time.

### Black box warning

Following the results of a large, randomized safety clinical trial evaluating tofacitinib in patients with RA, the FDA issued a black box warning for tofacitinib due to concerns regarding the increased risk of myocardial infarction, stroke, thromboembolic events and death in patients treated with tofacitinib in comparison to those treated with TNF blockers.<sup>57</sup> A higher rate of lymphoma was also observed in patients treated with tofacitinib in comparison to those treated with TNF blockers. There was also a higher rate of lung cancer in smokers treated with tofacitinib.<sup>57</sup>

### Safety checklist

As with current biological therapy, several considerations are required prior to initiating tofacitinib. We recommend referring to the prescriber treatment initiation checklist available on the electronic medicine compendium to ensure the relevant risks and screening tests are considered prior to

prescribing tofacitinib (<https://www.medicines.org.uk/emc/rmm/799/Document>) (Box 1). Caution needs to be exercised in patients with known liver and renal disease whilst will having implications for drug metabolism. Furthermore, based on the evidence highlighted above, those with cardiovascular risk factors, stroke, hypertension, obesity and diabetes are also unlikely to be ideal candidates for tofacitinib use.

The laboratory monitoring recommendations for patients taking tofacitinib include full blood count at baseline, after 4–8 weeks, and then 3-monthly thereafter. Lipid profile should be checked after 4–8 weeks, and liver enzymes should be monitored routinely.<sup>54</sup>

## Tofacitinib in special circumstances

### Use in acute severe UC

The rapid onset of action and short half-life have raised the prospect of using tofacitinib in the management of acute severe UC (ASUC). Data remain limited to a few case reports.<sup>30,60–64</sup> In three case series, 14 of 15 patients received 3 days high-dose intravenous steroids prior to rescue tofacitinib with a history of anti-TNF failure.<sup>30</sup> Eleven patients received standard induction dosing 10 mg BD, whereas the Michigan group used a higher dose of 10 mg three times daily.<sup>30,60</sup> Following tofacitinib rescue therapy, 13% required colectomy during that index admission and 20% within 6 months, with no difference in colectomy rates according to tofacitinib dose.<sup>30</sup> At the last follow-up, 47% remained in CFCR on maintenance therapy.<sup>30</sup> Kotwani et al. reported endoscopic remission in addition to CFCR at last follow-up in 2 of the 4 patients included in their small case series.<sup>63</sup> Overall, no major AEs were reported and notably no new thromboembolic events.<sup>30,61,64</sup>

More recently, a retrospective case–control study evaluated the efficacy of tofacitinib induction therapy in hospitalized patients with biologic-experienced ASUC.<sup>65</sup> Compared to

### Box 1. Vaccinations prior to commencing tofacitinib.<sup>58,59</sup>

- **Herpes zoster vaccine (live):** To be given at least 2 weeks (ideally 4 weeks) before starting treatment (test for VZV antibodies if concerns regarding lack of previous exposure). The non-live vaccine (Shingrix), should be preferred and is increasingly available<sup>58</sup>
- **Pneumococcal vaccine (live):** Preferably before starting therapy. Repeated at 5 years
- **Influenza vaccination (inactive):** To be given on an annual basis. (Intranasal preparation contains live virus)
- **BCG vaccination (live):** Using clinical history, chest X-ray and IFN $\gamma$  release assay testing to determine if vaccination required
- **Hepatitis B (inactive):** Recommended for seronegative patients. Measure anti-hepatitis B antibodies following vaccination
- **Measles, mumps and rubella (live):** If vaccination status is uncertain, serology should be checked and vaccination offered
- **Human Papilloma vaccination (inactive):** Recommended for both males and females

matched controls, there was a lower 90-day colectomy rate in the 40 patients who received tofacitinib with intravenous corticosteroids (hazard ratio 0.28, 95% CI 0.10–0.81;  $p=0.018$ ). The benefit was only statistically significant at tofacitinib 10 mg three times daily and not at 10 mg BD dosing.<sup>65</sup>

Although these initial reports suggest a role for tofacitinib in ASUC in selected patients, randomized controlled trials are needed to help determine the efficacy, optimum dose and safety in ASUC before it can be considered in routine clinical practice.

### Post-operative surgical outcomes

There are a few small retrospective reviews of surgical outcomes following preoperative tofacitinib exposure. Lightner reported 53 patients exposed to tofacitinib within 4 weeks of colectomy for medically refractory UC.<sup>66</sup> They noted an increased risk of venous thromboembolism with 7 (13.2%) cases in their cohort.<sup>66</sup> In contrast, in another study, no postoperative thrombotic complications were observed in 35 patients who underwent IBD-related surgery within 4 weeks of tofacitinib.<sup>67</sup> The authors also reported postoperative complications in 20% of patients exposed to tofacitinib. These complications included postoperative surgical site infections, pneumonia, peri-anal abscess, and one case of reoperation for small bowel resection.<sup>67</sup> These data are comparable to the rates of infectious complications reported in both anti-TNF exposed (20%) and unexposed (19.4%) patients in the prospective PUCINI trial.<sup>68</sup> Furthermore, Kani et al. concluded that preoperative tofacitinib exposure was not associated with an increased risk of 30-day postsurgical outcomes when compared with preoperative exposure to other biologics.<sup>69</sup>

### Extraintestinal manifestations

Tofacitinib is also approved for use in RA and psoriatic arthritis, making it appealing for the treatment of these extraintestinal manifestations (EIMs) in patients with UC.<sup>9,10</sup> In post hoc analysis of the OCTAVE data, 16.7% of patients with UC on 5 mg BD and 33% on 10 mg BD dosing reported improvement in IBD-related peripheral arthritis by week 52, whereas 18% on placebo reported worsening symptoms.<sup>70</sup> Although not licensed yet, phase II studies have shown tofacitinib is more effective than placebo in ankylosing spondylitis,<sup>71</sup> suggesting it may also be efficacious in axial spondyloarthritis.

Tofacitinib proved effective in phase III studies in chronic plaque psoriasis.<sup>72</sup> Upregulation of the JAK–STAT pathway has been observed in cutaneous EIMs, including pyoderma gangrenosum and erythema nodosum.<sup>73,74</sup> To date, only small case series are available reporting improvement of pyoderma gangrenosum with tofacitinib therapy.<sup>75,76</sup> The use of JAK inhibitors may be considered for cutaneous EIMs in the context of active UC, if anti-TNF fails or is contraindicated.<sup>73</sup> Regarding ocular EIMs, there are only reports of successful

treatment of refractory uveitis and scleritis with tofacitinib in two patients.<sup>74</sup>

### Tofacitinib in COVID-19

The SECURE-IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion for IBD) registry reported outcomes of 37 patients with IBD on tofacitinib therapy during the COVID-19 pandemic.<sup>77</sup> Overall, there was no difference in COVID-19 outcomes in the tofacitinib group compared with the non-tofacitinib treated cohort. None of the patients in the tofacitinib group were diagnosed with thromboembolic events.<sup>77</sup> Notably, JAK inhibitors, including baricitinib and ruxolitinib, are being studied in clinical trials for their potential role in COVID-19 management by blunting the cytokine storm.<sup>78,79</sup>

### Tofacitinib in pregnancy

There are limited safety data for tofacitinib use in pregnancy. As a small molecule, tofacitinib is likely to cross the placental barrier and be secreted in breast milk. Animal studies have shown teratogenic and foeticidal effects.<sup>25</sup> Rheumatological data of 47 pregnancies in women treated with tofacitinib and 15 pregnancies in women with UC treated with tofacitinib suggest no increased risk of fetal malformations or neonatal death compared with the general population.<sup>80–82</sup> Tofacitinib is not currently approved for use in pregnancy or breastfeeding, and the manufacturer advises effective contraception<sup>83</sup> during and up to 6 weeks after tofacitinib use.<sup>25</sup>

## Evolving paradigms

### Positioning of tofacitinib in the UC therapeutic algorithm

Tofacitinib and other JAK inhibitors address an unmet need in the armamentarium of IBD therapy. Owing to a lack of head-to-head clinical trials or comparative effectiveness studies with tofacitinib, there is currently no clear guidance on its correct positioning in the UC therapeutic algorithm. A myriad of factors deserve consideration regarding its positioning and include disease activity, speed of onset of action, prior biologic exposure, immunogenicity and route of administration as well as patient age, clinical comorbidities and the safety profile.

In a meta-analysis comparing efficacy and safety of first and second-line therapy in moderate-to-severe UC, tofacitinib ranked highest for induction of clinical remission (OR 11.88, 95% CI 2.32–60.89) and mucosal healing (OR 4.71, 95% CI 2.23–9.92) in patients with prior anti-TNF exposure.<sup>84</sup> It should be noted that, whilst this may enable positioning of tofacitinib as first-line following conventional therapy, the FDA restricted use to after failure of anti-TNF therapy from July 2019, following concerns with VTE from patients with RA exposed to tofacitinib 10 mg BD.<sup>43</sup> This risk has not been substantiated in the IBD literature. Direct head-to-head studies are needed to inform clinical decision-making and adequately position tofacitinib in the treatment paradigm.

### Biomarkers predicting response

With the increasing armamentarium of IBD therapy and drive for personalized IBD therapy, predictive biomarkers are eagerly awaited to help predict treatment response and redefine our therapeutic algorithm. Kolar et al. identified an early decrease in IL-4 levels as a potential biomarker of tofacitinib response.<sup>85</sup> In another study, a tofacitinib-specific mucosal genetic biomarker was identified that was significantly correlated with endoscopic response. The identified hub gene ( $p=1.5\times 10^{-9}$ , fold change 2.3) had a predictive accuracy for the response of 100% ( $p<0.001$ ).<sup>86</sup> Most promising is the PROPHETIC prospective study (NCT04576000), currently recruiting, that will assess molecular determinants of response or non-response to tofacitinib in UC.<sup>87</sup>

### Combining biologics with small molecule therapy

The concept of combining biologics in IBD management for incremental effect or indeed in the context of treatment refractoriness has gained interest in recent years. Data on the combined use of biologics with JAK inhibitors are limited. In one study of nine patients with UC treated with VDZ and tofacitinib, clinical response was observed in 62.5% of patients who were previously refractory to VDZ or tofacitinib monotherapy.<sup>88</sup> In a retrospective study of 42 patients (63% previously failed  $\geq 2$  biologics) treated with combination tofacitinib and biologics (VDZ 64%, UST 19%, infliximab 14%) with a median follow-up of 5 months, 67% achieved a clinical response by weeks 8–16 of combination therapy with no additional safety signals compared to tofacitinib monotherapy.<sup>89</sup> In another study of 50 patients, 15% were treated with tofacitinib and VDZ, 16% with anti-TNF and tofacitinib, and 6% with tofacitinib and UST.<sup>90</sup> Significantly more patients on combination therapy were in clinical and endoscopic remission at end of follow-up compared to baseline (50% versus 14%,  $p=0.0018$ ; and 34% versus 6%,  $p=0.0039$ ). In view of the small number of patients treated, it was not possible to assess if any particular combination was associated with increased efficacy or less AEs. Of the eight SAEs reported in the cohort, none occurred in the tofacitinib combination group, and 57% occurred in patients on concomitant immunomodulator therapy.<sup>90</sup> A recent systematic review and meta-analysis reported on dual biologic and combination tofacitinib therapy from 288 patients (76%) with CD with a median treatment duration of 24 weeks.<sup>91</sup> Overall, 58/288 (20%) cases of combination therapy with tofacitinib were included: 11% tofacitinib and VDZ (32/288), 6% UST and tofacitinib (16/288), and 3% anti-TNF and tofacitinib (10/288).<sup>91</sup> The pooled data demonstrated AE rates (31%) in line with previously reported rates seen with anti-TNF monotherapy. Pooled clinical and endoscopic remission rates were 59% (95% CI 42–74%) and 34% (95% CI 23–46%), respectively.<sup>91</sup> Larger prospective trials are needed to assess the efficacy, safety and optimum strategy of combination therapy with JAK inhibitors.

## Newer JAK inhibitors

See Table 2 for an overview of JAK inhibitors for UC and CD.

### Filgotinib

Filgotinib is a selective JAK1 inhibitor with once-daily (OD) oral dosing and that has been evaluated for use in CD and UC.<sup>92</sup> Safety and efficacy of filgotinib in moderate-to-severe CD and UC were reported in the FITZROY and SELECTION trials, respectively.<sup>93–95</sup> The FITZROY study was a 20-week multicentre phase II trial, randomizing 174 moderately-to-severely active CD, TNF-naïve and exposed patients, 3:1 to receive filgotinib 200 mg OD or placebo for 10 weeks.<sup>95</sup> The primary endpoint was clinical remission (CDAI <150) at week 10. After 10 weeks, based on CDAI response status, investigators reassigned patients to receive filgotinib 200 mg OD, 100 mg OD, or placebo for an additional 10 weeks in the second part of the study. Clinical remission at 10 weeks was significantly higher in the filgotinib arm (47%) compared to placebo (23%;  $p=0.0077$ ) with a safety profile comparable to placebo over 20 weeks.<sup>95</sup> Recruitment for a multicentre phase III trial of filgotinib for induction and maintenance of remission in moderately-to-severely active CD (DIVERSITY trial, NCT02914561) has been completed and results are awaited.<sup>96</sup>

The results from the SELECTION study (phase IIb/III) with an induction and maintenance phase were recently published.<sup>97</sup> In the induction trial, a total of 1348, biologic-naïve (induction study A,  $n=659$ ) or biologic-experienced (induction study B,  $n=689$ ) patients with moderately-to-severely active UC were randomized and treated with filgotinib (200 or 100 mg OD) or placebo. A significantly higher proportion of patients achieved clinical remission at week 10 (primary endpoint) compared with placebo in both the biologic-naïve (26.1% versus 15.3%,  $p=0.0157$ ) and biologic-experienced (11.5% versus 4.2%;  $p=0.0103$ ) arms.<sup>97</sup> In the maintenance trial, patients achieving clinical response or remission at week 10 in the filgotinib arm ( $n=664$ ), were rerandomized 2:1 to receive an induction dose of filgotinib or placebo and treated for a total of 58 weeks. At week 58, a significantly higher proportion of patients on filgotinib 100 mg (19.1% biologic naïve and 9.5% biologic experienced) and 200 mg (26.1% biologic naïve and 11.5% biologic experienced) were in clinical remission compared to placebo (15.3% biologic naïve and 4.2% biologic experienced) and a significantly higher proportion of patients on 200 mg filgotinib achieved key secondary endpoints, including CFCR, sustained clinical remission, MCS remission and endoscopic and histological remission compared with placebo.<sup>97</sup> Overall, the IR of AEs, SAEs and discontinuations due to AEs were similar in the filgotinib and placebo arms for both the induction and maintenance studies.

In November 2021, filgotinib received a European license for the treatment of adult patients with moderately-to-severely active UC who have failed or are intolerant to conventional treatment or biologic therapy.<sup>98</sup>

**Table 2.** Overview of JAK inhibitors for UC and CD.

Target	Name of the drug	Current status	Important completed clinical trials	Primary endpoint
<b>UC</b>				
Pan JAK inhibitor	Tofacitinib	Licensed for use in moderate-to-severe UC	Phase II (induction therapy) <sup>19</sup> OCTAVE I and II (induction therapy) <sup>20</sup> OCTAVE Sustain (maintenance therapy) <sup>20</sup>	Clinical response at 8 weeks Clinical remission at 8 weeks Clinical remission at 8 weeks
	Peficitinib	Discontinued after phase IIb in view of inefficacy for moderate-to-severe UC	Phase IIb (induction therapy) <sup>105</sup>	Clinical response at 8 weeks
JAK1 selective inhibitor	Filgotinib	Received EMA license for use in moderate-to-severe UC	Phase IIb/III, SELECTION trial (induction therapy) <sup>97</sup> Phase IIb/III, SELECTION trial (maintenance therapy) <sup>97</sup>	Clinical remission at 10 weeks Clinical remission at 10 weeks
	Upadacitinib	Awaiting regulatory approvals from FDA and EMA for use in moderate-to-severe UC	Phase IIb, U-ACHIEVE program (induction therapy) <sup>99</sup> Phase III U-ACCOMPLISH (induction therapy) <sup>101</sup> Phase III (maintenance therapy) <sup>102</sup>	Clinical remission at 8 weeks Clinical remission at 8 weeks Clinical remission at 52 weeks
<b>CD</b>				
Pan JAK inhibitor	Tofacitinib	Failed to show significant benefit in moderate-to-severe CD	Phase II (induction therapy) <sup>35</sup> Phase IIb (induction therapy) <sup>36</sup> Phase IIb (maintenance therapy) <sup>36</sup>	Clinical response at 4 weeks Clinical remission at 8 weeks Clinical remission at 26 weeks
JAK1 selective inhibitor	Filgotinib	Results from multicentre phase III results in moderate-to-severe CD, awaited	Phase II, FITZROY trial (induction therapy) <sup>95</sup> Phase III, DIVERSITY trial (induction therapy) <sup>96</sup> Phase III, DIVERSITY trial (maintenance therapy) <sup>96</sup>	Clinical remission at 10 weeks Clinical remission at 10 weeks Clinical remission at 58 weeks
	Upadacitinib	Phase III studies in moderate-to-severe CD, under way	Phase II, CELEST (induction therapy) <sup>100</sup> Phase II, CELEST (maintenance therapy) <sup>100</sup>	Clinical remission at 16 weeks Clinical remission at 52 weeks

CD, Crohn's disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; JAK, Janus kinase; UC, ulcerative colitis.

### Upadacitinib

Upadacitinib (UPA) is another selective JAK1 inhibitor being evaluated for the management of patients with UC and CD.<sup>99,100</sup> The phase II CELEST study assessed the safety and efficacy of UPA in patients with moderately-to-severely active CD either failing or intolerant to immunosuppressants or anti-TNF therapy.<sup>100</sup> It randomized 220 patients in 1:1:1:1:1 to receive immediate-release UPA 3 mg BD, 6 mg BD, 12 mg BD, 24 mg BD, 24 mg OD or placebo as induction therapy for 16 weeks, followed by rerandomization 1:1:1 to receive immediate-release UPA 3 mg BD, 12 mg BD or 24 mg OD as maintenance therapy

for 36 weeks. Significantly higher clinical remission rates were noted in the 6 mg BD arm compared with placebo (27% *versus* 11%;  $p < 0.1$ ), and a significant dose–response relationship was observed for endoscopic remission between the UPA *versus* placebo arms with efficacy maintained in the treatment arm for most endpoints till week 52. Numerically higher AEs were noted in the UPA arm compared with placebo but there was no relationship noted with the dose.<sup>100</sup>

The safety and efficacy of UPA was reported from a multicentre phase IIb study, part of an overarching U-ACHIEVE programme.<sup>99</sup> The trial randomized 250 patients with

moderately-to-severely active UC with inadequate response, loss of response or intolerance to conventional or biologic therapies to a treatment arm (7.5, 15, 30 or 45 mg OD extended-release UPA) or placebo for 8 weeks. At week 8, significantly higher clinical remission rates were noted in the treatment arm compared with none in the placebo arm (7.5 mg: 8.5%,  $p=0.052$ ; 15 mg: 14.3%,  $p=0.013$ ; 30 mg: 13.5%,  $p=0.011$ ; and 45 mg: 19.6%,  $p=0.002$ ). Compared with the placebo arm (2.2%), the treatment arm reported a significantly higher endoscopic improvement at week 8 (7.5 mg: 14.9%,  $p=0.033$ ; 15 mg: 30.6%,  $p<0.001$ ; 30 mg: 26.9%,  $p<0.001$ ; and 45 mg: 35.7%,  $p<0.001$ ). Similar incidences of AEs and discontinuation related to AEs were noted across the UPA groups with numerically higher events in the placebo group.<sup>99</sup>

In the phase III U-ACCOMPLISH study, a significantly higher proportion of patients receiving UPA 45 mg daily achieved clinical remission (33.5% *versus* placebo 4.1%) at 8 weeks.<sup>101</sup> Likewise, all ranked secondary endpoints (symptomatic, endoscopic histological improvements) were achieved in a significantly higher proportion of patients receiving UPA 45 mg daily *versus* placebo ( $p<0.001$ ).<sup>101</sup>

The efficacy and safety of UPA maintenance therapy were reported recently from the randomized phase III study.<sup>102</sup> Both UPA 15 and 30 mg met the primary endpoint of clinical remission at week 52, and all secondary endpoints. Significantly greater percentages of patients receiving 15 mg and 30 mg *versus* placebo achieved clinical remission (42.3% and 51.7%, *versus* 12.1%), endoscopic improvement (48.7% and 61.6%, *versus* 14.5%), maintenance of clinical remission (59.2% and 69.7%, *versus* 22.2%), CFCR (57.1% and 68.0%, *versus* 22.2%), maintenance of endoscopic improvement (61.6% and 69.5%, *versus* 18.9%), endoscopic remission (24.2% and 25.9%, *versus* 5.6%), maintenance of clinical response (63.0% and 76.6%, *versus* 18.8%) and histo-endoscopic mucosal improvement (34.8% and 49.3%, *versus* 11.8%) ( $p<0.001$  for all endpoints).<sup>102</sup> UPA 15 and 30 mg were both well tolerated and no new safety signals were observed.

The use of UPA in the management of UC is not yet approved. Regulatory applications have been submitted to the FDA and EMA for approval of UPA for the treatment of moderately-to-severely active UC, and the outcome is awaited.<sup>103</sup>

## Conclusion

Tofacitinib is the first-in-class and currently the only approved JAK inhibitor licensed for the treatment of moderately-to-severely active UC. Being a small molecule, its oral administration, rapid onset of action (as early as 3 days) and short half-life with high intestinal bioavailability are unique advantages. Furthermore, the lack of immunogenicity implicates a lower risk of loss of response over time typical of anti-TNF agents. Efficacy and effectiveness data from clinical trials and real-world evidence have demonstrated that tofacitinib can be effective even following corticosteroid, thiopurine, and anti-TNF and VDZ failure.<sup>20</sup>

There is an increased dose-related risk of venous thromboembolism with tofacitinib and it should therefore be used very cautiously in patients at high risk.<sup>44,45</sup> Caution also needs to be exercised in patients with cardiovascular risk factors, history of strokes, hypertension, obesity and diabetes. However, overall, the safety profile has been reassuring. Recent literature has also allayed anxieties regarding heightened risks of herpes zoster but vaccination prior to treatment is recommended as indeed with other biologic and immunomodulator agents. Economic modelling has demonstrated tofacitinib to be cost effective.<sup>104</sup>

The development of agents targeting the JAK–STAT pathway represents the dawn of a new era in abrogation of the immune-inflammatory pathway that triggers and perpetuates IBD. Whilst tofacitinib has established its place in UC therapy, we are at the threshold of a plethora of newer JAK inhibitors seeking imminent licensing and others in development, aiming to complement our therapeutic armamentarium and the promise of a better future.

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