Janus Kinase Inhibitors for the Management of Patients With Inflammatory Bowel Disease

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Abstract: In recent years, knowledge about the pathophysiology of inflammatory bowel disease (IBD) has led to the development of novel therapies and biologics with differing mechanisms of action. A major innovation has been the development of small molecules. Tofacitinib was the first pan–Janus kinase (Jak) inhibitor approved for the treatment of IBD, targeting the 4 isoforms of cytokine-associated Jaks (Jak1, Jak2, Jak3, and tyrosine-protein kinase 2). Compared with biologic agents, novel small molecules have a short half-life, a rapid onset of action, and no immunogenicity, but they are associated with a potentially increased risk of off-target side effects. These differences in properties between biologic and oral small molecule therapies may be important when considering their relative treatment positioning and role in clinical practice. Although tofacitinib has been demonstrated to be highly effective as both first- and second-line therapy for ulcerative colitis, concerns about safety, including the risk of infection, venous thromboembolism, major adverse cardiovascular events, and malignancy, have dampened enthusiasm for its widespread use. Subsequently, several Jak inhibitors with more selective profiles, and potentially improved safety while maintaining treatment efficacy, are currently in late-stage clinical trials for use in patients with IBD. This article summarizes the current data regarding the use, safety, and efficacy of Jak inhibitors in patients with IBD.

Keywords
Inflammatory bowel disease, Janus kinase inhibitors, small molecules, ulcerative colitis, clinical trials

Chronic inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and Crohn's disease (CD), which are disabling, relapsing, and remitting disorders of uncertain etiology. In recent years, further evidence has accumulated to support that UC and CD result from an exaggerated immune response to an environmental trigger in genetically susceptible hosts.[1-4] Considerable progress has been made in the treatment of both diseases, notably the advent of monoclonal antibody therapies, and success with anticytokine and anti-integrin therapies in particular. Although monoclonal antibody therapy has been

a paradigm shift in management, many patients still do not respond. For example, approximately 30% of patients treated with tumor necrosis factor (TNF) antagonists are primary nonresponders, and another 20% to 40% of TNF antagonist responders will experience secondary loss of response.[5,6] Loss of response can be related to the development of antibodies to biologics or immune escape mechanisms. Although surgical rates have decreased in parallel with the availability of advanced treatments for IBD, bowel resection continues to be necessary in a substantial proportion of patients for the management of medically refractory disease.[7-9] Consequently, there remains an unmet need to develop treatments with alternative mechanisms of action to improve rates of remission achieved with current agents. The development of small molecules, specifically Janus kinase (Jak) inhibitors, may help to address this unmet need.

Jaks are intracellular proteins that consist of 4 different isoforms: tyrosine kinases Jak1, Jak2, and Jak3 and nonreceptor tyrosine-protein kinase (Tyk) 2.[10,11] This family was identified by Wilks in 1989,[12] and Tyk2 was the first gene member cloned and synthesized in 1990 by Firmbach-Kraft and colleagues.[13] Jaks are named after Janus, the 2-faced Roman god of doorways, beginnings, and transitions, because Jaks have 2 phosphate-transferring domains: one domain exhibits the kinase activity (JH1) and the other negatively regulates the kinase activity (JH2).[14]

Cytokines are proteins that can bind to different types of receptors. Type 1 and 2 cytokine receptors are associated intracellularly with Jak tyrosine kinases. Type 1 receptors have common subunits: γ-chain (CD132), β-chain (CD131), and glycoprotein 130 (gp130 or CD130). Receptors with a γ-chain subunit bind to interleukin (IL)-2, IL-4, IL-7, IL-9, and IL-15, and their intracellular signaling is through Jak1 and Jak3. Receptors with a β-chain subunit bind to IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor, signaling through Jak2. Receptors with gp130 bound to IL-6 or IL-11 signal through Jak1, and those bound to IL-12 signal through Tyk2.[15,16] Likewise, type 2 receptors bound to interferon (IFN)-α, IFN-β, IL-10, or IL-20 signal through Jak1, and those bound to IFN-γ signal through Jak1 and Jak2.[15,16] After cytokine binding, the type 1 and 2 cytokine receptor subunits bring their intracellular tails close to the Tyks, and Jak phosphorylates the tyrosine receptor residues, activating the signal transducer and activator of transcription (STAT), a family of DNA-binding proteins that, once reaching the nucleus, regulates the expression of genes relevant to immune and inflammatory cellular responses.[10,17] Cytokines more involved in gut cell homeostasis and IBD pathophysiology are IL-2, IL-6, IL-10, IFN-γ, IL-12, IL-23, and IL-9.

Jak proteins are expressed in all cell types, except for Jak3, which is predominantly expressed in hematopoietic cells.[18] Several human diseases have been related to mutations and polymorphisms in Jak and STAT genes. For instance, mutations in Jak2 can cause polycythemia vera, essential thrombocythemia, and myelofibrosis, and mutations in Jak1 and Jak3 are associated with T-cell acute lymphoblastic leukemia and breast cancer.[19,20]

Jak1 and Jak2 deficiency phenotypes have not been described in humans, as these are incompatible with life.[21] Jak3 deficiency induces severe combined immunodeficiency secondary to the absence of γ-chain subunit at the type 1 cytokine receptor, and the complete absence of Jak3 leads to a phenotype of deep T-lymphocyte and natural killer cells deficit with susceptibility to life-threatening infections. Although lymphocyte B-cell counts are preserved, they present some functional abnormalities, especially related to antibody production.[22,23]

Jak inhibitors are orally administered small molecules that have a rapid onset of action and lack of immunogenicity. They act by competitively blocking the adenosine triphosphate–binding site in the JH1 domain through noncovalent interactions.[17] Multiple Jak inhibitors have been developed with different selectivity profiles for blocking 1 or more of the intracellular tyrosine kinases Jak1, Jak2, Jak3, and Tyk2, and act by downregulating the Jak-STAT signaling pathway, interfering in the pathogenesis of immune-mediated disorders, including IBD.[10,11] Although Jak inhibitors are not specific therapies and can affect multiple cytokine-related IBD pathways, their dose-dependent lack of selectivity can carry a higher risk of off-target adverse events (AEs), which may be improved with more cytokine-selective or organ-specific molecules.[17]

This article aims to summarize the evidence pertaining to the use, safety, and efficacy of Jak inhibitors in patients with IBD[10] (see eTable at www.gastroenterologyandhepatology.net).

Tofacitinib

Tofacitinib (Xeljanz, Pfizer) is an oral pan-Jak inhibitor that was initially approved in 2012 for the treatment of moderate-to-severe rheumatoid arthritis (RA)[24] and in 2017 for psoriatic arthritis.[25] In 2018, the European Medicines Agency (EMA)[26] and the US Food and Drug Administration (FDA)[27] initially approved tofacitinib for the treatment of patients with moderate-to-severe UC, and in 2019 for patients after an inadequate response or intolerance to TNF antagonists.[28,29]

Ulcerative Colitis

Tofacitinib for the treatment of moderate-to-severe UC was initially evaluated in a phase 2, double-blind, placebo-

Table 1. Remission Rates for Tofacitinib vs Placebo in the OCTAVE 1 and 2 Trials in Patients With and Without Prior TNF Antagonist Failure[32]

	Prior TNF Antagonist Failure			No Prior TNF Antagonist Failure		
	Placebo N=124	Tofacitinib 10 mg BID N=465	Difference	Placebo N=110	Tofacitinib 10 mg BID N=440	Difference
Patients in Remission (n/%)	1/0.8%	53/11.4%	10.6% (95% CI, 7.0%-15.7%); *P*<.01	13/11.8%	106/24.1%	12.3% (95% CI, 5.0%-19.5%); *P*<.01

BID, twice daily; TNF, tumor necrosis factor.

controlled, randomized controlled trial (RCT) that enrolled 194 patients randomized to 0.5 mg, 3 mg, 10 mg, or 15 mg of tofacitinib twice daily (BID) or placebo for 8 weeks and then followed to week 12. The primary endpoint of clinical response occurred in 32% (10/31; *P*=.39), 48% (16/33; *P*=.55), 61% (20/33; *P*=.10), and 78% (38/49; *P*<.001) of patients in the tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg groups, respectively, compared with 42% (20/48) of patients assigned to placebo. Rates of the secondary endpoint of clinical remission (the usual endpoint for drug registration in UC) were also higher for the tofacitinib 3 mg (33%; *P*=.01), 10 mg (48%; *P*<.01), and 15 mg (41%; *P*<.01) groups than for the placebo group (10%).[30]

Given the encouraging results, this initial study was followed by 2 induction and 1 maintenance phase 3, double-blind, placebo-controlled RCTs.[31] The induction studies, OCTAVE 1 and 2, included 598 and 541 patients, respectively, with moderate-to-severe UC who were randomized to tofacitinib 10 mg BID or placebo for 8 weeks. The primary endpoint of clinical remission (total Mayo score ≤2 with no subscore >1 and rectal bleeding subscore=0) at week 8 was reached in 18.5% of patients who received tofacitinib compared with 8.2% of those in the placebo arm (*P*=.007) in the OCTAVE 1 trial, and in 16.6% vs 3.6% (*P*≤.001) in the OCTAVE 2 trial. In both trials, efficacy of tofacitinib was greater than placebo, irrespective of previous TNF antagonist exposure (Table 1). The secondary endpoint, mucosal healing (Mayo endoscopic subscore ≤1) at week 8, was observed in 31.3% of patients in the tofacitinib arm vs 15.6% in the placebo arm (*P*<.001) in OCTAVE 1, and in 28.4% vs 11.6% (*P*<.001), respectively, in OCTAVE 2.[31]

The maintenance trial, OCTAVE Sustain, included 593 patients with UC who had previously achieved clinical response (decrease of ≥3 points and ≥30% of the total Mayo score from baseline with a decrease of ≥1 point or a total score of 0 or 1 for the rectal bleeding subscore) during the induction trials. Patients were rerandomized to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, or placebo for 52 weeks. The primary endpoint of clinical remission at week 52 was achieved in 34.3% (68/198), 40.6% (80/197), and 11.1% (22/198) of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms, respectively (*P*<.001 for both treatment arms vs placebo). The secondary endpoint of mucosal healing at week 52 occurred in 37.4% (74/198), 45.7% (90/197), and 13.1% (26/198) of the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms, respectively (*P*<.001 for both treatment arms vs placebo). Corticosteroid-free remission was achieved by 35.4% (23/65), 47.3% (26/55), and 5.1% (3/59) of the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms, respectively (*P*<.001 for both treatment arms vs placebo). A subgroup of patients that did not respond after 8 weeks of induction continued tofacitinib 10 mg BID for 8 more weeks, achieving a late clinical response rate of 52.2% (154/295).[31,32]

The long-term open-label extension (OLE) of the OCTAVE studies assessed dose de-escalation of tofacitinib 10 mg BID to 5 mg BID in 66 patients who had previously achieved and maintained clinical remission after 52 weeks of treatment with tofacitinib 10 mg BID. Conversely, dose escalation to tofacitinib 10 mg BID was attempted in 57 patients who had previously achieved response during induction but had lost response during the maintenance phase while on tofacitinib 5 mg BID. For patients in the dose de-escalation group, 84.1% (53/63) maintained clinical response and 74.6% (47/63) maintained clinical remission at 12 months. For patients in the dose escalation group, 64.9% (37/57) recaptured clinical response and 49.1% (28/57) recaptured clinical remission at 12 months.[33]

The speed of onset of tofacitinib in UC was further investigated in a post hoc analysis of OCTAVE 1 and 2, which demonstrated that patients who received tofacitinib 10 mg BID vs placebo were more likely to have a reduction in stool frequency subscore (mean reduction from baseline of -0.27 vs -0.11; *P*<.01) and rectal bleeding subscore (-0.30 vs -0.14; *P*<.01) as early as 3 days after starting therapy.[34]

Owing to the potential of the drug to deliver rapid control of disease activity, tofacitinib has been used off-

Table 2. Comparative Efficacy of Tofacitinib and Different Biologic Therapies for Inducing Clinical Remission in Biologic-Naive and -Experienced Patients With Moderate-to-Severe Ulcerative Colitis[38]

	Infliximab	Adalimumab	Golimumab	Vedolizumab	Ustekinumab
Tofacitinib Biologic-Naive[a]	1.91 (0.83-4.38)	1.1 (0.76-2.75)	0.76 (0.33-1.76)	0.84 (0.39-1.82)	0.96 (0.38-2.45)
Tofacitinib Biologic-Experienced[a]	N/A	11.05 (1.79-68.41)	N/A	6.18 (1.00-38.00)	0.97 (0.11-8.72)

[a]Odds ratio (95% CI).
N/A, not available.

label in hospitalized patients with acute severe UC (ASUC), at higher doses such as 10 mg 3 times a day (TID) for 9 doses. One case series of 4 patients who had failed intravenous (IV) corticosteroids or TNF antagonists reported that 3 of 4 patients achieved clinical remission.[35] Also, individual case reports have suggested that tofacitinib might be effective for cases of severe colitis that have failed a TNF antagonist.[36] A retrospective case-control study of 40 biologic-experienced patients with ASUC requiring IV corticosteroids who received tofacitinib and were matched to 113 control patients found that patients who received tofacitinib had a lower risk of colectomy at 90 days (hazard ratio [HR], 0.28; 95% CI, 0.10-0.81; *P*=.018). Furthermore, when risk of colectomy was stratified by treatment dose, the most protective dose was tofacitinib 10 mg TID (HR, 0.11; 95% CI, 0.02-0.56; *P*=.008) compared with tofacitinib 10 mg BID (HR, 0.66; 95% CI, 0.21-2.09; *P*=.5).[37] However, this is off-label use, and these observations should be assessed in a controlled clinical trial.

A recent post hoc analysis that pooled data from the phase 3 induction and maintenance trials as well as the dose de-escalation subpopulation in OCTAVE Open showed that remission after induction (week 8) in the placebo and tofacitinib groups without prior failure to TNF antagonists was 11.8% vs 24.1%, respectively (treatment difference from placebo, 12.3%; 95% CI, 5.0%-19.5%; *P*<.01). In patients with prior failure to 1 TNF antagonist, clinical remission rates were 1.2% vs 12.5% (treatment difference from placebo, 11.3%; 95% CI, 7.0%-15.7%; *P*<.01), and in patients with prior failure to 2 or more TNF antagonists, clinical remission rates were 0.0% vs 9.2% (treatment difference from placebo, 9.2%; 95% CI, 4.6%-13.7%; *P*<.05), respectively. Regarding the mechanism for TNF antagonist loss of response, clinical remission rates were 1.4% vs 7.5% (treatment difference from placebo, 6.2%; 95% CI, 2.0%-10.3%; *P*<.05) in the placebo and tofacitinib groups with prior primary loss of response, and 0.0% vs 16.6% (treatment difference from placebo, 16.6%; 95% CI, 11.2%-21.9%; *P*<.01) for those with secondary loss of response, respectively. The consistent treatment effects show that the efficacy of tofacitinib was greater than placebo, regardless of previous exposure to TNF antagonists, the number of TNF antagonists previously used, and the mechanism of loss of response.[32]

A recent network meta-analysis compared the efficacy of drugs used for the treatment of moderate-to-severe UC in prior TNF antagonist–exposed and biologic-naive patients. This network meta-analysis included 15 RCTs for induction of remission in biologic-naive and -experienced patients with moderate-to-severe UC (n=3747) treated with infliximab, adalimumab, golimumab (Simponi, Janssen), vedolizumab (Entyvio, Takeda), tofacitinib, or ustekinumab (Stelara, Janssen). Efficacy of tofacitinib to induce clinical remission compared with other agents in patients with moderate-to-severe UC showed no superiority in biologic-naive patients; however, in biologic-experienced patients, tofacitinib and ustekinumab were superior to adalimumab and vedolizumab in this subgroup of patients (Table 2).[38]

Given the previous findings, the current American Gastroenterological Association clinical practice guidelines recommend the use of tofacitinib or ustekinumab for the treatment of moderate-to-severe UC in patients with prior biologic exposure.[39]

Crohn's Disease

Tofacitinib has also been studied in patients with CD. In a phase 2 RCT, 139 patients with moderate-to-severe CD received tofacitinib 1 mg, 5 mg, or 15 mg BID or placebo for 4 weeks. The primary endpoint, clinical response (decrease in the Crohn's Disease Activity Index [CDAI] of ≥70 points from baseline score), was observed in 36.1% (13/36; *P*=.467), 57.6% (19/33; *P*=.466), 45.7% (16/35; *P*≥.999), and 47.1% (16/34) of patients in the tofacitinib 1 mg, 5 mg, and 15 mg, and placebo arms, respectively. For the secondary endpoint, clinical remission, results were similar, with none of the tofacitinib doses achieving significantly different results compared with placebo.[40] Given the historically high placebo rates in CD trials, modern studies not only assess clinical activity but also

endoscopic disease activity as inclusion criteria. This particular study enrolled patients on the basis of CDAI scores between 220 and 450, using endoscopic assessment to define disease extension but not to assess mucosal inflammation to confirm endoscopic disease activity, which may explain the unprecedently high placebo rates obtained.

Panés and colleagues conducted 2 RCTs in 280 patients with moderate-to-severe CD. During induction, patients received tofacitinib 5 mg BID (n=86) or 10 mg BID (n=86), or placebo (n=91) for 8 weeks, followed by a 26-week maintenance period for patients who achieved clinical response or remission during induction (n=180). For induction, clinical remission was not significantly different between tofacitinib arms and placebo (*P*=.325 and *P*=.392 for tofacitinib 5 mg BID and 10 mg BID vs placebo, respectively); nonetheless, the mean change in C-reactive protein from baseline between tofacitinib 5 mg BID and 10 mg BID and placebo was significantly different (*P*<.001 and *P*<.0001 for 5 mg BID and 10 mg BID vs placebo, respectively), showing evidence of biologic activity.[41]

Other open-label studies and real-world data have suggested some efficacy of tofacitinib as maintenance therapy; nonetheless, the results have not been strong enough to pursue the phase 3 trial for tofacitinib in patients with CD.[42-44]

Upadacitinib

Upadacitinib (Rinvoq, AbbVie) is a selective oral Jak1 inhibitor that was initially approved in 2019 by the FDA for the treatment of patients with moderate-to-severe RA.[45] A recent head-to-head trial in patients with RA previously exposed to biologic therapy (N=612) showed that upadacitinib 15 mg once daily (OD) (n=303) was superior to IV abatacept (n=309), with remission rates of 30% and 13.3%, respectively (difference, 16.8%; 95% CI, 10.4%-23.2%; *P*<.001).[46] Another head-to-head trial that compared upadacitinib 15 mg orally OD (n=651), adalimumab 40 mg subcutaneously every 2 weeks (n=327), and placebo (n=651) for patients with RA who had prior failure to methotrexate showed similar results, with remission rates of 18%, 10%, and 4%, respectively (*P*≤.001 for upadacitinib vs adalimumab or placebo).[47] Upadacitinib is currently under development for the treatment of patients with UC and CD.

Ulcerative Colitis

A phase 2b, placebo-controlled RCT evaluated upadacitinib for induction therapy in moderate-to-severe UC patients with previous inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressive agents, and/or biologic therapies. The U-ACHIEVE study enrolled 250 patients to upadacitinib 7.5 mg, 15 mg, 30 mg, or 45 mg or placebo for 8 weeks; overall, 227 patients completed the study. The primary endpoint of clinical remission (total Mayo score ≤2 with no subscore of >1) was observed in 8.5% (*P*=.052), 14.3% (*P*=.013), 13.5% (*P*=.011), and 19.6% (*P*=.002) of patients on upadacitinib 7.5 mg, 15 mg, 30 mg, and 45 mg, respectively, and in 0% of patients on placebo. The secondary endpoint of endoscopic improvement (Mayo endoscopic subscore of ≤1) was observed in 14.9% (*P*=.033), 30.6% (*P*<.001), 26.9% (*P*<.001), and 35.7% (*P*<.001) of patients on upadacitinib 7.5 mg, 15 mg, 30 mg, and 45 mg, respectively, and in 2.2% of patients on placebo. Histologic improvement, defined as any decrease from baseline in Geboes Score, was observed in 31.9% (*P*=.003), 51.0% (*P*<.001), 44.2% (*P*<.001), and 48.2% (*P*<.001) of patients on upadacitinib 7.5 mg, 15 mg, 30 mg, and 45 mg, respectively, and in 6.5% of patients on placebo.[48]

Recently, two phase 3 induction trials that assessed efficacy and safety of upadacitinib in patients with moderate-to-severe UC failing conventional therapy and/or biologic agents have been presented in abstract form. In the phase 3 U-ACHIEVE trial, 26.1% of patients receiving upadacitinib 45 mg OD (N=319) achieved the primary endpoint of clinical remission at week 8 vs 4.8% in the placebo group (N=153) (difference, 21.6%; 95% CI, 15.8%-27.4%; *P*<.001).[49] Moreover, similar results were obtained in the identically designed U-ACCOMPLISH trial, which reported that 33.5% of patients receiving upadacitinib (N=341) achieved the primary endpoint of clinical remission vs 4.1% in the placebo group (N=174) (difference, 29.0%; 95% CI, 23.2%-34.7%; *P*<.001).[50] Given the promising results from these phase 2 and 3 studies, the full phase 3 data as well as maintenance and OLE results are eagerly awaited.

Crohn's Disease

The phase 2, placebo-controlled RCT CELEST evaluated upadacitinib 3 mg, 6 mg, 12 mg, or 24 mg BID, upadacitinib 24 mg OD, or placebo for an induction period of 16 weeks followed by a maintenance period of 36 weeks in 220 patients with moderate-to-severe CD. During induction, the coprimary endpoint of clinical remission (average daily stool frequency of ≤1.5 and abdominal pain score of ≤1.0, with neither score worse than the baseline value) was observed in 13% (5/39), 27% (10/37; *P*<.1), 11% (4/36), 22% (8/36), and 14% (5/35) of patients receiving upadacitinib 3 mg, 6 mg, 12 mg, and 24 mg BID, and upadacitinib 24 mg OD, respectively, and in 11% (4/37) of patients receiving placebo at week 16. A clear dose-response relationship was not observed for clinical remission. However, for the second coprimary

endpoint, endoscopic remission (Simple Endoscopic Score for CD ≤4 and reduction of ≥2 points from baseline with no subscore >1) rates of 10% (4/39; *P*<.1), 8% (3/37), 8% (3/36; *P*<.1), 22% (8/36; *P*<.1), and 14% (5/35; *P*<.05) were observed in the upadacitinib 3 mg, 6 mg, 12 mg, and 24 mg BID, and 24 mg OD groups, respectively, and in 0% (0/37) of patients who received placebo. During the maintenance phase at week 52 of the study, among the 94 patients who achieved modified intention to treat clinical response after induction, clinical remission was achieved in 25.0%, 28.6%, 41.4%, and 31.6% of patients who received upadacitinib 3 mg, 6 mg, and 12 mg BID, and upadacitinib 24 mg OD, respectively; corresponding rates for endoscopic remission were 15.9%, 21.3%, 24.4%, and 25.5%, respectively.[51] Collectively, these data indicate a signal for efficacy of upadacitinib in patients with CD. Phase 3 trials are underway in patients with moderate-to-severe CD who have had an inadequate response or were intolerant to biologic therapy (NCT03345836 [active, not recruiting], NCT03345849 [recruiting], NCT03345823 [enrolling by invitation]).

Filgotinib

Filgotinib (Gilead Sciences) is a Jak1 selective inhibitor approved in 2020 by the EMA for the treatment of patients with moderate-to-severe RA at a dose of 200 mg OD.[52] Recently, in the phase 3 FINCH study, patients with active RA (N=1252) were randomized to filgotinib 200 mg OD with weekly methotrexate (n=416), filgotinib 100 mg OD with weekly methotrexate (n=207), filgotinib 200 mg OD alone (n=210), or weekly methotrexate alone (n=416), showing that remission rates at week 24 were higher with filgotinib 100 mg or 200 mg plus methotrexate or filgotinib 200 mg OD compared with methotrexate monotherapy (43%, 54%, and 42% vs 29%, respectively; *P*≤.001 for all comparisons).[53]

For UC, the SELECTION induction phase 2b/3 studies randomized patients with moderate-to-severe UC who were either biologic naive (cohort A, n=659) or with previous failure to biologics (cohort B, n=625) to filgotinib 200 mg OD, filgotinib 100 mg OD, or placebo. The primary endpoint, clinical remission at week 10, was achieved in significantly higher proportions of patients treated with filgotinib 200 mg than placebo in both biologic-naive (26.1% [64/245] vs 15.3% [21/137]; *P*=.0157) and biologic-experienced (11.5% [30/262] vs 4.2% [6/142]; *P*=.0103) patients.[54] Furthermore, the biologic-naive patients who received filgotinib 200 mg achieved significantly higher endoscopic remission (12.2% [30/245] vs 3.6% [5/137]; *P*=.0047) and histologic remission (35.1% [86/245] vs 16.1% [22/137]; *P*<.0001) rates compared with placebo.[54]

In the maintenance phase, patients who received filgotinib during induction therapy were rerandomized to continue filgotinib (100 mg or 200 mg OD) or receive placebo, and patients who received placebo during induction continued to receive placebo. At week 58, clinical remission rates were significantly higher for patients on filgotinib 200 mg (37.2% vs 11.2%; *P*<.025) and filgotinib 100 mg (23.8% vs 13.5%; *P*<.05) compared with placebo. Moreover, patients receiving filgotinib 200 mg maintenance therapy also achieved significantly higher rates of 6-month corticosteroid-free clinical remission (27.2% vs 6.4.0%; *P*=.0055), endoscopic remission (15.6% vs 6.1%; *P*=.0157), and histologic remission (38.2% vs 13.3%; *P*<.0001) at week 58 than patients receiving placebo.[55] Currently, the phase 3, long-term extension of the SELECTION study (NCT02914535) is evaluating the long-term safety of filgotinib in patients with UC.

In CD, the phase 2 FITZROY trial enrolled 174 patients with moderate-to-severe CD who were either biologic naive (n=73) or who had previously failed biologic therapy (n=99) and randomized them to filgotinib 200 mg OD or placebo. Overall, clinical remission (CDAI score <150) was observed in 47% (60/128) of patients who received filgotinib 200 mg OD compared with 23% (10/44) of patients assigned to placebo (*P*=.007). Furthermore, this difference relative to placebo was higher for patients in the biologic-naive group (60% [34/57] vs 13% [2/16]).[56] Two phase 3 trials in patients with moderate-to-severe CD are currently underway. The DIVERSITY trial (NCT02914561) is recruiting both biologic-naive and -experienced patients with moderate-to-severe CD to evaluate the efficacy and safety of filgotinib during induction and maintenance, with a long-term extension planned (DIVERSITY LTE; NCT02914600). In addition, two phase 2 trials for fistulizing CD are under development, DIVERGENCE 1 (NCT03046056) for patients with small bowel CD and DIVERGENCE 2 (NCT03077412) for patients with perianal fistulizing CD.

Peficitinib

Peficitinib (Astellas) is an oral pan-Jak inhibitor with moderate selectivity for Jak3 for the treatment of patients with moderate-to-severe RA at a dose of 100 mg or 150 mg OD. A phase 2b, dose-ranging, double-blind, placebo-controlled RCT enrolled 219 patients with moderate-to-severe UC. Participants were randomized to receive peficitinib 25 mg, 75 mg, or 150 mg OD, peficitinib 75 mg BID, or placebo. The primary endpoint, dose response measured by the change in total Mayo score at week 8 from baseline, did not show a linear relationship; however, greater proportions of patients in the peficitinib 75

mg OD, 150 mg OD, and 75 mg BID arms achieved the secondary endpoints of clinical response, clinical remission, and mucosal healing at week 8 than the placebo and peficitinib 25 mg OD groups.[57] No studies are currently registered for further evaluation of peficitinib in patients with UC or CD.

Other Janus Kinase Inhibitors

Several additional Jak inhibitors are being developed for IBD treatment. TD-1473 (izencitinib, jointly developed by Theravance and Janssen Biotech) is a poorly absorbed pan-Jak inhibitor designed for selective activity in the gastrointestinal tract. In murine colitis models, local efficacy was demonstrated despite minimal systemic plasma drug concentrations.[58] Conversely, high biologically active colonic tissue drug concentrations indicated that targeting the gut compartment might be an effective strategy to minimize AEs. A phase 1b study that randomized patients with moderate-to-severe UC to TD-1473 20 mg, 80 mg, or 270 mg or placebo for 28 days of treatment showed that low drug plasma exposure and biologically active colonic tissue drug concentrations could be achieved. Although the study was not powered for efficacy analyses, the results showed that a higher proportion of patients achieved clinical response, endoscopic response, and improvement in all TD-1473 groups than placebo.[59] Recently, TD-1473 failed to meet the primary efficacy endpoint of change in the total Mayo score at week 8 in patients with moderate-to-severe UC.[60]

Tyk2 mediates the signaling of IL-10, IL-12, IL-23, and IFN, and in vitro studies demonstrated that its inhibition led to loss of function and impaired signaling of these cytokines but was not associated with increased risk of infections or malignancies.[61] The selective Tyk2 inhibitor deucravacitinib (Bristol Myers Squibb) failed to meet the primary efficacy endpoint of clinical remission at week 12 in patients with moderate-to-severe UC.[62] Brepocitinib (Pfizer; a selective Jak1 and Tyk2 inhibitor) and PF-06826647 (Pfizer; a Tyk2/Jak2 inhibitor) are currently undergoing phase 2 studies for the treatment of moderate-to-severe UC and CD. Results from these ongoing trials are awaited.

Safety Profiles of Janus Kinase Inhibitors

Considerable data are available regarding the safety of Jak inhibitors in patients treated for IBD and other immune disorders. A systematic review of 82 studies analyzed safety data of 66,159 patients exposed to Jak inhibitors for different immune disorders, including RA, psoriasis, IBD, and ankylosing spondylitis, with 87.16% of patients exposed to tofacitinib. The incidence rates (IRs) of AEs and severe AEs (SAEs) were 42.69 per 100 patient-years and 9.98 per 100 patient-years, respectively, and the overall relative risk (RR) of AEs and SAEs was 1.01 (95% CI, 0.97-1.06) and 0.98 (95% CI, 0.83-1.15), respectively.[63] A systematic review and meta-analysis that evaluated the efficacy and safety profiles of different Jak inhibitors (tofacitinib, filgotinib, peficitinib, upadacitinib, and TD-1473) compared with placebo in patients with UC and CD showed that patients treated with Jak inhibitors were overall not at a significantly higher risk for AEs (RR, 1.02; 95% CI, 0.97-1.09; *P*=.412) compared with placebo.[64]

A systematic review and meta-analysis by Ma and colleagues that evaluated Jak inhibitors in UC and CD trials showed that 7 studies evaluated infectious AEs, noting that Jak inhibitors were associated with a higher risk of infections overall (RR, 1.4; 95% CI, 1.18-1.67; *P*<.001), especially upper respiratory tract infections.[64] Furthermore, in IBD trials a higher rate of patients with herpes zoster (HZ) was observed in the treatment arm (4 cases in CD trials and 19 cases in UC trials) vs placebo (0 cases in CD trials and 3 cases in UC trials).[64]

Infections

Treatment with Jak inhibitors has been associated with a higher risk of HZ infection. According to the results of a systematic review analyzing safety data of 48,093 patients exposed to Jak inhibitors, the RR of HZ was significantly higher than placebo (RR, 1.72; 95% CI, 1.07-2.76).[63]

A study analyzing the risk of HZ in 1157 UC patients receiving tofacitinib showed an HZ overall IR per 100 patient-years of tofacitinib exposure of 4.07 (95% CI, 3.14-5.19), with higher rates among patients receiving tofacitinib 10 mg BID (IR, 4.25; 95% CI, 3.18-5.56) than 5 mg BID (IR, 3.45; 95% CI, 1.78-6.02). Other risk factors identified were older age (HR, 1.58 for every 10-year increment; 95% CI, 1.34-1.87; *P*<.0001), previous exposure to TNF antagonists (HR, 1.92; 95% CI, 1.15-3.21; *P*=.0122), and Asian ethnicity (HR, 1.76; 95% CI, 0.97-3.19; *P*=.0612).[65]

An integrated safety analysis including 1157 patients (1613 patient-years of exposure) receiving tofacitinib 5 mg or 10 mg showed a statistically higher IR of HZ among patients who received tofacitinib 10 mg BID (IR, 6.6; 95% CI, 3.2-12.2) vs placebo (IR, 1.0; 95% CI, 0.0-5.4), with an overall HZ IR of 4.1 (95% CI, 3.1-5.2) among patients exposed to tofacitinib.[66]

Specific strategies are available to manage the risk of HZ. One key factor is to increase patients' awareness regarding HZ and its related symptoms, and also to develop a high index of suspicion among health care workers. HZ classically presents as a dermatomal rash affecting 1 or 2 chest dermatomes. However, when complicated,

Table 3. Laboratory Follow-Up Recommendations in Patients Using Janus Kinase Inhibitors

Laboratory Parameter	Follow-Up
LDL and HDL levels	4-8 weeks after initiation of therapy and every 6 months thereafter
Serum creatinine levels	Baseline and every 12 months
Creatine kinase	Baseline and every 3 months
Liver enzymes	Baseline, 4-8 weeks after initiation of therapy, and every 3 months thereafter
Cytopenias	Baseline, 4-8 weeks after initiation of therapy, and every 3 months thereafter

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

HZ can result in multidermatomal involvement, postherpetic neuralgia (PHN), disseminated skin disease, and neurologic or ophthalmologic involvement. Because immunosuppressed patients are at higher risk for complicated or atypical HZ presentations, a high index of suspicion must be maintained. A cross-sectional study of 36,170 patients showed a prevalence rate of 7.7% (95% CI, 7.5-8.0) for HZ and 2.3% (95% CI, 2.2-2.5) for PHN; moreover, 29.8% of patients who previously had HZ developed PHN.[67] The current American College of Gastroenterology guideline recommends that patients over 50 years consider vaccination against HZ. For the prevention of HZ and related complications, there are 2 types of vaccines, live attenuated and recombinant. The attenuated live HZ vaccine is administered as 1 dose, can be used in immunocompetent adults over 60 years, and, if used in immunocompromised patients, should be administered at least 30 days before starting any immunosuppressors.[68] The recombinant nonlive HZ vaccine is administered as 2 doses, is approved by the FDA for immunocompetent adults over the age of 18 years, and can be used in patients who are already immunosuppressed. The Advisory Committee on Immunization Practices advises the use of the inactivated recombinant HZ vaccine rather than the nonlive vaccine.[69]

Metabolic Disorders

Hyperlipidemia A post hoc analysis of the same 1157 patients treated with tofacitinib in UC trials showed that, especially among those receiving tofacitinib 10 mg BID rather than 5 mg BID, patients receiving tofacitinib had elevations in total cholesterol and low- or high-density lipoprotein, achieving maximum levels at week 8 that remained relatively stable until week 61 of follow-up. These elevations were dose-dependent, reversible, and not related to a higher risk of major cardiovascular events (MACEs), with an overall IR of 0.24 (95% CI, 0.07-0.62) in the tofacitinib arms.[70]

A pooled analysis of 22 RCTs assessing MACEs in 10,701 patients treated with Jak inhibitors showed a RR of MACEs of 1.07 (95% CI, 0.56-2.03) and, when considering only placebo-controlled RCTs, a RR of 1.09 (95% CI, 0.54-2.21).[63]

Serum Creatinine, Creatine Kinase, and Liver Enzyme Elevations There are previous reports of serum creatinine, liver enzyme, and creatine kinase elevations associated with Jak inhibitors, and no reported cases of associated liver failure or rhabdomyolysis.[66,71] The integrated safety analysis of 1157 tofacitinib-treated patients with moderate-to-severe UC showed that no patients met liver enzyme elevation criteria (2 sequential aspartate aminotransferase [AST] or alanine aminotransferase [ALT] elevations ≥3 times the upper limit of normal [ULN] and at least 1 bilirubin value ≥2 × ULN, or 2 sequential AST or ALT elevations ≥5 × ULN) for discontinuation of Jak inhibitor therapy. Furthermore, 1 (0.1%) patient experienced a serum creatinine elevation greater than 50% in 2 sequential measurements and greater than 0.5 mg/dL over baseline that required therapy discontinuation, and 8 (0.7%) patients met laboratory criteria for treatment discontinuation given creatine kinase elevations, with 1 patient experiencing rhabdomyolysis as part of the placebo group in OCTAVE Sustain at 7.4 months after receiving the last dose of tofacitinib 10 mg BID.[66]

Cytopenias Given the relationship between Jak2 signaling and hematopoiesis, treatment with Jak inhibitors may alter blood cell counts.[72] Tofacitinib has been related to an initial decrease in hemoglobin level and neutrophil, platelet, and lymphocyte counts in psoriasis treatment. Nevertheless, these changes were slight and reversible.[73-75] A safety analysis from OCTAVE Sustain reported minimal changes in hemoglobin and absolute lymphocyte count variations, with 13 of 1157 (1.2%) patients discontinuing therapy given 2 sequential hemoglobin measurements less than 8.0 g/dL or a decrease of greater than 30% from baseline hemoglobin, and 10 of 1157 (0.9%) patients meeting criteria for therapy discontinuation given 2 sequential absolute lymphocyte counts less than 500/mm.[66]

Overall, these metabolic changes are likely of minimal clinical consequence, and the risk might be ameliorated by Jak inhibitor selectivity. The current laboratory follow-up recommendations for Jak inhibitors are listed in Table 3, with lipid disorders likely the most important to monitor in IBD patients, who are more often diagnosed at an early age and exposed to higher cardiovascular (CV) risk in the long term.

Thromboembolic Disease

The first safety warning for tofacitinib regarding venous thromboembolism (VTE) was issued by the FDA and EMA in 2019 based upon a postmarketing long-term safety trial in patients with RA that presented a higher risk of pulmonary thromboembolism and death in patients with RA receiving tofacitinib 10 mg BID. These patients were over the age of 50 years and had at least 1 CV risk factor.[76,77] Given these findings, the FDA and EMA have not approved the use of tofacitinib 10 mg BID for RA, and this dose is approved only in patients with moderate-to-severe UC.

Notwithstanding this potential risk, a pooled analysis of 10 RCTs comprising 5143 patients exposed to Jak inhibitors showed a RR of 0.9 (95% CI, 0.32-2.54) for deep vein thrombosis (DVT) and pulmonary embolism (PE).[63] As an FDA requirement, a phase 4 clinical trial (ORAL Surveillance; NCT02092467) that compared the safety of tofacitinib vs the TNF antagonists adalimumab and etanercept was conducted in 4362 patients with RA who were over 50 years, had at least 1 CV risk factor, and were receiving background methotrexate. Patients were randomized to tofacitinib 5 mg BID (n=1455) or 10 mg BID (n=1456) or a TNF antagonist (n=1451). For MACEs, the HRs for tofacitinib 5 mg BID or 10 mg BID vs a TNF antagonist were 1.24 (95% CI, 0.81-1.91) and 1.43 (95% CI, 0.94-2.18), respectively, and for malignancies the HRs were 1.47 (95% CI, 1.00-2.18) and 1.48 (95% CI, 1.00-2.19), respectively. Thus, the prespecified noninferiority criteria were not met for both coprimary endpoints.[78]

Patients with IBD are at increased risk of thromboembolic disease because of the hypercoagulability associated with inflammation.[79] Accordingly, the concern raised in RA regarding VTE is relevant. In a post hoc analysis of 1157 UC patients who received at least 1 dose of tofacitinib 5 or 10 mg once daily in any phase 2, phase 3, or OLE tofacitinib in UC trials, the overall IR of DVT (1/1157) was 0.04 events/100 patient-years of exposure (95% CI, 0.00-0.23) and for PE (4/1157) was 0.16 (95% CI, 0.04-0.41). All of these events occurred in patients over 50 years who were receiving tofacitinib 10 mg BID and had at least 1 thromboembolism risk factor along with UC during the OLE period of the trials.[80]

A meta-analysis by Yates and colleagues assessed 42 placebo-controlled RCTs of Jak inhibitors in different immune-mediated diseases, evaluating 6542 patient exposure years to Jak inhibitors compared with 1578 patient exposure years for placebo.[81] This meta-analysis observed 15 VTE events among patients treated with Jak inhibitors (IR, 0.23 events/100 patient-years; 95% CI, 0.12-0.38) and 4 VTE events in patients exposed to placebo (IR, 0.25 events/100 patient-years; 95% CI, 0.07-0.73). Although these results are reassuring, they are contradictory to the previously published data and the current warnings around VTE risk, which could be explained by the meta-analysis' exclusion of long-term RCTs and the tendency of most thromboembolic events to occur after extended drug exposure.[81]

Given preliminary reports from the ORAL Surveillance postmarketing safety study, the FDA recommends avoiding use of Jak inhibitors in patients over 50 years with at least 1 CV risk factor, and also recommends using the lowest effective dose and for the shortest duration needed to achieve or maintain therapeutic response in patients with UC.[82] Recently, the FDA concluded that there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with tofacitinib, and has required revisions to the boxed warning for all currently approved Jak inhibitors to include this potential risk. The FDA further recommends limiting the use of these agents to certain patients who have not responded or cannot tolerate 1 or more TNF antagonists.[83]

Risk of Malignancy

Nonmelanoma Skin Cancer Safety data from a post hoc analysis of RCTs with 8524 patients exposed to Jak inhibitors showed an overall RR of nonmelanoma skin cancer (NMSC) of 1.05 (95% CI, 0.47-2.35), and, when excluding studies with active comparator arms, the RR was 1.22 (95% CI, 0.50-2.95).[63]

Other Malignancies The same study found that a pooled analysis of 21 RCTs including 9916 patients exposed to Jak inhibitors showed an overall RR for malignancy of 1.39 (95% CI, 0.68-2.85), and, when considering only placebo-controlled RCTs, a RR of 1.50 (95% CI, 0.68-3.32).[63]

The ORAL Surveillance phase 4 clinical trial also evaluated risk of malignancies (excluding NMSC) in patients using tofacitinib 5 mg BID or 10 mg BID or a TNF antagonist. The most common malignancy reported was lung cancer. Overall, the HRs of malignancies for tofacitinib 5 mg BID or 10 mg BID vs a TNF antagonist were 1.47 (95% CI, 1.00-2.18) and 1.48 (95% CI, 1.00-2.19), respectively, not achieving the noninferiority criteria for either tofacitinib dose[78] (NCT02092467).

In a safety analysis from the OCTAVE studies, patients were analyzed as 3 cohorts: induction (n=1220), maintenance (n=592), and overall cohort, which included OCTAVE Sustain and OLE (n=1157). In the overall group, 11 patients from the OLE study developed a non-NMSC malignancy, of which 8 patients had been exposed to TNF antagonists and 11 patients to thiopurines, with an IR of malignancy of 0.7 (95% CI, 0.3-1.2). The

reported cases followed no specific pattern, with 1 case reported for each type of malignancy (cervical cancer, hepatic angiosarcoma, cholangiocarcinoma, cutaneous leiomyosarcoma, Epstein-Barr virus–associated lymphoma, renal cell carcinoma, essential thrombocythemia, acute myeloid leukemia, adenocarcinoma of colon, lung cancer, and breast cancer).[66]

Pregnancy, Breastfeeding, and Male Spermatogenesis

Studies in animals show that supratherapeutic doses of Jak inhibitors during pregnancy are teratogenic and feticidal.[84-86] Unlike monoclonal antibodies, small molecules cross the placenta during the first trimester, leading to concern regarding fetal risk for the class.[87] Empiric data in humans are sparse and based upon case reports. Safety databases of tofacitinib for UC, RA, and psoriasis show a total of 74 pregnant women exposed to tofacitinib, with 37 healthy newborns, 1 neonate with congenital pulmonary valve stenosis, 12 spontaneous abortions, 13 terminated pregnancies for medical reasons, and 11 lost to follow-up or pending outcome. Also, noninterventional data report 42 pregnant women exposed to tofacitinib, resulting in 7 healthy newborns, 1 neonate with ventricular septum defect, 3 spontaneous abortions, 1 terminated pregnancy for medical reasons, and 33 lost to follow-up or pending outcome.[87] Given the limited data on pregnancy outcomes in women using Jak inhibitors, the EMA recommends against the use of Jak inhibitors during pregnancy.[88]

No assessments have been reported regarding the risk to breastfed infants in women receiving Jak inhibitors. Current recommendations indicate not to breastfeed while taking tofacitinib.[89]

Findings in clinical animal studies of filgotinib included impaired spermatogenesis and histopathologic effects on male reproductive organs (testes and epididymis),[90] and these effects are being investigated by 2 clinical trials, one in patients with moderate-to-severe IBD (NCT03201445) and the other in patients with RA, psoriatic arthritis, ankylosing spondylitis, or nonradiographic axial spondyloarthritis (NCT03926195).

Conclusion

Jak inhibitors offer multiple advantages when compared with TNF antagonists, are orally administered and nonimmunogenic, have predictable pharmacokinetics, and are more economic than parenteral drugs. Currently, tofacitinib is approved for treatment of patients with UC, and other Jak inhibitors are under study with promising results for management of patients with UC and CD. Concerns about the safety profiles of these drugs require further investigation, especially in long-term and real-world studies.

Disclosures

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eTable. Characteristics of Jak Inhibitors

Drug (Selectivity)	Pharmacokinetics	UC Efficacy Data	CD Efficacy Data
Tofacitinib[1-6] (Jak3/Jak1 > Jak2 > Tyk2)	Half-life approximately 3 hours Clearance 70% hepatic metabolism and 30% renal elimination	Phase 3 OCTAVE: *Clinical remission 10 mg vs placebo at week 8* OCTAVE 1: 18.5% vs 8.2% OCTAVE 2: 16.6% vs 3.6% *Clinical remission 5 mg and 10 mg vs placebo at week 52* OCTAVE Sustain: 34.3% and 40.6% vs 11.1% OCTAVE open-label extension: • Dose escalation to 10 mg BID after failure with 5 mg BID: At 12 months, 65% recaptured clinical response and 49% achieved remission • Dose de-escalation from 10 mg to 5 mg BID in patients previously in remission: 84% of patients maintained response and 75% remained in remission	Phase 2 Induction week 4: No significant differences in clinical response rates between tofacitinib 1 mg (36%), 5 mg (58%), 15 mg (46%), and placebo (47%) Induction week 8: No significant differences in clinical remission rates between tofacitinib 5 mg (44%), 10 mg (43%), and placebo (37%) Maintenance week 26: No significant differences in clinical response or remission rates between tofacitinib 5 mg (39.5%), 10 mg (55.8%), and placebo (38.1%)
Upadacitinib[7,8] (Jak1 > Jak2/Jak3)	Half-life approximately 4 hours Clearance 80% hepatic metabolism and 20% renal elimination	Phase 2 U-ACHIEVE: *Clinical remission at week 8* 7.5 mg: 8.5% (*P*=.052) 15 mg: 14.3% (*P*=.013) 30 mg: 13.5% (*P*=.011) 45 mg: 19.6% (*P*=.002) Placebo: 0%	Phase 2 CELEST (induction): *Clinical remission at week 16* 3 mg BID: 13% 6 mg BID: 27% (*P*<.1) 12 mg BID: 11% 24 mg BID: 22% 24 mg QD: 14% Placebo: 11% *Endoscopic remission at week 16* 3 mg BID: 10% (*P*<.1) 6 mg BID: 8% 12 mg BID: 8%(*P*<.1) 24 mg BID: 22%(*P*<.01) 24 mg QD: 14%(*P*<.05) Placebo: 0% CELEST (maintenance): *Clinical remission at week 52* 3 mg BID: 25% 6 mg BID: 28.6% 12 mg BID: 41.4% 24 mg BID: 31.6% *Endoscopic remission at week 52* 3 mg BID: 15.9% 6 mg BID: 21.3% 12 mg BID: 24.4% 24 mg BID: 25.5%

(Table continues on following page)

eTable. *(Continued)* Characteristics of Jak Inhibitors

Drug (Selectivity)	Pharmacokinetics	UC Efficacy Data	CD Efficacy Data
Filgotinib[9,10] (Jak1 > Jak2/Jak3/Tyk2)	Half-life 5-6 hours for parent compound and 18-22 hours for active metabolite	Phase 2b/3 SELECTION (induction): *Clinical remission at week 10* Biologic-naive: 100 mg OD: 19.1% (*P*=.34) 200 mg OD: 26.1% (*P*=.0157) Placebo: 15.3% Biologic-experienced: 100 mg OD: 9.5% (*P*=.06) 200 mg OD: 11.5% (*P*=.01) Placebo: 4.2% SELECTION (maintenance): *Clinical remission at week 58* 100 mg OD: 23.8% (*P*=.04) Placebo: 13.5% 200 mg OD: 37.2% (*P*<.0001) Placebo: 11.2%	Phase 2 FITZROY (induction): *Clinical remission at week 10* 200 mg OD: 47% (*P*=.0077) Placebo: 23%
Peficitinib[6,11,12] (Jak3 > Jak1/Jak2)	Half-life 7-13 hours	Not approved	Not approved
TD-1473[6,13] (Jak1, Jak2, Jak3 intestinally restricted)	Half-life 4-44 hours	Phase 2b/3 recruiting	Phase 2 recruiting
PF-06651600[6] (Jak3)	Unknown	Phase 2 recruiting	Phase 2 recruiting
PF-06700841[6] (Jak1, Tyk2)	Half-life 1-1.5 hours	Phase 2 recruiting	Phase 2 recruiting
BMS-986165[14]	Half-life 8-15 hours	Phase 2 recruiting	Phase 2 recruiting

BID, twice daily; CD, Crohn's disease; Jak, Janus kinase; QD, 4 times daily; Tyk, tyrosine-protein kinase; UC, ulcerative colitis.

eTable References

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