Are All Janus Kinase Inhibitors for Inflammatory Bowel Disease the Same?

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Abstract: Ulcerative colitis and Crohn's disease are chronic, progressive inflammatory bowel diseases (IBDs) and are without a known cure. Janus kinase (JAK) is a family of cytosolic tyrosine kinases that mediate signal transduction in response to extracellular stimuli. Abrogating the proinflammatory cytokine signaling cascades using JAK inhibitors (jakinibs) has been shown to be highly effective in the treatment of numerous inflammatory diseases, including IBD. Jakinibs currently licensed for moderate-to-severe IBD include the first-generation, nonselective tofacitinib and the second-generation JAK1-selective inhibitors filgotinib (licensed outside of the United States) and upadacitinib; several other jakinibs in the therapeutic pipeline are in various stages of clinical development. The jakinib class of small-molecule drugs share numerous commonalities such as their oral administration, nonimmunogenicity, short half-life, rapid onset of action, and the same class-wide regulatory restrictions owing to safety concerns. However, jakinibs differ on several fronts, translating into important clinical practice points for health care providers managing IBD patients. This article provides an overview of the jakinib class in IBD, examines how each drug differs in terms of pharmacology as well as efficacy and safety, and offers perspectives on challenges that remain and future opportunities.

Keywords
Janus kinase inhibitors, selectivity, inflammatory bowel disease, ulcerative colitis, Crohn's disease

Inflammatory bowel disease (IBD) is an umbrella term for a group of incurable chronic inflammatory diseases of the gastrointestinal tract that are divided into 3 clinical subtypes: ulcerative colitis (UC), Crohn's disease (CD), and IBD-unclassified. The etiology remains incompletely understood but is thought to involve an interplay of environmental factors in genetically predisposed patients. The altered intestinal microbiome, epithelial barrier defects, and dysregulated immune responses from the loss of T-cell and B-cell tolerance to antigenic stimuli are also

thought to play an integral role in disease etiopathogenesis.[1,2] Uncontrolled inflammation and disease progression lead to disability and a profoundly negative impact on patient quality of life.[3-5] The discovery of cytokines as the key players in the pathogenesis of inflammatory diseases has paved the way for substantial therapeutic advances over the past 20 years. The therapeutic focus to date has largely centered on immunosuppression using cytokine and leukocyte antitrafficking approaches. However, rates of treatment failure and intolerance of existing therapies remain high, engendering a vastly research-active area to seek promising treatments or treatment strategies to fulfill these unmet needs.

Janus kinase (JAK) inhibitors (jakinibs) are a potent class of orally administered drugs, which are used for several inflammatory, autoimmune, and myeloproliferative diseases. In 2011, ruxolitinib (Jakafi, Incyte) became the first jakinib to be approved by the US Food and Drug Administration (FDA) for the treatment of myelofibrosis; this was followed by tofacitinib (Xeljanz, Pfizer) in 2012 for the treatment of rheumatoid arthritis (RA).[6,7] For IBD, 3 jakinibs have been approved for moderate-to-severe IBD: tofacitinib and filgotinib (Jyseleca, Galapagos NV) for UC and more recently upadacitinib (Rinvoq, AbbVie) for both UC and CD. It should be noted that filgotinib is licensed by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency but does not have FDA approval for any indication. Jakinibs hold several advantages over monoclonal antibodies: they are rapidly acting and potent stemming from their rapid absorption after oral administration and effect on a broad range of cytokines; they lack immunogenicity; they have short half-lives; and they have more predictable pharmacokinetics.[8] However, first- and second-generation jakinibs are not all the same, which may have implications for their use in clinical practice. There have been several advances in this rapidly evolving field over the past 12 months. This article provides a contemporaneous overview of jakinibs for IBD, including how they differ in their pharmacology, safety, and efficacy from clinical trial and real-world studies.

Role of Janus Kinase

The JAK signal transducer and activator of transcription (JAK-STAT) activation pathway is a central communication node that rapidly transduces extracellular signals to the nucleus and is ubiquitously involved in each aspect of the human immune system. This fundamental role in hematopoiesis and both adaptive and innate immunity has made it an attractive target for the treatment of myeloproliferative and inflammatory diseases.[9] The JAK-STAT pathway was first discovered in the early 1990s during attempts to elucidate how interferons (IFNs) effected gene transcription.[10,11] It is now known to be essential for the signaling cascade of greater than 50 factors, including interleukins (ILs), colony-stimulating factors, and hormones, which regulate a wide range of cellular processes.[12,13]

Isoforms and Selectivity

JAKs are proteins that are constitutively associated with the intracellular domains of type I and type II cytokine receptors.[14] The class I cytokine receptor family includes 3 receptors—the common gamma (γc), the common beta (βc), and the gp130—which are defined by their use of a common signal-transducing chain for the formation of hetero- and homo-oligomeric signaling complexes.[15] Growth hormone and erythropoietin receptors signal as homodimeric pairs and also belong to this class. The class II cytokine receptor family includes receptors for the type I, type II, and type III IFNs together with the IL-10 cytokine family. Importantly, each receptor family interacts with and signals through a distinct subset of JAKs.

JAKs function as tyrosine kinases, enzymes that catalyze the adenosine triphosphate (ATP)-mediated phosphorylation of select tyrosine residues in target proteins, and were first discovered by Wilks in 1989.[16] The subsequent discoveries of all JAKs by 1994 led to a family of proteins as they are known today and are comprised of 4 members: JAK1, JAK2, JAK3, and nonreceptor tyrosine-protein kinase 2 (TYK2).[17] JAK3 is predominantly expressed in hematopoietic cells, whereas JAK1, JAK2, and TYK2 are ubiquitously expressed. JAK3 plays critical roles in immune homeostasis and lymphopoiesis, JAK1 is important in mediating inflammatory cytokine signals, and JAK2 in mediating myelopoiesis and erythropoiesis. JAK isoforms consist of 4 domains common to all JAK proteins: the Band-4.1, ezrin, radixin, moesin (FERM) and SH-2-like domains, which mediate binding to the receptor's intracellular domain; the pseudokinase domain, which has low level autoregulatory catalytic activity although previously thought to lack all enzyme activity; and the tyrosine kinase domain, responsible for most, if not all, of the phosphoryl transfer activity of JAKs.[13] These domains are also known as JAK homology (JH) domains and are numbered sequentially from 1 to 7 from the carboxyl terminus to the amino terminus such that the kinase domain is known as JH1 and the SH-2-like and FERM domains are referred to as JH3-7. The kinase (JH1) domain is homologous across the isoforms (eg, JAK3 shares 84% of the residues in this region with JAK1, 87% with JAK2, and 80% with TYK2).[18] Therefore, jakinibs that inhibit this site are selective but not specific and are dependent on a number of factors,

Table 1. In vitro Isoform Selectivity of Available JAK Inhibitors for IBD

	Enzyme assay IC50 (nM)						
	JAK1	JAK2	JAK3	TYK2	JAK2:JAK1	JAK3:JAK1	TYK2:JAK1
Tofacitinib	15.1	77.4	55.0	489	5.1	3.6	32.4
Filgotinib	363	2400	>10,000	2600	6.6	>27.5	7.2
Upadacitinib	8	600	139	N/A	75	17.4	N/A

IBD, inflammatory bowel disease; IC50, half maximal inhibitory concentration; JAK, Janus kinase; N/A, not applicable; TYK2, nonreceptor tyrosine-protein kinase 2. Adapted from Choy.[19]

including individual genetics, jakinib dose, cell type, and tissue penetration.[18,19] This selectivity at higher doses, for example, as assessed by in vitro STAT phosphorylation/cytokine release studies, is significantly diminished.[18,19] Tofacitinib is a pan-jakinib with preferential selectivity for JAK1 and JAK3, whereas filgotinib and upadacitinib are JAK1-selective. Table 1 highlights the concentration of jakinib needed to inhibit 50% of the isoform activity (IC50), with lower IC50 values indicating higher potency.

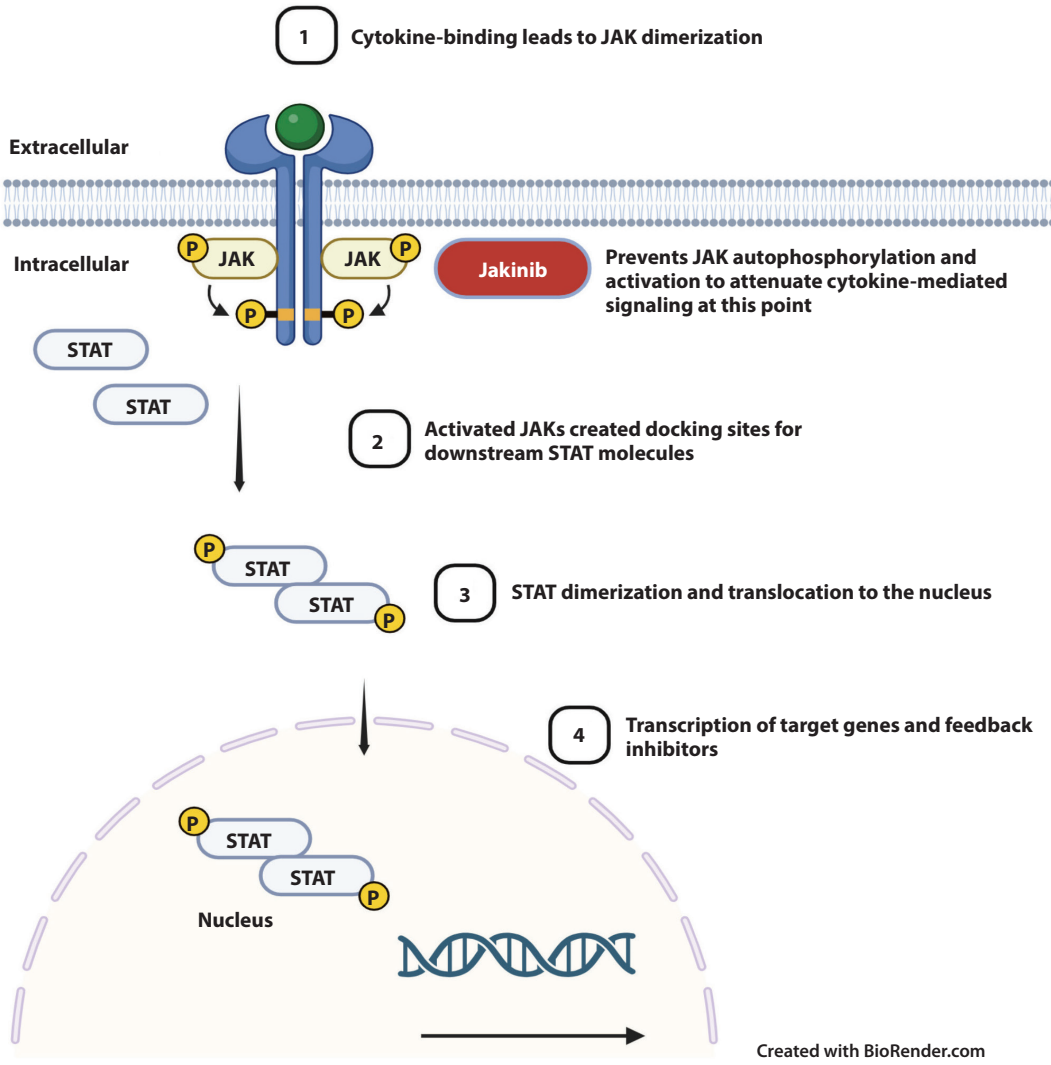
Activation and Negative Regulation

The signaling cascade is activated by extracellular stimuli, mediated by receptor-associated JAKs, and propagated via the cytoplasm to the nucleus to effect gene transcription (Figure). Upon ligand binding and receptor dimerization, receptor chains are brought into proximity that result in their transphosphorylation and the formation of an activated signaling complex. Further phosphorylation creates receptor-docking sites for downstream STAT proteins that include STAT1, STAT2, STAT3, STAT4, STAT5, and STAT6. STATs undergo tyrosine phosphorylation and disassociate from the receptor to form homo- or heterodimers, which translocate to the nucleus to modulate the transcriptional program involved in critical cellular functions. The JAK-STAT signaling pathway is negatively regulated in several ways. First, it is negatively regulated by protein tyrosine phosphatases (PTPs), a group of enzymes that remove phosphate groups from phosphorylated tyrosine residues on JAKs and STATs. CD45, also known as PTP-receptor type C, is a transmembrane PTP that prevents JAK phosphorylation. Second, the JAK-STAT signaling pathway is negatively regulated by cytokine-inducible SH2 domain–containing proteins and the suppressor of cytokine signaling proteins, which can either block JAK activation, block STAT receptor docking, or promote their ubiquitin–proteasome-mediated degradation. Third, the JAK-STAT signaling pathway is negatively regulated by the protein inhibitor of activated STAT, which prevents STAT binding to DNA and leads to transcription-activation failure. Finally, signal transduction can be abrogated by jakinibs as discussed in the following section.

Janus Kinase Inhibitor Pharmacology

Tofacitinib, filgotinib, and upadacitinib reversibly bind onto the ATP site on the catalytic cleft of the kinase domain to prevent JAK phosphorylation and activation. In turn, this prevents STAT phosphorylation and dimerization and thus terminates the ensuing signaling cascade. Key cytokines involved in the pathogenesis of IBD that are inhibited by these jakinibs include: IFN-γ (JAK1/JAK2), which enhances the intestinal response to luminal pathogens; IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 (JAK1/JAK3), which are key players in the adaptive immune system involved in B-cell development and Th1, Th2, and Th17 differentiation; and IL-12, IL-13, IL-23, and type 1 IFN (TYK2), which are thought to be implicated in a range of proinflammatory processes, including Th1/Th17 differentiation and the defective epithelial gut barrier.[20,21]

Tofacitinib and upadacitinib are rapidly absorbed with plasma concentrations peaking within 60 minutes following oral administration with terminal elimination half-lives of 3 hours and 6 to 16 hours, respectively.[22,23] Filgotinib is extensively metabolized by carboxylesterase isoform 2 (CES2) to form its primary active metabolite, GS-829845. GS-829845 has a similar JAK1 selectivity profile but has a 10-fold reduced activity and up to 20-fold increased systemic exposure compared with the parent compound.[24] Maximum plasma concentrations peak between 1 and 3 hours after the dose, with terminal half-lives of 5 to 11 hours for filgotinib and 20 to 27 hours for GS-829845.[24] All 3 jakinibs reach a steady plasma state between 2 and 4 days. Cytochrome profiling shows that tofacitinib and upadacitinib are both metabolized predominantly by hepatic cytochrome P450 34A isozyme (CYP3A4). Therefore, they should be avoided in patients



Family	Cytokine(s)	JAKs involved	STATs involved	Key processes
γc	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	JAK1, JAK3	STAT1, STAT3, STAT5	T-cell proliferation and survival Treg-cell and B-cell function
ßc	IL-3, IL-5, GM-CSF	JAK1, JAK2	STAT1, STAT3, STAT5	Hematopoietic growth factor B-cell development, eosinophils
gp130	IL-6, IL-11, IL-27, OSM	JAK1, JAK2, TYK2	STAT1, STAT3	T-cell proliferation and survival T-cell memory, Treg-cell function
IL-12	IL-12, IL-23	JAK2, TYK2	STAT3, STAT4	T-cell differentiation Lymphocyte effector function
IFN	IFNα, IFNß, IFNγ	JAK1, JAK2, TYK2	STAT1, STAT2, STAT3	Antiviral responses Inflammation
Homodimeric	GH, EPO, TPO, G-CSF, GM-CSF	JAK2	STAT3, STAT5	Hematopoiesis Growth factor response

Figure. Activation of the JAK-STAT pathway and key cellular processes regulated.

EPO, erythropoietin; G-CSF, granulocyte-colony stimulating factor; GH, growth hormone; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; OSM, oncostatin M; P, phosphate; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; Treg, regulatory T; TYK2, nonreceptor tyrosine-protein kinase 2.

Table 2. Currently Licensed JAK Inhibitors for Inflammatory Bowel Disease

	Tofacitinib	Filgotinib[a]	Upadacitinib
Manufacturer	Pfizer, United States	Galapagos NV, Belgium	AbbVie, United States
Selectivity	JAK3 > JAK2 > JAK1	JAK1 > JAK2 > JAK3 and TYK2	JAK1 > JAK2 and JAK3
UC indication	FDA approved in 2018	Not FDA approved	FDA approved in 2022
CD indication	Unlicensed	Unlicensed	FDA approved in 2023
Induction dose	10 mg bid for 8-16 weeks	200 mg qd for 10-22 weeks	45 mg qd for 8-16 weeks
Maintenance dose	5 or 10 mg bid	200 mg qd	15 or 30 mg qd
Terminal half-life	~3 hours	5-11 hours for parent compound 20-27 hours for GS-829845	6-16 hours
Peak plasma concentration	1 hour	1-3 hours	1 hour
Steady plasma state	24-48 hours	2-3 days for parent compound 4 days for GS-829845	4 days
Metabolism	65% hepatic (CYP3A4 and CYP2C19)	Intestinal (CES2 [primarily]) and hepatic (CES1)	34% hepatic (CYP3A4 and CYP2D6)
Liver disease	Avoid Child-Pugh C	Avoid Child-Pugh C	Avoid Child-Pugh C
Renal disease	↓ dose if CC <30 mL/min	↓ dose if CC <60 mL/min	↓ dose if CC <30 mL/min
Concomitant IMM studied	None	Thiopurine and methotrexate	Methotrexate
Additional indications	RA, PsA, AS, JIA	RA	RA, PsA, AS, AD

AD, atopic dermatitis; AS, ankylosing spondyloarthritis (radiographic and nonradiographic); bid, twice daily; CC, creatinine clearance; CD, Crohn's disease; CES, carboxylesterase; CYP, cytochrome P450; FDA, US Food and Drug Administration; IMM, immunomodulator; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; qd, once daily; RA, rheumatoid arthritis; TYK2, nonreceptor tyrosine-protein kinase 2; UC, ulcerative colitis.

[a]Filgotinib is not licensed in the United States.

with advanced liver disease (Child-Pugh C). Plasma exposures can be affected by medications that strongly inhibit or induce CYP3A4. Filgotinib is less prone to drug interactions as it is metabolized by CES2, which is primarily found in the intestine and to a lesser extent in the liver. Filgotinib is renally cleared and consequently, the creatinine clearance threshold for dose reduction is lower than for tofacitinib and upadacitinib.[24] Table 2 summarizes the key characteristics of these drugs.

Tofacitinib

Tofacitinib is a first-generation jakinib with long-term efficacy and safety data through clinical trials and observational studies, which are not yet available for the newer jakinibs.

Ulcerative Colitis

Tofacitinib is the first to be FDA approved for the treatment of moderate-to-severe UC, following the pivotal OCTAVE trial in 2018.[25] In the United States, jakinibs are licensed for use after an inadequate response or intolerance to one or more anti–tumor necrosis factor α (TNF) agents. As is typical for trials conducted with a view to seek FDA market authorization, the phase 3 OCTAVE trial consisted of 2 identically designed induction trials (OCTAVE 1 and 2) and 1 maintenance trial, OCTAVE Sustain. The primary endpoint of clinical remission at 8 and 52 weeks was met with significance above placebo in all 3 trials (Table 3). At week 52 for OCTAVE Sustain, remission occurred in 34% of patients in the 5-mg tofacitinib group and 41% in the 10-mg tofacitinib group vs 11% in the placebo group (P<.001).[26] OCTAVE Open was an open-label long-term

Table 3. Summary of Pivotal Trials for Licensed JAK Inhibitors in Inflammatory Bowel Disease

Trials		Treatment phase	# of patients	Primary outcome	Key findings[a]
Ulcerative colitis[b]					
Tofacitinib[26]	OCTAVE 1	Induction	598	CR[c] at week 8	CR in 18.5% (tofacitinib 10 mg bid) vs 8.2% (placebo)
	OCTAVE 2	Induction	541	CR at week 8	CR in 16.6% (tofacitinib 10 mg bid) vs 3.6% (placebo)
	OCTAVE Sustain	Maintenance	593	CR at week 52	CR in 34.3% (tofacitinib 5 mg bid) vs 40.6% (tofacitinib 10 mg bid) vs 11.1% (placebo)
Filgotinib[39]	SELECTION STUDY A	Induction	659	CR at week 10	CR in 26.1% (filgotinib 200 mg qd) vs 15.3% (placebo)
	SELECTION STUDY B	Induction	689	CR at week 10	CR in 11.5% (filgotinib 200 mg qd) vs 4.2% (placebo)
	SELECTION	Maintenance	664	CR at week 58	CR in 37.2% (filgotinib 200 mg qd) vs 11.2% (placebo) CR not significantly different between filgotinib 100 mg qd and placebo at week 10 but significant by week 58
Upadacitinib[50]	U-ACHIEVE	Induction	474	CR at week 8	CR in 26% (upadacitinib 45 mg qd) vs 5% (placebo)
	U-ACCOMPLISH	Induction	522	CR at week 8	CR in 34% (upadacitinib 45 mg qd) vs 4% (placebo)
	U-ACHIEVE[4]	Maintenance	681	CR at week 52	CR in 53.6% (upadacitinib 30 mg qd) vs 40.4% (upadacitinib 15 mg qd) vs 10.8% (placebo)
Crohn's disease					
Upadacitinib[60]	U-EXCEL	Induction	526	CR and endoscopic response[c] at week 12	CR in 49.5% (upadacitinib 45 mg qd) vs 29.1% (placebo); endoscopic response in 45.5% (upadacitinib 45 mg qd) vs 13.1% (placebo)
	U-EXCEED	Induction	495	CR and endoscopic response at week 12	CR in 38.9% (upadacitinib 45 mg qd) vs 21.1% (placebo); endoscopic response in 34.6% (upadacitinib 45 mg qd) vs 3.5% (placebo)
	U-ENDURE	Maintenance	502	CR and endoscopic response at week 52	CR in 47.6% (upadacitinib 30 mg qd) vs 37.3% (upadacitinib 15 mg qd) vs 15.1% (placebo); endoscopic response in 40.1% (upadacitinib 30 mg qd) vs 27.6% (upadacitinib 15 mg qd) vs 7.3% (placebo)

bid, twice daily; CR, clinical remission; JAK, Janus kinase; qd, once daily.

[a]All findings statistically significant unless stated otherwise; filgotinib is not licensed in the United States.

[b]Definition similar across the ulcerative colitis trials and defined as a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0. For filgotinib studies, a 1-point decrease in stool frequency from induction baseline for a subscore of 0 or 1 was required and for the upadacitinib studies, the Physician Global Assessment was removed owing to subjectivity.

[c]CR defined as Crohn's Disease Activity Index <150, and endoscopic response defined as a fall in Simple Endoscopic Score for Crohn's Disease >50% from baseline.

extension study, which enrolled a total of 944 patients, including nonresponders from OCTAVE Induction 1 and 2 and completers/treatment failures from OCTAVE Sustain. At 3 years of treatment, 65% and 37% of patients had endoscopic improvement, and 59% and 34% maintained or achieved remission with tofacitinib 5 mg and 10 mg twice daily (bid), respectively, supporting long-term efficacy beyond the 12-month maintenance study.[27] The RIVETING trial, which included patients from OCTAVE Open, demonstrated the efficacy of dose reduction and showed that 77% of patients in stable remission on the 10-mg bid dosage maintained remission at week 26 following dose reduction to 5 mg bid. Patients in deep endoscopic remission and those without prior anti-TNF therapy failure were more likely to maintain remission.[28]

The safety and efficacy of tofacitinib for the treatment of UC are reinforced by a plethora of observational studies in the real world, including comparatively large cohorts, with some reporting longer-term outcomes.[29-33] A systematic review with meta-analysis of 17 studies and 1162 UC patients was conducted by Taxonera and colleagues and reported short- to medium-term outcomes, and the primary endpoint of clinical remission was met by 35% of patients at week 8, 47% at weeks 12 to 16, and 38% at month 6.[33] A recent prospective study by Straatmijer and colleagues included 110 patients who were almost exclusively anti-TNF experienced and found that tofacitinib was effective in inducing corticosteroid-free remission in 32% of patients after 2 years of treatment.[31] Overall, findings from the real world support the clinical trial findings, and no unexpected safety conclusions were drawn.

Crohn's Disease

Tofacitinib does not have approval for the treatment of CD, although off-label use in the real world appears to show effectiveness.[34,35] The safety and efficacy of tofacitinib in CD were studied in two phase 2 trials, and no significant difference from placebo in the primary efficacy endpoint of clinical response was seen.[36-38] Phase 3 clinical trials were not pursued.

Other Indications

Tofacitinib has a total of 5 indications. Approval was first received for RA in 2012 followed by psoriatic arthritis (PsA) in 2017 and UC in 2018. More recently, tofacitinib has been approved for ankylosing spondylitis (AS) and juvenile idiopathic arthritis.

Filgotinib

Filgotinib is a JAK1-selective jakinib approved for the treatment of moderate-to-severe UC in the United Kingdom, Europe, and Japan.

Ulcerative Colitis

The safety and efficacy of filgotinib were assessed in SELECTION, a phase 2b/3 randomized, placebo-controlled trial, which enrolled 1348 patients across 2 induction arms in a 2:2:1 ratio of filgotinib 100 mg once daily, filgotinib 200 mg once daily, and placebo.[39] These 10-week induction studies showed significance above placebo for the primary endpoint of clinical remission, which was also seen at the end of the maintenance trial at week 58, which included 664 responders from the induction studies. Table 3 summarizes these results. At the 200-mg dose, all primary and secondary endpoints were met. Although the 100-mg dose demonstrated significance for the primary outcome at week 58, this was not achieved at week 10. At present, the phase 3 extension of the SELECTION study is evaluating the long-term safety of filgotinib in patients with UC with an estimated study completion date of September 2026.[40] There is a dearth of published real-world studies assessing filgotinib for UC, which are limited to small cohorts only and show that the drug is effective and well tolerated.[41-43] Outcomes of the Galapagos-sponsored prospective, observational real-world study (GALOCEAN) are awaited.[44]

Crohn's Disease

Filgotinib is not approved for CD as the registration trial (DIVERSITY) results were disappointing. The induction cohorts enrolling 1374 patients with moderate-to-severely active CD failed to meet the coprimary endpoints of endoscopic response and clinical remission at week 10.[45] Furthermore, a phase 2 trial (DIVERGENCE 1) assessing the safety and efficacy of filgotinib in small bowel CD also did not show statistically significant differences against placebo.[46]

Other Indications

Filgotinib has the fewest approved indications; aside from UC, it is available for the treatment of RA in the European Union, United Kingdom, and Japan. Filgotinib does not have approval in the United States for any indication. The FDA rejected a drug application for the treatment of moderate-to-severe RA based on testicular toxicity concerns from preclinical studies and expressed concerns regarding the overall benefit-risk profile of the filgotinib 200-mg dose.[47] Although subsequent studies showed filgotinib had no measurable impact on semen parameters or sex hormones in men with active IBD or inflammatory rheumatic diseases, FDA approvals were not pursued.[48,49]

Upadacitinib

Upadacitinib is a second-generation jakinib with preferential selectivity to JAK1.

Ulcerative Colitis

The efficacy of upadacitinib for the treatment of moderate-to-severe UC was established following the U-ACHIEVE and U-ACCOMPLISH phase 3 trials.[50,51] In the two 8-week replicate induction studies, a total of 996 patients were randomly assigned to receive upadacitinib 45 mg once daily or placebo. A more objective primary endpoint (Adapted Mayo score) was assessed at week 8 and week 52, which excluded the subjective Physician Global Assessment subscore from the full Mayo score. Both induction studies met the primary endpoint with treatment differences of 22% and 29% above placebo for each of the trials (Table 3). A total of 681 responders were re-randomly assigned to the maintenance doses of 15 mg once daily or 30 mg once daily; at 52 weeks, all prespecified primary and secondary endpoints were met with remarkable superiority over placebo and adjusted treatment differences of 30% and 43%, respectively.[50] Indirect comparisons of clinical trial data suggest a greater clinical efficacy with upadacitinib over tofacitinib but robust comparative data are needed.[52] Real-life studies for upadacitinib in UC are very limited but suggest no new safety signals and promising effectiveness, including in those with prior tofacitinib failure.[53-57] The largest of these studies (n=44) shows an 8-week remission rate of 82% in an entirely biologic-refractory cohort, with remission rates of 78% in the tofacitinib-exposed group.[53] The ongoing prospective study PROFUNDUS sponsored by AbbVie aims to evaluate upadacitinib use in routine clinical practice.[58]

Crohn's Disease

Upadacitinib is the first jakinib and first oral treatment to be licensed for CD and received FDA approval in May 2023.[59] The authorization application was supported by the results of two 12-week induction studies (U-EXCEL and U-EXCEED) that included 1021 patients and a 52-week maintenance study (U-ENDURE) that included 502 patients.[60] Notwithstanding a largely biologic-experienced group with a median disease duration of 7 years, the rates of clinical remission and endoscopic response (coprimary endpoints) at weeks 12 and 52 were striking. The proportion of patients in remission in the induction studies was nearly twice as high with upadacitinib compared with placebo and at least 3 times as high for endoscopic response. For the maintenance study, the difference above placebo was 2- to 3-fold higher for remission vs placebo and 6 times higher for endoscopic response. Differences of this magnitude have not been seen in prior registration CD trials and should be a real source of optimism for patients and health care professionals alike. Real-world studies with short-term outcomes also demonstrate that upadacitinib is rapidly acting and effective in treatment-refractory cohorts.[53,61,62] The study by Friedberg and colleagues (n=40) showed clinical remission rates surpassing 70% at 8 weeks in a cohort where 89% had previously received 2 or more advanced therapies.[53] The ongoing U-ENDURE long-term extension and the prospective real-world CD study (UPlift) will provide essential data regarding durable efficacy, long-term safety, and generalization to everyday practice.[63]

Other Indications

Upadacitinib has the greatest number of approved indications among jakinibs for IBD with a total of 7. These indications include UC, CD, RA, PsA, atopic dermatitis, nonradiographic axial spondyloarthritis, and AS. Because patients with one immune-mediated inflammatory disease are more likely to develop another, this is of particular importance for IBD patients who may require treatment of one or more concurrent diseases.[64]

Safety

Most adverse events related to jakinibs are predictable, mild to moderate in severity, and relatively straightforward to manage. Presently, based on safety, there is little to separate the 3 IBD-approved jakinibs, although tofacitinib has the best characterized safety profile. First, tofacitinib is the most widely used jakinib as it has been on the market for the longest across several indications, and second, it has been the subject of a lengthy FDA-mandated safety study. Safety concerns for jakinibs have been in the spotlight since an FDA warning highlighting the risk of venous thromboembolism (VTE) was first issued in July 2019 based on the interim findings of the ORAL Surveillance trial.[65] This was a postmarketing, noninferiority, randomized, open-label safety trial comparing tofacitinib with anti-TNF agents in RA patients 50 years of age and older with at least 1 cardiovascular risk factor; the increased incident rate of cancer and major adverse cardiovascular events (MACE) observed has resulted in regulatory restrictions across all jakinibs for all inflammatory diseases.[66]

In the United States, jakinibs are restricted to after anti-TNF therapy failure or intolerance.[67,68] Although the safety committees of the EMA and the MHRA have not restricted jakinib first-line use, they have stated that jakinibs should be used at the lowest effective dose and only used in certain patient groups if no suitable treatment alternative exists. These patients consist of persons aged 65 years and older, patients with increased risk of major cardiovascular problems or cancer, and current smokers or those with a significant smoking history.[69,70] Filgotinib and upadacitinib are not subject to such an FDA-mandated study, but robust long-term safety data

from ongoing and upcoming studies are warranted to prompt regulatory reconsideration of the black box labels and help determine the benefit-risk ratio of individual jakinibs.

Arterial and Venous Thromboembolic Disease Risk

Chronic systemic inflammation is intricately involved in the etiopathogenesis of atherogenesis and therefore is a significant risk factor for cardiovascular disease and MACE, defined as a fatal or nonfatal myocardial infarction or ischemic stroke.[71] IBD patients present a moderately increased risk of cardiovascular disease, particularly during a flare of disease.[72-74] Tofacitinib was shown to increase the risk of MACE in the ORAL Surveillance study when compared with anti-TNF agents in an already cardiovascular-risk enriched population, with a hazard ratio (HR) of 1.33 (95% CI, 0.91-1.94).[66] However, this risk has not been observed in patients with IBD treated with jakinibs.[75] Jakinibs are also associated with dyslipidemia for reasons that have yet to be elucidated. These reversible changes include dose-dependent increases of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol without affecting the HDL:LDL ratio.[76] While the risk of MACE is low for IBD patients, proactive steps should be taken to identify and address modifiable cardiovascular risk factors such as lipid lowering and smoking cessation.

Inflammation is a well-known risk factor for VTE owing to its propensity to induce a hypercoagulable state; this risk is increased in patients with immune-mediated inflammatory diseases.[77,78] VTE was seen more frequently at the 10-mg bid dose, but the study was not powered to compare VTE risk across treatments.[66] However, two large meta-analyses of 5143 and 6542 jakinib-exposed patients across all inflammatory diseases did not find an increased risk.[79,80] For now, guidance states that jakinibs should be used with caution in patients with risk factors for VTE.

Risk of Cancer Excluding Nonmelanoma Skin Cancer

Compared with the general population, IBD may be associated with an increased risk of overall cancer and cancer-specific mortality.[81] The ORAL Surveillance study demonstrated an increased cancer incidence (most commonly lung cancer) with jakinibs compared with anti-TNF agents (HR, 1.48; 95% CI, 1.04-2.09).[66,82] In a recent meta-analysis that incorporated 62 randomized trials, 16 long-term extension studies, and 82,366 person-years of jakinib exposure, the risk of malignancy did not differ significantly between jakinib and placebo but was associated with a higher incidence of malignancy when compared with anti-TNF agents.[83] These results were largely affected by the ORAL Surveillance study.[66] Cancers from jakinib exposure are rare; however, until this risk is precisely defined, jakinibs should be avoided in patients with risk factors for cancer.

Infection Risk

The most common infections affecting the IBD-approved jakinibs in the trial programs were nasopharyngitis, upper respiratory tract infections, and influenza.[26,39,50,60] The incident rate of serious infections across all jakinibs was 2.81/100 person-years and included pneumonias as well as urinary tract and skin infections.[80] The most prominent infection is a dose-dependent increase in herpes zoster reactivation, which is associated with the jakinib class and may be explained by the JAK1-mediated suppression of IFN, which has an antiviral role.[84] In network meta-analyses, upadacitinib ranked as the most likely drug to increase risk of herpes zoster.[85] Most cases seen are not serious, affect a single dermatome, and do not require treatment withdrawal. Using the lowest possible jakinib dose and vaccination against varicella zoster reactivation are the best ways of mitigating this risk.

Pregnancy and Breastfeeding

In preclinical studies, tofacitinib, filgotinib, and upadacitinib were shown to be teratogenic at supratherapeutic doses.[86-88] Tofacitinib has recently been shown to pass into human breast milk.[89] Maternal and fetal outcomes following jakinib exposure are scarce; however, the present recommendation is that the use of jakinibs should be discontinued during pregnancy and lactation.

Future Perspectives

There are several jakinibs in clinical development, such as brepocitinib (TYK2/JAK1), ritlecitinib (JAK3/TEC), and ivarmacitinib (JAK1), with promising phase 2 results for UC.[21,90,91] Jakinibs hold several advantages over biologics and should be considered for IBD patients with moderate-to-severe disease following a careful risk-benefit assessment.[92] As this drug class expands, there are a number of questions pertaining to jakinib use in everyday clinical practice that remain unanswered. Which is the safest and most effective jakinib to induce and maintain durable long-term IBD remission? Rephrased differently, where should each jakinib be positioned in the class of jakinibs? Are JAK1-selective inhibitors safer than pan-JAK inhibitors? Where in the overall treatment algorithm should jakinibs be positioned to maximize therapeutic outcomes? Is a jakinib likely to be effective in case of prior jakinib failure or intolerance? What is the role of jakinibs in the treatment of acute severe UC or other aspects of IBD management (eg, perianal disease, extraintestinal manifestations, or pouchitis)? A small evidence base for

these gaps is already developing. For example, case series and observational studies have shown that jakinibs owing to their potency and rapidity of onset can prevent colectomy in hospitalized patients with acute severe UC and that jakinibs can be an effective treatment in patients with refractory chronic pouchitis.[93-97] Combining a jakinib alongside a biologic with an established safety profile, such as vedolizumab (Entyvio, Takeda) or an anti–IL-23 agent, also appears an attractive prospect to treat aggressive disease and prevent corticosteroid use, hospitalization, and surgery.[98]

Conclusion

Jakinibs represent a novel class of small-molecule drugs for the treatment of chronic inflammatory diseases, an arena that hitherto has been dominated by antimetabolite immunomodulators and monoclonal antibodies. This emerging class of drugs now has 3 IBD-approved jakinibs worldwide and 2 in the United States, each with distinct profiles although all are subject to regulatory restrictions owing to safety concerns. While substantial progress has been made in this area to facilitate the availability of yet another class of drugs for IBD patients with uncontrolled disease, further research (and time) is clearly required to address outstanding knowledge gaps and will require a combination of head-to-head trials, various well-designed controlled and uncontrolled observational studies, and outcomes from the ongoing long-term extension studies.

Disclosures

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