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User's guide to JAK inhibitors in inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), are remitting and relapsing disorders of the gastrointestinal tract, highlighted by the dysregulation of pro- and anti-inflammatory mediators, which lead to mucosal damage. These conditions cause a significant burden worldwide as primary and secondary treatment failure rates remain high even with our current therapeutic options. This emphasizes the need for continued advancement in treatment efficacy with improved safety profiles. Novel disease-targeting therapeutics have been developed, most recently being the Janus kinase inhibitors (JAKi). JAKi serve as a promising new class of non-immunogenic small molecule inhibitors that modulate inflammatory pathways by blocking the critical role that Janus kinase (JAK) proteins play in mediating the innate and adaptive immune responses. Tofacitinib has been shown to be therapeutically efficacious, to have a tolerable safety profile, and to be available for adult patients with moderate-to-severe UC. This review was designed to serve as an overview and as practical guidance for medical practitioners. Author recommendations and appraisals of the quality of evidence throughout this article are based solely on personal opinion and are not the outcome of a formal methodology followed by a consensus group.

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are immune-mediated, chronic inflammatory bowel diseases that are relapsing and remitting, leading to significant morbidity and decreased quality of life in those affected. The abnormal mucosal immune response seen in these diseases is believed to be triggered by the interaction of environmental factors and gut microbiota in a genetically susceptible host. Currently, the treatment paradigm for IBD is to treat early in the disease course. Current treatment options, specifically for UC, include aminosalicylates, corticosteroids, thiopurines, cyclosporine and biologic therapies, such as tumor necrosis factors inhibitors (TNFi), anti-interleukins and anti-integrins (López-Sanromán et al., 2021). The treatment goal in IBD aims at controlling active and chronic inflammation, prevention of disease progression, and induction of clinical, biochemical and endoscopic remission (Turner et al., 2021; Pippis and Yacyshyn, 2020).

Over the last two decades, the introduction of TNFi has significantly improved treatment outcomes for moderate-to-severe IBD refractory to their anti-inflammatory and immunomodulatory counterparts (Chimenti et al., 2021). The mainstay of treatment for moderate-to-severe IBD is TNFi. Given their biochemical structure, these therapies have a predisposed risk of developing neutralizing antibodies (10%–20% incidence), which can lead to loss of efficacy and hypersensitivity reactions (López-Sanromán et al., 2021; Moss et al., 2013). Even in 'today's biologic therapy landscape, rates of adverse reactions, such as infection and malignancy, as well as primary and secondary treatment failure remain high (López-Sanromán et al., 2021; Chaparro and Gisbert, 2016). Lack of response to therapy is as high as 50%, with cumulative relapse rates as high as 67%–83% after 10 years (Fernández-Clotet et al., 2019; Ma et al., 2019a). These treatment failures lead to increased corticosteroid use, limited therapeutic options, and disease complications (Chimenti et al., 2021; Al-Bawardy et al., 2021).

Due to an improved understanding of IBD pathophysiology and the variability/loss of clinical response to previous therapeutic options, novel agents have been designed. Such novel agents aim to improve treatment response rates with safer side effect profiles. These most recent novel agents, Janus kinase inhibitors (JAKi), are small molecule inhibitors that act on signal transduction from within the cell, specifically inhibiting signal-transducing tyrosine kinases, the Janus kinases (López-Sanromán et al., 2021). Small molecule inhibitors offer the ease of administration, rapid onset of action, short half-lives, and lack of immunogenicity compared to their biologic counterparts (Rubin et al., 2021a).

2. Janus kinases

Cytokines trigger multiple different signaling pathways and play a significant role in the inflammatory pathogenesis of IBD (Pippis and

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Abbreviations

ASUC	acute severe ulcerative colitis
AEs	adverse events
ATE	arterial thromboembolism
BID	twice daily
CV	cardiovascular
CD, CI	confidence interval, Crohn's disease
CDAI	Crohn's disease Activity Index
DVT	deep vein thrombosis
EIMs	extraintestinal manifestations
EPO	erythropoietin
FDA	Food and Drug Administration
HR	hazard ratio
HZ	herpes zoster
HDL-c	high-density lipoprotein cholesterol
IR	incidence rate
IBD	inflammatory bowel diseases
IFN	interferon
JAK	Janus kinase
JAKi	Janus kinase inhibitors
JAK-STAT	Janus kinase signal transducer and activator of transcription
IL	interleukin
LDL-c	low-density lipoprotein cholesterol
LTE	long-term extension
MACEs	major cardiovascular events
NMSC	non-melanoma skin cancer
OLE	open-label, long-term extension
QD	once daily
PY	person-years
PsA	psoriatic arthritis
PE	pulmonary embolism
RCTs	randomized controlled trials
RRS	Reynolds Risk Score
RA	rheumatoid arthritis
SAEs	serious adverse events
TC	total cholesterol
TNFi	tumor necrosis factors inhibitor
TB	tuberculosis
TYK2	tyrosine kinase 2
UC	ulcerative colitis
VTE	venous thromboembolism

Yacyshyn, 2020). One signaling pathway involved in the inflammation seen in IBD is the Janus Kinase Signal Transducer and Activator of Transcription (JAK-STAT) pathway. This pathway is mediated by specific cytokines such as IL-5, IL-6, IL-9, IL-13, IL-21, and IL-23 (Virtanen et al., 2019). The JAK family comprises four non-receptor tyrosine kinase enzymes constitutively associated with cytokine receptors' intracellular domains: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) (Chimenti et al., 2021; Al-Bawardy et al., 2021). The Janus kinases interact with a family of seven STATs: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. JAK1 is associated with IL-2, IL-6, IFN-γ and IFN-α. JAK 2 is associated with IL-6, IL-12, IL-23, IFN-γ, IFN-α and EPO. JAK3 is associated with IL-2. TYK2 is associated with IL-12, IL-23, and IFN-α. Each JAK has distinct functions, but there is also some overlap. The JAK-STAT pathways affect cell growth, differentiation, maturation, migration, and survival and are also involved in innate immunity, adaptive immunity, and hematopoiesis (JAK2*). Understanding the significant role of each JAK pathway, especially regarding its vital role in inflammatory disease, is crucial in designing novel therapeutic targeting agents (Danese et al., 2019).

Cytokines use different specific pairings of individual JAKs associated with particular cytokine receptors (Table 1). The interaction leads to different transduction signals, which induce specific responses to various stimuli (López-Sanromán et al., 2021). The JAK-STAT pathway is critically involved in innate and adaptive immunity and transmits extracellular signals into intracellular processes. The pathogenesis in IBD is believed to be driven by an imbalance of anti-inflammatory and pro-inflammatory mediators, which interrupt the resolution of disease and perpetuate continued inflammation and disease burden (Hernandez-Rocha and Vande Casteele, 2020). The pathway highlights the importance of targeting and blocking the enzymatic activity and imbalance that this pathway may cause in the chronic inflammatory dysregulation seen in UC (López-Sanromán et al., 2021; Chimenti et al., 2021). It is one postulated advantage of JAK inhibition as compared to other biologics such as TNFi, anti-integrin inhibitors, or anti-interleukins (Pippis and Yacyshyn, 2020).

Table 1
Ulcerative colitis specific cytokines and associated janus kinases.

Cytokine Receptors	Associated JAKs
IL-5	JAK 2
IL-6	JAK-1, JAK-2, TYK-2
IL-9	JAK-1, JAK-3
IL-13	JAK-1, JAK-3, TYK-2
IL-21	JAK-1, JAK-3
IL-23	JAK-2, TYK-2

IL, interleukin; JAK, Janus kinase; TYK2, tyrosine kinase 2.

Cytokines bind to their specific receptor at the lymphocyte cell surface and activate intracellular domain domain-bound JAKs via dimerization within the JAK-STAT pathway. This results in autophosphorylation of JAKs near the receptor's cytoplasmic domain (López-Sanromán et al., 2021). The phosphorylated sites on the intracellular domains serve as docking stations for STAT molecules within the cell cytoplasm (Chimenti et al., 2021). Docking is followed by phosphorylation of the STAT molecules by the activated receptor-associated JAKs. The phosphorylated STATs dimerize and then detach from the receptor chains translocating to the nucleus, where they rapidly target gene promoters to regulate gene transcription and translation (Fig. 1). This plays a role in expressing target genes and producing cytokines involved in numerous cellular functions, immunity, inflammatory responses, and intestinal epithelial barrier (López-Sanromán et al., 2021; Hernandez-Rocha and Vande Casteele, 2020).

3. Janus kinase inhibitors

3.1. Tofacitinib

In May 2018, tofacitinib, a non-selective, small synthetic molecule JAKi was approved by the FDA in moderate-to-severe active UC. Tofacitinib is formulated as an oral agent in contrast to the current subcutaneous and intravenous formulations of the most commonly used biologic agents on the market (Al-Bawardy et al., 2021). Tofacitinib, a pan-JAKi, modulates the JAK-STAT signaling pathway intracellularly by inhibiting phosphorylation and activation of STATs, preferentially at the point of JAK1 and JAK3, and to a lesser extent JAK 2 (higher doses) by competing with ATP for binding to the Janus kinase domain (López-Sanromán et al., 2021; Chimenti et al., 2021) (Fig. 1). This therapeutic was designed to reversibly reduce the activity of one or more JAK isoforms, affecting the crucial step in the downstream signaling of both the innate and adaptive immune responses (Pippis and Yacyshyn, 2020).

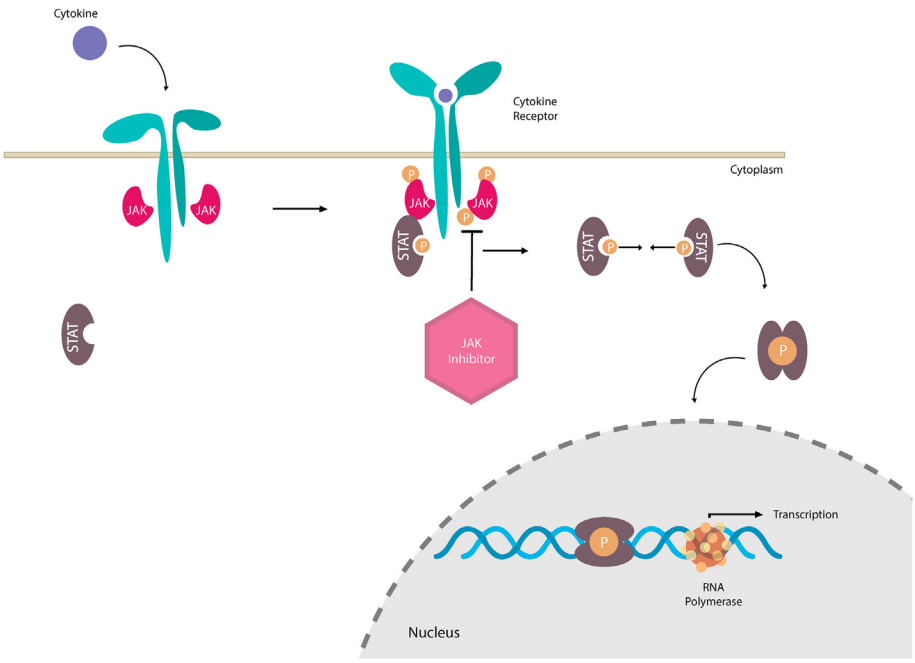

Fig. 1. (Color) Overview of the steps involved in cytokine signaling via the Janus kinase pathway and the therapeutic target for JAK inhibitors. Cytokines bind to cell-surface receptors; after ligand stimulation, receptors undergo conformational changes, and JAKs become approximated. Paired JAKs and receptors undergo phosphorylation which allows STATs to bind to the receptor. Activated JAKs then phosphorylate docked STATs. Activated STATs then dimerize and migrate to the nucleus, where they act as transcription factors that bind DNA and regulate gene transcription. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.2. Efficacy

The efficacy of tofacitinib in inducing and maintaining clinical and endoscopic remission was demonstrated in three phase III trials: OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain. Over 1100 patients with moderate-to-severe active UC in the OCTAVE Induction 1 and 2 trials were randomized in a 4:1 ratio to oral tofacitinib 10 mg twice daily (BID) or placebo for 8 weeks. The primary efficacy endpoint in the OCTAVE Induction trials was clinical remission defined as a total MAYO score of $\leq$2, with no subscore >1 and a rectal bleeding subscore of 0 at 8 weeks. In OCTAVE Induction 1, 18.5% of tofacitinib treated patients achieved the primary endpoint at week 8 versus only 8.2% of placebo recipients ($p = 0.007$). In OCTAVE Induction 2, 16.6% of tofacitinib treated patients achieved the primary endpoint at week 8 versus only 3.6% of placebo recipients ($p < 0.001$). The primary endpoint achieved statistical significance in both patients previously treated with anti-TNF agents and those that were anti-TNF naïve. Clinical response (3 point and 30% reduction in Mayo score) occurred in 55%–60% of patients treated with tofacitinib versus 29%–33% placebo recipients ($p < 0.001$) in both OCTAVE Induction trials. Mucosal healing (MAYO endoscopic subscore of $\leq$1) was reached in 28%–31% of patients treated with tofacitinib versus 12%–16% of placebo recipients in both OCTAVE Induction studies ($p < 0.001$). Overall, induction of clinical response, remission, and mucosal healing at 8 weeks were significantly higher in the tofacitinib arm than placebo (Sandborn et al., 2017). In a 2018 meta-analysis analyzing randomized controlled trials (RCT) of biologic experienced patients with UC, tofacitinib was found to have the most substantial treatment effect regarding induction of clinical remission (OR, 11.88; 95% CI, 2.32–60.89), and induction of mucosal healing (OR, 4.7; 95% CI, 2.2–9.9) (Singh et al., 2018). Post-hoc analyses from OCTAVE 1 and 2 Induction trials revealed a statistically significant improvement in stool frequency (28.8% vs. 17.9%, $p < 0.01$) and rectal bleeding (32% vs. 20.1%, $p < 0.01$), occurring within 3 days of treatment with tofacitinib versus placebo, which depicts the achievement of better outcomes at day 15 and week 8 (Hanauer et al., 2019).

Patients who completed OCTAVE Induction 1 or 2 and had a partial clinical response to therapy were enrolled into OCTAVE Sustain trial and were re-randomized to receive maintenance therapy with tofacitinib 5 mg BID, 10 mg BID, or placebo for 52 weeks. Of these patients, 88% received tofacitinib during the induction trial, and 30% were in remission upon entering OCTAVE Sustain. The primary endpoint in OCTAVE Sustain was clinical remission at 52 weeks. Clinical remission was achieved in 41% of tofacitinib 10 mg BID recipients, 34% of tofacitinib 5 mg BID recipients, and 11% of placebo recipients, both dosages reaching clinical significance ($p < 0.001$). Clinical response, sustained mucosal healing (MAYO endoscopic subscore of $\leq$1), and sustained steroid-free remission were secondary endpoints in which both doses of tofacitinib reached clinical significance compared to placebo at 52 weeks (Sandborn et al., 2017).

Tofacitinib efficacy is related to clinical response and improved health-related quality of life parameters based on patient objective assessments. Using the Inflammatory Bowel Disease Questionnaire (IBDQ) [>170 points] in the OCTAVE 1 and 2 induction trials, 40%–43% of tofacitinib recipients achieved this endpoint versus 17%–22% of placebo recipients. In OCTAVE Sustain, 38% of tofacitinib recipients achieved this endpoint versus 14% of placebo recipients. Tofacitinib was also shown to improve 36-Item Short Form Survey (SF 36) scores compared to placebo. The authors concluded that tofacitinib improves the health-related quality of life throughout week 52 (Sandborn et al., 2017).

A recent systematic review and meta-analysis of seventeen studies ($n = 1162$) evaluated the real-world effectiveness of tofacitinib for moderate-to-severely active UC. Clinical remission was evaluated at week 8, weeks 12–16, and month 6 in eleven different studies. Remission was achieved in 34.7% of patients at week 8 (95% CI 24.4–45.1), 47% at weeks 12–16 (95% CI 40.3–53.6), and 38.3% at month 6 (95% CI 29.2–47.5). Response to tofacitinib was achieved in 62.1%, 64.2%, 50.8%, and 41.8% of patients at week 8, weeks 12–16, month 6, and month 12, respectively. Five studies were evaluated regarding corticosteroid-free remission which was achieved in 38.4%, 44.3%, 33.6%, and 31% of patients at week 8, weeks 12–16, month 6, and month 12, respectively. Mucosal healing was achieved in 48.3% and 45.3% of patients at week 8 and weeks 12–16, respectively. Biologic-naïve patients (11.6%) were also determined to have had a significantly higher rate of response at week 8 (OR 1.38; 95% CI 1.03–1.84). This real-world data regarding the use of tofacitinib in this highly refractory patient population corroborates and strengthens tofacitinib's effectiveness in UC as seen in clinical trials (Taxonera et al., 2021).

In regards to acute severe ulcerative colitis (ASUC), despite the current standard of care consisting of intravenous corticosteroids, as well as a rescue therapy consisting of infliximab or cyclosporine, more than 30%

of patients with ASUC require colectomy. Recently, a small retrospective case-control study from the University of Michigan evaluated the efficacy of tofacitinib induction in biologic-experienced patients admitted with ASUC requiring intravenous corticosteroids. Forty patients received tofacitinib and were matched 1:3 to controls (n = 113). Tofacitinib was determined to be protective against colectomy at 90 days compared with matched controls (HR 0.28; 95% CI 0.10–0.81; p = 0.018). When stratified according to treatment dose, 10 mg three times daily (TID) was protective (HR 0.11; 95% CI 0.02–0.56; p = 0.008), whereas 10 mg BID was not significantly protective (HR 0.66; 95% CI 0.21–2.09; p = 0.5). Rate of complications and steroid dependence were reportedly similar between tofacitinib and controls (Berinstein et al., 2021). This data corroborates similarly reported case series in which tofacitinib with concomitant intravenous corticosteroids has been shown to be an effective induction strategy in biologic-experienced patients hospitalized with ASUC (Kotwani et al., 2020). These studies were not designed to identify the safety, optimal dosing, frequency, or duration of tofacitinib for ASUC and therefore larger multi-center prospective studies are warranted.

Tofacitinib 10 mg BID was also studied in two phase II/IIb induction trials and one phase IIb maintenance trial to analyze its efficacy in treating moderate-to-severe CD using tofacitinib 10 mg BID (Sandborn et al., 2014; Panés et al., 2017). The primary induction endpoint of a Crohn's disease Activity Index (CDAI) score of <150 points at 8 weeks was not achieved, nor was the primary endpoint of CDAI score of <150 points at 26 weeks of maintenance therapy (Hernandez-Rocha and Vande Casteele, 2020).

Author's Recommendation.

Tofacitinib is currently recommended in patients with moderate-to-severe UC at an induction dose of 10 mg BID for at least 8 weeks, followed by maintenance dosing of 5 mg BID. In those who do not achieve therapeutic goal at the 8th week, the 10 mg BID induction dose can be extended for an additional 8 weeks. If adequate therapeutic response is not achieved by week 16 of twice daily 10 mg dosing, this should be considered a therapeutic failure and tofacitinib should be discontinued.

Moderate recommendation; Medium quality of evidence.

Under the expert consultation of an IBD specialist, an accelerated tofacitinib 10 mg TID induction with intravenous corticosteroids may be considered at admission as initial co-therapy for patients with ASUC in whom have failed a biologic previously and/or have a high C-reactive protein and low albumin.

Weak recommendation; Low quality of evidence.

4. Safety

The safety of tofacitinib in UC patients was studied in the OCTAVE Clinical Programme and an ongoing, open-label, long-term extension (OLE) study. Thus far, the total duration of follow-up that has been analyzed has reached 6.8 years, which includes 1157 patients and over 2581.3 person-years (PY) of exposure. Overall, adverse events (AEs), serious adverse events (SAEs), and discontinuations have generally remained stable in the tofacitinib OCTAVE Clinical Programme since inception (≤6.8 years) (Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su). In a recent systematic review and meta-analysis of seventeen studies (n = 1162), the incidence rate (IR) of serious adverse events was (8.9 per 100 PY) (Taxonera et al., 2021).

Compared to placebo, the most commonly reported adverse events (AEs) for tofacitinib in the OCTAVE Clinical Programme were headache, nasopharyngitis, respiratory tract infections, nausea, and arthralgias. This was consistent with the safety profile observed in patients with active rheumatoid arthritis (RA) and psoriatic arthritis (PsA) treated with tofacitinib (Hernandez-Rocha and Vande Casteele, 2020). Angioedema and urticaria have been observed, some of which were serious events and may represent drug hypersensitivity (XELJANZ, 2020). In the early UC clinical trials, the higher rate of infections seen in the tofacitinib group compared to placebo was mild to moderate in severity (Hernandez-Rocha and Vande Casteele, 2020). Five deaths (0.4% of the total population) were reported in the entire treated population. One patient suffered an aortic dissection during the induction period while taking tofacitinib 10 mg BID. Four other patients died during the OLE period due to acute myeloid leukemia, hepatic angiosarcoma, malignant melanoma and pulmonary embolism in the setting of metastatic cholangiocarcinoma. The overall IR of death was 0.19 (95% CI 0.06–0.44) (Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su). More recently, worldwide post-marketing surveillance case safety reports regarding SAEs, received in the Pfizer safety database, for tofacitinib in patients with UC have been analyzed from May 30, 2018 (first regulatory approval) to August 25, 2020. This analysis estimated PY of exposure based on worldwide sales data and the calculated daily regimens of tofacitinib 5 or 10 mg BID. Worldwide post-marketing exposure to tofacitinib was calculated at 8916 PY during the 27-month reporting period. Overall, 4226 case reports were received and included 12103 AEs. SAEs comprised 1839 of the 12103 AEs. Among the 4226 cases reported, 1141 (27.0%) included an SAE and 18 (0.4%) were fatal. The estimated reporting rate (per 100 PY) for infections was 3.28, 1.26 for vascular disorders, 0.74 for respiratory disorders, 0.55 for neoplasms and 0.50 for cardiac disorders. Caution should be taken when interpreting these data due to the intrinsic limitations of post-marketing surveillance programs and reliance on estimated reporting rates. Overall, most reported AEs were non-serious and consistent with those reported in tofacitinib clinical trials (Rubin et al., 2021b). In general, including real-world data, the overall safety profile in patients with UC has been manageable and consistent with that of other UC therapies, including the TNFi (Taxonera et al., 2021; Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su; Pantavou et al., 2019).

Author's Recommendation.

Tofacitinib should be used at the lowest effective dose and for the shortest duration needed to achieve and maintain therapeutic response.

Strong recommendation; Strong quality of evidence.

4.1. Laboratory abnormalities

Tofacitinib is a pan-JAK inhibitor, critical in JAK2 signaling, which is involved in hematopoiesis. Tofacitinib has been shown to lead to a mild but reversible initial decrease in all three major cell line lineages, which stabilized over time in the long-term extension (LTE) trials (Schulze-Koops et al., 2017). In the large registration clinical trials, serum aminotransferase elevations occurred in 28%–34% of tofacitinib treated subjects compared to 25% in comparator arms and 10% in placebo recipients. These elevations were typically mild and transient, but values above 3 times the upper limit of normal occurred in 1%–2% of patients on tofacitinib compared to less than 1% on placebo. The elevations occasionally led to early discontinuations but more often resolved even without dose adjustment. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. Since approval and more wide-scale availability of tofacitinib, there have been

no published reports of hepatotoxicity associated with its use. However, a proportion of patients do develop serum aminotransferase elevations, which leads to drug discontinuation (LiverTox: Clinical and Re, 2012). If any significant adverse changes occur regarding major cell lines or serum aminotransferases, tofacitinib therapy should be interrupted or discontinued until the abnormality is resolved.

Author's Recommendation.

Consider obtaining a pretreatment complete blood count (CBC) and hepatic function panel (HFP) on all patients who are planned to start tofacitinib therapy. Caution should be taken when prescribing tofacitinib in patients with anemia, leukopenia and elevated aminotransferases.

Consider monitoring CBC and HFP at 4–8 weeks of therapy and every 3 months thereafter.

Moderate recommendation; Low quality of evidence.

4.2. Infections

4.2.1. Herpes zoster

In the initial analysis of the OCTAVE Clinical Programme (n = 1157; 1612.8 PY of exposure), 65 (5.6%) total cases of herpes zoster (HZ) were identified, and (51/65) involved one or two dermatomes with an IR of 4.1 (95% CI 3.1–5.2) (Winthrop et al., 2018). These results are similar to those in clinical trials for RA and psoriasis (Winthrop et al., 2014, 2017a). Disseminated Zoster was seen in (11/65) of the cases, of which one was complicated by encephalitis and only 5 study participants (7.7%) withdrew due to their infection (Winthrop et al., 2018). Of note, some cases required temporary discontinuation and up to 85% of cases resolved with antiviral therapy. There was a statistically significant difference in the IR of HZ infection regarding patients treated with tofacitinib 10 mg BID (6.6 per 100 PY); approximately 5% of the patients) versus non-statistically significant, but numerically higher rates seen in tofacitinib 5 mg BID (IR 2.1; 95% CI 0.4–6.0); 1.5% of the participants) and placebo (IR 1.0; 95% CI 0–5.4); 0.5% of participants (Winthrop et al., 2018). This likely demonstrates a dose-dependent, risk relationship. Independent risk factors for HZ infection were determined to be older age (>65 years old) (HR 1.58; 95% CI 1.34–1.87) and prior TNFi failure (HR 1.92; 95% CI 1.15–3.21). Although it did not reach statistical significance, Asian race trended toward higher risk (HR 1.76; 95% CI 0.97–3.19). The incidence rate of herpes zoster did not appear to be affected with the increasing length of treatment duration with tofacitinib (Winthrop et al., 2018). In the most recent safety analysis from global clinical trials (up to 6.8 years), 92 HZ [non-serious and serious] events occurred in 87/1157 participants (7.5%) with an IR of 3.48 (95% CI 2.79–4.30) and a median [range] time to onset of 474 [13–1799] days. Of those events, none resulted in death and 92.1% were non-serious (Winthrop et al., 2021a). As previously determined in earlier analyses, the incidence ratios of HZ were numerically higher with tofacitinib 5 mg BID versus placebo and statistically higher with tofacitinib 10 mg BID versus placebo. Opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients (IBD and RA) who were treated with tofacitinib 10 mg BID (Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su). In a recent systematic review and meta-analysis of seventeen studies (n = 1162), the IR of HZ was (6.9 per 100 PY) (Taxonera et al., 2021).

Herpes zoster infection should be treated with antiviral therapy in conjunction with guidance of an infectious disease expert in all IBD patients regardless of immune status. In the immunosuppressed, current recommendations are to treat for at least 7 days and at least 2 additional days after all skin lesions have crusted over. Oral antivirals can be used in uncomplicated cases, while intravenous antivirals should be used in complicated diseases. Herpes zoster ophthalmicus is considered an ophthalmologic emergency (Colombel, 2018; Agrawal et al., 2020). As noted above, most patients can continue tofacitinib therapy during HZ infection. Some patients may have to be temporarily held until the infection resolves (Winthrop et al., 2014, 2017a, 2017b, 2018; Agrawal et al., 2020; Lal et al., 2015). Overall, there appears to be a 5–6% risk of herpes zoster with greater than one year of tofacitinib 10 mg BID treatment and risk is minimal during the induction phase of therapy.

4.2.2. Other infections

The incidence rate of serious infections (defined as any infectious adverse event that requires hospitalization or parenteral antimicrobials) with tofacitinib treatment was (0.9%) versus (0%) with placebo in the OCTAVE Induction studies, but similar in all three treatment groups in the OCTAVE Maintenance trial (Sustain) (Sandborn et al., 2017). In the total patient cohort up to 6.8 years, the IR for severe infections was 1.70 (95% CI 1.24–2.27) without any fatal outcomes (Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su). More recently, treatment data (up to 9.5 years) on patients with RA and at least one cardiovascular risk factor, found an increased risk of serious and fatal infections in patients over the age of 65, most notably with long-term treatment of tofacitinib 10 mg BID. Most patients who developed serious infections leading to hospitalization and death took concomitant immunosuppressants, such as corticosteroids and methotrexate. The most commonly reported serious infections, excluding HZ, are urinary tract infection, pneumonia, cellulitis, appendicitis, and diverticulitis (López-Sanromán et al., 2021; Wollenhaupt et al., 2019).

In the total cohort of 1157 patients examining up to 6.8 years of follow-up (2581.3 PY), opportunistic infections, excluding HZ, were uncommon with an IR of 0.15 (95% CI 0.04–0.38) without a positive correlation to longer treatment duration. Only four cases were reported, which include invasive fungal infections (histoplasmosis and pulmonary cryptococcosis), cytomegalovirus hepatitis, and cytomegalovirus colitis, without report of tuberculosis (TB) (Winthrop et al., 2021a). The risk of TB with tofacitinib in pooled RA trials data varied with background risk in the population; IR was 0.02 (95% CI 0.003–0.15) in low-, 0.08 (95% CI 0.03–0.21) in medium-, and 0.75 (95% CI 0.49–1.15) in high incidence countries. In phase 3 studies, there was no TB case reported in the 263 patients with latent TB infection who were given isoniazid prophylaxis concurrently with tofacitinib. Ideally, treatment for latent TB should be initiated before tofacitinib use. Hepatitis B and herpes virus reactivation has been reported (Agrawal et al., 2020; Winthrop et al., 2016). The risks and benefits of treatment with tofacitinib should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection, or those who have lived or traveled in areas of endemic TB or mycoses. Signs and symptoms of infection should be closely monitored during and after treatment. Specifically, monitoring for the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection before initiating therapy.

Author's Recommendation.

Tofacitinib should be avoided in patients with active, serious infections or chronic, recurring infections. If a serious infection occurs, tofacitinib should be held until the infection resolves.

Prior to initiating tofacitinib therapy, testing for latent tuberculosis (QuantiFeron-TB Gold assay) and checking hepatitis B status (HBVsAg, HBVsAb & HBVcAb) should be completed. Perform annual TB risk assessment and consider re-testing if high risk (including travel to endemic region).

Strong recommendation; Moderate quality of evidence.

4.2.3. Vaccinations

Patients with IBD are at higher risk for severe infections, which is further increased by using biologics, immunomodulators, and corticosteroids. Patients with IBD should be appropriately vaccinated following current vaccination guidelines regarding immunosuppressive agents and IBD before initiating tofacitinib therapy. The HZ risk associated with tofacitinib use can be mitigated with vaccination of the Recombinant, Adjuvanted Zoster Vaccine (Shingrix®). This vaccine is administered in two intramuscular doses, two months apart. It has been shown to prevent HZ infection in 97.2% (95% CI 93.7–99.0) of persons older than 50 years, including those older than 70 years of age (Agrawal et al., 2020; Lal et al., 2015). Live vaccines (Zostavax®) are contraindicated in the setting of immunosuppressive therapy.

Author's Recommendation.

> Initial dose of Shingrix® should be administered prior to starting tofacitinib therapy to significantly mitigate risk of infection. The second dose should be administered two months after the first. Live vaccines should be avoided.
>
> Strong recommendation; Moderate quality of evidence.

4.2.4. Thromboembolic events

When the FDA first approved tofacitinib, they required the manufacturer (Pfizer Inc.) to conduct a post-marketing safety study, ORAL Surveillance, in patients with RA taking methotrexate. The trial studied two doses of tofacitinib (5 mg BID and 10 mg BID) in comparison to a TNFi. Patients were required to be at least 50 years old and have at least one cardiovascular risk factor. In February 2019 and July 2019, the FDA warned that interim trial results showed an increased risk of venous thromboembolism (VTE) (19 cases; IR 7.0) among 3884 PY follow up in the tofacitinib 10 mg BID group (not 5 mg BID) vs. 3 cases among 3982 PY follow up in the anti-TNF treated group. VTE risk was 5 times greater than what was seen with TNFi therapy. All-cause mortality was also higher (1.8x) with the 10 mg BID dosage, including sudden cardiovascular death. Due to these concerning results, the 10 mg BID treatment group was reduced to 5 mg BID for safety. The FDA approved a Boxed Warning to the tofacitinib prescribing information based on this data (Ma et al., 2019b). As a result, tofacitinib 10 mg BID or tofacitinib XR 22 mg once daily (QD) is not recommended for the treatment of RA or PsA (Safety Study of Tofacitin, 2092).

A post hoc analysis recently investigated the incidence of VTE and arterial thromboembolism (ATE) from the tofacitinib RA, PsA, and psoriasis development programs (n = 12,410), which included patients age 50 or older with at least one cardiovascular risk factor and treated with either tofacitinib (5 mg or 10 mg) or a TNFi. Venous thromboembolic events and ATE IRs in the tofacitinib RA, PsO, and PsA programs were similar across tofacitinib doses. These findings were consistent with observational data and published IRs of other treatments. Incidence ratios of thromboembolic events were elevated in patients with baseline cardiovascular or VTE risk factors and were consistent with those observed in the ad hoc safety analysis data. One notable difference was that the IR for PE was greater in patients treated with tofacitinib 10 mg BID (IR 0.54 (95% CI 0.32–0.87), compared to patients with baseline cardiovascular risk factors treated with tofacitinib 10 mg BID in the RA development program (IR 0.24 (95% CI 0.13–0.41) (Mease et al., 2020). In a study that analyzed over 34,000 RA patients receiving either tofacitinib or a TNFi, there was a numerically high but non-significant rate of VTE (<1 case per 100 PY) (Desai et al., 2019).

When analyzing the OCTAVE Clinical Programme (n = 1157; 2581.3 PY exposure; up to 6.8 years of safety data), four (0.3%) patients had a PE (IR 0.15; 95% CI 0.04–0.38) and one (0.1%) had a DVT (IR 0.04; 95% CI 0.00–0.21). This study participant was diagnosed with a DVT after a long-haul flight and simultaneously managed for an infected leg wound sustained in a recent motorcycle accident. All five patients had previous risk factors for thromboembolism (one prior DVT and PE, one with phlebothrombosis and stroke, one was receiving oral contraceptives for dysfunctional uterine bleeding, and one with advanced malignancy). The risk was highest with tofacitinib 10 mg BID dosing (Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su). Of note, even in the setting of UC flare, a known risk factor for DVT and PE, there were no reported events of DVT or PE in either tofacitinib treatment arm in the OCTAVE Induction trials (Siegmund, 2020). The TROPIC consortium studied the real-world safety of tofacitinib in UC and found that 2 patients (0.8%) of the 260 patients developed a VTE (both of whom had significant other comorbidities). The real-world data was consistent with the tofacitinib registration trials (Deepak et al., 2021). Continued analysis and long-term safety data on tofacitinib 10 mg BID in UC are ongoing.

The FDA recommends against prescribing tofacitinib in patients at risk for thrombosis, including arterial thrombosis, DVT, and PE (rug Safety Communica, 2021). It is still unclear if the increased venous thromboembolic events seen in specific JAKi trials can be attributed to the medications themselves, the underlying disease, individual patient risk factors, or a combination of the above. Therefore, tofacitinib should be used with caution. Tofacitinib may increase the risk of DVT, PE, and ATE in high-risk patients: history of VTE, hypercoagulable state, smoking, immobilization or reduced mobility, recent major surgery or trauma, MI in the previous 3 months, age >50 years, comorbid cardiovascular conditions, malignancy, obesity, lower limb paralysis, use of combined oral contraceptives or hormonal replacement therapy or frequent long flights (Agrawal et al., 2020).

Author's Recommendation.

> Tofacitinib should be used with caution in patients with risk factors for VTE.
>
> Long-term use of tofacitinib 10 mg BID should be avoided especially in high-risk populations. After the 8-to-16-week induction period for the treatment of moderate-to-severe UC, tofacitinib dosing should be reduced to 5 mg BID in order to mitigate VTE risk.
>
> Strong recommendation; High quality of evidence.

4.2.5. Major cardiovascular events and lipids

Patients with chronic inflammatory diseases, such as IBD, RA, and psoriasis, have a slightly increased risk of cardiovascular morbidity due to the underlying chronic inflammation (Singh et al., 2014; Mantel et al., 2015; Solomon et al., 2015). Major cardiovascular events (MACEs) were uncommon in the pooled analyses of the OCTAVE Clinical Programme (n = 1157; 2581.3 PY) of patients who were treated with tofacitinib (IR 0.26 per PY; 95% CI 0.11–0.54), in which 83.9% received 10 mg BID dosing. When analyzing up to 6.8 years of patient follow-up, 7 (0.6%) patients who received tofacitinib had a confirmed MACE: acute coronary syndrome, acute myocardial infarction, aortic dissection, cerebellar hemorrhage, hemorrhagic stroke, cerebrovascular accident, and myocardial infarction. Of note, many of these patients had four or more baseline risk factors, including dyslipidemia (Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su). The fatal event of aortic dissection occurred in a male patient aged 39 years who had untreated baseline hyperlipidemia (LDL-c, 189 mg/dL; total-c, 308 mg/dL); this event was considered by the investigator to be

unrelated to study treatment (Sands et al., 2021). In the recently completed post-marketing safety study, ORAL Surveillance, results show a higher occurrence of MACEs in RA patients treated with both doses of tofacitinib (IR 0.98; 95% CI 0.79–1.19) compared to patients treated with a TNFi (IR 0.73; 95% CI 0.52–1.01). For tofacitinib, the most frequently reported MACE was myocardial infarction. In those subjects with a higher prevalence of known risk factors for MACEs, a higher occurrence of events was seen across all treatment groups (Safety Study of Tofacitin, 2092).

Tofacitinib treatment was associated with a dose-dependent increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c) compared to placebo at week 8, without an increase in MACEs (López-Sanromán et al., 2021; Sandborn et al., 2017). These changes stabilized after 4–8 weeks of treatment and returned to baseline upon cessation of tofacitinib. Notably, the predictors of cardiovascular risk such as TC/HDL and LDL/HDL ratios were unchanged. The Reynolds Risk Score [RRS], a predictor of 10-year cardiovascular events taking into account C-reactive protein and traditional risk factors, remained unchanged with tofacitinib therapy (Agrawal et al., 2020; Sands et al., 2020). These findings corroborate the ones found in clinical trials assessing changes in lipids and MACE risk with tofacitinib in RA and PsA (Kremer et al., 2009; Gladman et al., 2019). When analyzing up to 6.8 years of the OCTAVE Clinical Program cohort, 7.7% of the studied population was prescribed a new lipid-lowering agent and 1.9% required increased adjustment in dosing (López-Sanromán et al., 2021; Sands et al., 2021). A negative clinical impact of these changes has not been clinically observed.

Author's Recommendation.

Baseline fasting lipid profile should be checked as well as 4–8 weeks after starting treatment with tofacitinib.

Moderate recommendation; Moderate quality of evidence.

4.2.6. Malignancy

The prescribing information for tofacitinib carries a boxed warning regarding the increased risk of malignancy (XELJANZ, 2020). The IR for malignancy, excluding non-melanoma skin cancer (NMSC), was (0.75 per 100 PY; 95% CI 0.46–1.16) when analyzing the entire OCTAVE Clinical Programme (up to 6.8 years follow-up). Overall, there were 20 cases of malignancy excluding NMSC. There was no apparent clustering of malignancy types, and IRs were stable over time. Malignancy (including NMSC) was highest in patients treated with tofacitinib 10 mg BID in the LTE study. Of note, a portion of the studied patients had also previously been treated with thiopurines and TNFi. The IR for NMSC was 0.73 per 100 PY (95% CI 0.44–1.13) in the updated analysis. Nineteen patients (1.7%) developed NMSC, of which 17 had been exposed to thiopurines and 15 had been exposed to TNFi (Sandborn, Panés, D'Haens, Sands, Panaccione, Ng, Jones, Lawendy, Kulisek, Mundayat, Su; Lichtenstein et al., 2019; Lichtenstein et al., 2021).

A network meta-analysis in 2017 analyzed the risks of malignancies related to tofacitinib and biological drugs in RA in RCTs and LTEs and determined that there were marginal numerical differences in the incidence rate of solid and hematological malignancies and non-melanoma skin cancers for all TNFi (OR 1.01; 95% CI 0.72–1.42) and for tofacitinib (OR 1.15; 95% CI 0.24–5.47) (Maneiro et al., 2017). The recently completed post-marketing tofacitinib safety study in RA showed a higher occurrence of malignancy (excluding NMSC) in RA patients treated with both doses of tofacitinib (IR 1.13; 95% CI 0.94–1.35) compared to patients treated with a TNFi (IR 0.77; 95% CI 0.55–1.04). For tofacitinib in the post-marketing safety study, the most frequently reported malignancy (excluding NMSC) was lung cancer. Other cancers of note were pancreatic and prostate cancer. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications (Safety Study of Tofacitin, 2092).

Author's Recommendation.

Tofacitinib should be used with caution in those who have a history prior malignancy, other than successfully treated NMSC. Patients who are on tofacitinib therapy should undergo annual dermatologic skin examinations.

Strong recommendation; Moderate quality of evidence.

4.2.7. Elderly

Most of the data regarding serious adverse events in elderly patients is derived from the rheumatoid arthritis clinical trials. Serious infections risk was higher in older patients (≥65 years) taking tofacitinib 10 mg BID when compared to younger patients (<65 years). However, this risk was similar between age groups in the tofacitinib 5 mg BID and adalimumab groups. These results suggest an effect modification by age for tofacitinib 10 mg BID (Zhu and Ran, 2021; Winthrop et al., 2021b). In the post-marketing safety study on tofacitinib in RA, older patients (≥50 years) and with ≥1 cardiovascular risk factor were identified as having a higher frequency of PE and all-cause mortality when receiving tofacitinib 10 mg BID versus those receiving anti-TNF agent (Safety Study of Tofacitin, 2092; Zhu and Ran, 2021). RCT and real-world data regarding safety risks in elderly patients with UC receiving tofacitinib are still being collected and analyzed.

Author's Recommendation.

Due to an increased risk of infections and VTE in *older* patients (≥65 years), tofacitinib should only be considered if no suitable alternative treatment is available.

Moderate recommendation; Low quality of evidence.

4.2.8. Pregnancy

The literature is sparse regarding the safety of tofacitinib during pregnancy and breastfeeding. Most of our knowledge is derived from experimental animal models. This animal-derived data is published in the tofacitinib prescribing information and includes evidence that tofacitinib is teratogenic, but does not affect male fertility or sperm quality and functionality (XELJANZ, 2020). Given its small molecular size, it is assumed that tofacitinib crosses the placenta, but this has not been investigated in human models (Mahadevan et al., 2018).

Of the minimal data regarding exposure to tofacitinib in those with UC during the periconceptional period or during pregnancy, 11 cases of maternal exposure and 14 cases of paternal exposure have been analyzed. The outcomes included two miscarriages, two medically induced abortions, no congenital malformations, no fetal or neonatal deaths, and 15 healthy newborns (Mahadevan et al., 2018). This limited UC sample data corroborates similar outcome analyses seen in RA and psoriasis populations exposed to tofacitinib (Clowse et al., 2016). Conclusive, voluminous, long-term exposure data in the real world is lacking, especially concerning lactation in humans. Available data are insufficient to establish a drug-associated risk of major congenital disabilities, miscarriage, or adverse maternal or fetal outcomes (XELJANZ, 2020).

Author's Recommendation.

At this time, due to the paucity of data, pregnancy and breast-feeding should represent exclusion criteria for tofacitinib use. Tofacitinib should be avoided in women planning pregnancy.

Low recommendation; Low quality of evidence.

5. Positioning in the treatment armamentarium

Sulfasalazine and systemic corticosteroids were the first medical therapies approved for UC and have undergone multiple new formulations due to undesirable safety profiles and efficacy. This spurred the creation of corticosteroid-sparing agents such as thiopurines, methotrexate, and other immunomodulators. Potential SAEs, such as leukopenia, pancreatitis, hepatitis, and leukemia are a concern (Hernandez-Rocha and Vande Casteele, 2020). The limited efficacy and side effect profiles of these "conventional therapies" and an ever-improving understanding of the pathophysiology of IBD, prompted the creation of biologic agents that target specific mediators of immunological and inflammatory pathways. Biologic therapies have single-handedly changed the treatment paradigm from symptomatic control to one of both clinical and endoscopic remission, thereby improving long-term treatment outcomes (Hernandez-Rocha and Vande Casteele, 2020; Reinink et al., 2016). The most notable disadvantage of TNFi therapies is the potential for developing drug antibodies which may lead to loss of drug response and infusion reactions (Vermeire et al., 2018). Since the early 2000s, the IBD armamentarium has gained multiple TNFi agents and newer biologics that target interleukins and integrins.

In 2012, the advent of JAKi proved to be a novel approach regarding therapeutics in the treatment of immune-based, inflammatory diseases. This new class of medications was formulated as non-immunogenic, orally delivered, small molecule therapies with predictable pharmacokinetics instead of their monoclonal antibody counterparts. The most challenging aspect physicians now face with the multitude of therapeutic options available today is that the literature lacks a robust number of head-to-head RCTs in UC. These trials are essential for evidence-based recommendations for treatment algorithms or changes in therapy in the case of failures. Head-to-head trials of tofacitinib compared to other TNFi for UC treatment are warranted to inform clinical decision-making with greater confidence (Hernandez-Rocha and Vande Casteele, 2020).

In the current treatment algorithm for moderate to severe UC, one must first exclude infectious complications. First-line medical therapy includes aminosalicylates, such as mesalamine, at a sufficient dose as combined systemic and local therapy. For a disease that does not respond to topical therapy, corticosteroids such as MMX-budesonide for mild-to-moderate disease or systemic corticosteroids at a dose of 1 mg/kg body weight can be added. Once the clinical and endoscopic disease is controlled, steroids should be tapered and mesalamine should be continued. In patients who are corticosteroid dependent and unsuccessful in sustaining remission, an immunomodulator, such as azathioprine (2–3 mg/kg), should be added to an anti-TNFi or consideration be given to an anti-interleukin or anti-integrin based on clinical disease manifestations. In patients with disease that is refractory to corticosteroids, anti-TNFi should be initiated with or without azathioprine (2–3 mg/kg) versus a selection of anti-interleukin or anti-integrin therapy, explicitly tailored to the 'patient's disease (EIMs, patient preferences) (Siegmund, 2020).

Since the FDA drug and safety warning in 2019 regarding the potential risk of VTE and death seen in RA patients receiving 10 mg BID of tofacitinib, the FDA has now restricted tofacitinib to the treatment of adult patients with moderate-to-severe active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Even so, tofacitinib remains an attractive second-line agent for the treatment of UC given the TNFi non-responder rate of approximately 30%, the loss of response rate of TNFi therapy of approximately 23%–46% (Roda et al., 2016), and the lower response rate seen with therapies such as vedolizumab and ustekinumab in TNFi experienced patients (Singh et al., 2020). The data from the OCTAVE Clinical Programme shows that tofacitinib works equally well in both TNF naïve and TNF experienced patients (Sandborn et al., 2017) as opposed to other treatment strategies in which we see a decreased response rate in patients who have been previously exposed to TNFi (Feagan et al., 2013; Sands et al., 2019).

Unlike the other available biologic therapies, as noted in the post-hoc analyses of data from the two phase 3 OCTAVE 1 and 2 Induction trials, tofacitinib 10 mg BID showed rapid and significant symptomatic improvement in moderate-to-severe active UC, occurring within 3 days of treatment versus placebo (Hanauer et al., 2019). This allows one to judge the clinical response to therapy reasonably quickly, avoiding unnecessary AEs in unresponsive patients. To date, only infliximab has been reported to show a symptomatic effect before 2 weeks of therapy (Hernandez-Rocha and Vande Casteele, 2020; Hanauer et al., 2019). Recently, tofacitinib and ustekinumab were determined to be significantly superior to adalimumab and vedolizumab for the induction and maintenance of clinical remission in patients with moderate to severe UC who failed TNFi therapy (Singh et al., 2020).

A significant portion of patients who are affected with IBD experience EIMs. In a phase 2 trial, tofacitinib 5 mg and 10 mg BID was shown to be more efficacious than placebo regarding signs, symptoms and objective endpoints in ankylosing spondylitis (axial spondyloarthropathy) (Siegmund, 2020; van der Heijde et al., 2017). Tofacitinib has also been shown to be efficacious in peripheral involvement, thus making it a potential choice in patients with either axial or peripheral arthritis, unlike ustekinumab which is not effective for axial spondyloarthropathy (Siegmund, 2020; Deodhar et al., 2019). Tofacitinib is potentially situated as the preferred second-line therapy in patients who prefer the ease of administration and are also plagued by EIMs.

Lastly, pharmacokinetics and comorbid illnesses must be taken into account. Tofacitinib is eliminated by hepatic metabolism (70%) and renal excretion (30%). Therefore, unlike monoclonal antibody therapies, the dose of tofacitinib should be reduced in half in patients with moderate to severe renal dysfunction (including ESRD on dialysis) and in moderate hepatic dysfunction (e.g., tofacitinib 10 mg BID should be reduced to tofacitinib 5 mg BID and tofacitinib 5 mg BID to tofacitinib 5 mg QD). Tofacitinib should be avoided in severe hepatic impairment (Dowty et al., 2014).

Author's Recommendation.

Choice in therapeutic should always involve a joint decision-making approach as well as severity of disease, age, comorbidities, safety profile, prior exposure to TNFi, onset of action, route of *administration*, among others.

Tofacitinib should be given special attention to older individuals with cardiovascular risk factors and should be avoided in patients with high risk of VTE and pregnant patients.

In the U.S., Tofacitinib should be considered a second-line therapy for the treatment of moderate-to-severe UC that is refractory or intolerant to anti-TNF therapy and requires a rapid, long-term response, especially in cases with extraintestinal manifestations of UC.

Strong recommendation; Moderate quality of evidence.

6. Next generation of JAK inhibitors

Over the last several years, there have been many breakthroughs in the pursuit of improving the efficacy and safety profiles of JAKi. In the process of developing the next generation of JAKi, attention has been turned to more selectivity against specific JAK isoforms and gut restrictive, systemic sparing formulations for the treatment of IBD (Hernandez-Rocha and Vande Casteele, 2020; Voss et al., 2014).

6.1. Filgotinib

Filgotinib is an oral JAKi with preferential selective inhibition of JAK 1 (Dowty et al., 2019). Filgotinib has shown efficacy in the treatment of both CD and UC. The efficacy and safety of filgotinib in CD were evaluated in a phase II, double-blinded, placebo-controlled randomized clinical trial (FITZROY). Participants were randomized to filgotinib 200 mg QD or placebo and monitored for response at week 10. Based on the response, patients were again randomized to filgotinib 200 mg, filgotinib 100 mg, or placebo QD for another 10 weeks. The primary endpoint of clinical remission [defined as CDAI <150] at week 10 was achieved in a significantly higher proportion of patients in the filgotinib groups compared to placebo (47% vs. 23%; $p = 0.0077$). The rate of clinical remission at week 10 was 60% ($n = 34$) in TNFi naïve participants versus 37% ($n = 26$) in TNFi experienced participants. A numerically higher but non-significant difference was noted in the endoscopic response and mucosal healing rate in all filgotinib groups. Serious infections were noted in 3% of the filgotinib group, with none reported in the placebo group up to 20 weeks of follow-up (Al-Bawardy et al., 2021; Vermeire et al., 2017). These results have prompted a phase II trial evaluating filgotinib in perianal fistulizing CD (NCT03077412) and a phase III clinical trial of filgotinib in CD (NCT02914561; NCT02914600), both still in progress (Al-Bawardy et al., 2021).

The efficacy and safety of filgotinib in UC were evaluated in a phase IIB/III study (SELECTION), which evaluated filgotinib in the induction and maintenance for moderate to severe UC. Biologic naïve and experienced participants were included, and each cohort was randomized to either once-daily filgotinib 200 mg, filgotinib 100 mg, or placebo. The composite primary endpoint of endoscopic, rectal bleeding and stool frequency remission (defined as Mayo endoscopic subscore ≤ 1, rectal bleeding subscore of 0, stool frequency subscore decrease of 1 or more points from baseline and ≤ 1) rates were significantly higher in the filgotinib 200 mg groups (26.1% in the biologic naïve cohort and 11.5% in the biologic experienced cohort) compared to the placebo groups. There were four total cases of HZ in the filgotinib groups. Three cases were reported in the filgotinib 200 mg group and one in the filgotinib 100 mg group. There was one case of PE reported in the filgotinib 200 mg group. Patients who achieved clinical remission or response after 10 weeks of induction therapy with either filgotinib or placebo entered the maintenance study ($n = 664$). Those who received placebo induction remained in the placebo maintenance arm, while patients randomized to the filgotinib induction were re-randomized to filgotinib induction dose (continue 200 mg or 100 mg) maintenance arm or placebo arm. The composite primary endpoint of endoscopic, rectal bleeding and stool frequency remission at week 58 was achieved in 37.2% in the filgotinib 200 mg group versus 11.2% in the placebo group ($p < 0.0001$) and 23.8% in the filgotinib 100 mg group versus 13.5% in the placebo arm ($p < 0.0420$). Overall, filgotinib was well tolerated. There was one case of HZ in the filgotinib 200 mg group and one in the 100 mg group. Two cases of VTE were reported in the placebo group but none in the filgotinib group (Al-Bawardy et al., 2021; Feagan et al., 2021).

6.2. Upadacitinib

Upadacitinib is an oral JAKi with preferential selective inhibition of JAK 1. At this time, it is approved for the treatment of patients with RA with moderate to severe activity who are intolerant to or have failed methotrexate therapy. In the phase II clinical trial (CELEST), participants with moderate to severe CD ($n = 220$) who failed immunosuppressants or biologics were assigned to either upadacitinib: 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID, or placebo for 16-weeks of induction therapy. Following the induction period, participants were randomized again to upadacitinib: 3 mg BID, 12 mg BID, or 24 mg QD for 36 weeks of maintenance therapy. At week 16, there was no statistically significant difference in clinical remission rates between the treatment groups and placebo. Although, endoscopic remission at week 12 and week 16 was significantly higher in the upadacitinib groups than placebo. The investigators concluded that higher doses of upadacitinib were associated with higher rates of endoscopic remission. Regarding safety, there were higher incidences of infections and severe infections during the induction period in participants receiving upadacitinib (including three cases of HZ) versus those receiving placebo (Al-Bawardy et al., 2021; Sandborn et al., 2020a). Phase III trials of upadacitinib for CD are currently in progress (NCT03345836, NCT03345823) (Al-Bawardy et al., 2021).

In the phase IIb clinical trial (UC-ACHIEVE), participants with moderate to severe UC ($n = 250$) who failed or were intolerant to immunosuppressive or biologic therapy were assigned to either upadacitinib: 7.5 mg QD, 15 mg QD, 30 mg QD, 45 mg QD or placebo for 8 weeks of induction therapy. Clinical remission was significantly higher in the 15 mg (14.3%; $p = 0.013$), 30 mg (13.5%; $p = 0.011$), and the 45 mg groups (19.6%; $p = 0.002$) versus 0% in the placebo group. Endoscopic response and mucosal healing at week 8 (Mayo endoscopic subscore of ≤ 1) was achieved in all upadacitinib groups: 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%; $P < 0.001$) versus placebo showing a dose dependent relationship. Regarding safety, one case of HZ and one participant with PE and DVT (diagnosed 26 days after treatment discontinuation) were reported in the upadacitinib 45 mg QD group (Al-Bawardy et al., 2021; Sandborn et al., 2020b). Phase III trials of upadacitinib for UC are currently in progress (NCT03653026, NCT03006068, NCT02819635) (Al-Bawardy et al., 2021).

6.3. TD-1473

TD-1473 is an oral gut-selective pan-JAKi designed to limit the systemic toxicity of pan-JAK inhibition. In a phase Ib trial examining the safety and proper dosing of TD-1473, 40 participants with moderate to severe UC were assigned to once-daily TD-1473 doses: 20 mg, 80 mg, or 270 mg or placebo for 28 days. Thirty-five out of the forty participants in this study were naïve to TNFi. The clinical response rate was 55% in the 270 mg group versus 20% in the 20 mg and 80 mg groups and 11% in the placebo group. This trial was not powered for outcomes ($n = 40$), and therefore statistical analyses were not performed. Trends in endoscopic improvement and reductions in fecal calprotectin and C-reactive protein levels were observed with TD-1473. Overall adverse event rates were similar in the TD-1473 groups 38.7% and 44.4% in the placebo group (Al-Bawardy et al., 2021; Sandborn et al., 2020c). Phase IIb/III studies of TD-1473 for moderate to severe UC are ongoing (NCT03758443, NCT03920254). There is also a phase II study of TD-1473 in moderate to severe CD currently in progress (NCT03635112) (Al-Bawardy et al., 2021).

7. Conclusion

IBD is a chronic, progressive disease with high morbidity and increasing incidence rates word-wide (Molodecky et al., 2012). The use of JAKi is a novel targeted therapeutic approach in the treatment of IBD. JAKi represent a medication class with favorable and predictable pharmacokinetics, lack of immunogenicity, and ease of administration over their biologic counterparts due to their small molecular size. Tofacitinib has shown efficacy in the treatment of moderate to severe UC in clinical trials and real-world experiences. Thus far, tofacitinib's safety profile has generally remained stable and acceptable when managed per expert

recommendations and utilized as indicated. Continued real-world clinical practice data are still needed and will assist in determining the ideal positioning of this treatment in the future. The future of JAKi is promising regarding the continued maximization of efficacy and improvement in safety profiles and tolerability with the new development of more selective and intestinally restrictive therapies.

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Ethics

No approval of the institutional review committee was needed.

CRediT authorship contribution statement

Ted A. Spiewak: Conceptualization, Writing – original draft, Writing – review & editing. **Anish Patel:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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