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Review

Unveiling the Potential of JAK Inhibitors in Inflammatory Bowel Disease

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Abstract: Background: Janus kinase (JAK) inhibitors represent a novel class of oral therapies showing efficacy in treating ulcerative colitis (UC) and Crohn's disease (CD), challenging conventional treatment paradigms. Summary: This review provides an overview of the potential novel uses of JAK inhibitors, focusing on their current approved indications and exploring possibilities beyond these indications. Tofacitinib and filgotinib are approved for UC, while upadacitinib is approved for both UC and CD. Additionally, their potential in acute severe UC, as steroid alternatives, and in managing fistulizing CD or extraintestinal manifestations are discussed. Key Message: JAK inhibitors play an important role in IBD (inflammatory bowel disease) treatment; however, clinicians must balance their promising efficacy with safety concerns. Individualized care and vigilance are essential for optimizing therapeutic benefits while mitigating potential adverse effects. Further research is necessary to clarify their efficacy, safety, and potential applications.

Keywords: ulcerative colitis; Janus kinase inhibitors; tofacitinib; filgotinib; upadacitinib

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1. Introduction

Biologic therapy, commonly known as biologic drugs or biologics, comprises medications derived from living organisms or their components. Notably, among the array of biologic therapies, Janus kinase (JAK) inhibitors emerge as promising agents. JAKs constitute a vital group of intracellular, non-receptor tyrosine kinases pivotal for transducing cytokine-mediated signals through the JAK-STAT pathway [1]. The JAK family, their associated Signal Transducers and Activators of Transcription (STAT) proteins, the cytokine ligands they respond to, and their pivotal roles in the immune system are displayed in the table below (Table 1).

Table 1. The JAK family, their associated Signal Transducers and Activators of Transcription (STAT) proteins, the cytokine ligands they respond to, and their pivotal roles in the immune system.

JAK Family Member	Associated STAT Protein	Cytokine Ligands	Role in Immune System
Jak1	STAT1, STAT3, STAT5, STAT6	IL-2, IL-6, IL-10, IL-12, IL-23, IFN-Y, GM-CSF, G-CSF	Regulation of immune responses, hematopoiesis, inflammation
Jak2	STAT1, STAT3, STAT5	Erythropoietin (EPO), Thrombopoietin (TPO), IL-3,IL-5, IL-6, IL-12, IL-23	Hematopoiesis, erythropoiesis, megakaryopoiesis

Table 1. *Cont.*

JAK Family Member	Associated STAT Protein	Cytokine Ligands	Role in Immune System
Jak3	STAT1, STAT3, STAT5	IL-2, IL-4,IL-7,IL-9,IL-15, IL-21	Development and function of immune cells, especially lymphocytes
Tyrosine kinase 2 (Tyk2)	STAT1, STAT3, STAT4	IFN-a, IFN-B, IL-12, IL-23	Regulation of innate and adaptive immune responses

Furthermore, Table S1 as a Supplementary Table outlines the approved indications and potential applications of JAK inhibitors in inflammatory bowel diseases (IBD) and related conditions. Tofacitinib, upadacitinib, and filgotinib have emerged as significant players in this therapeutic landscape, offering diverse applications beyond their initial approvals. This review focuses on these three JAK inhibitors, synthesizing current knowledge and paving the way for future investigations.

2. Mechanism of Action of JAK Inhibitors

JAK inhibitors, including tofacitinib, upadacitinib, and filgotinib, represent a class of small molecule therapies with potential in treating IBD. Administered orally, these drugs offer advantages such as convenience, rapid onset of action, and the absence of antidrug antibody responses [1]. The target of these drugs is the JAK Signal Transducers and Activators of Transcription (STAT) pathway, a central mediator of inflammatory cytokine signaling. Figure 1 provides a schematic diagram of the mechanism of action of each JAK inhibitor.

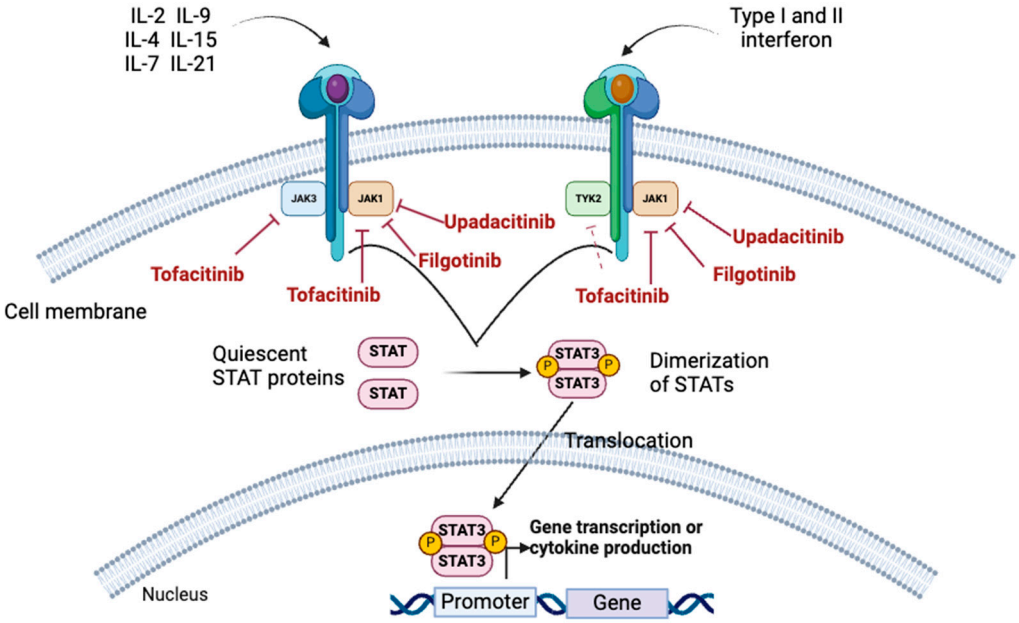

Figure 1. Mechanism of action the 3 JAK inhibitors.

Tofacitinib is a pan-JAK inhibitor, predominantly inhibiting JAK1 and JAK3, with lesser effects on JAK2 and TYK2. It was the first JAK inhibitor approved for UC [1,2].

Upadacitinib selectively targets JAK1, modulating key cytokine signaling, with affected proteins including IL-2, IL-4, IL-7, IL-9, IL-15, IL-21, and type I and II interferons [2],

and it has been approved for both UC and CD. Similarly, filgotinib, a JAK1-selective inhibitor, has been approved for UC in the EU, UK, and Japan and shows promise in CD, although its efficacy in CD is still under investigation.

3. Approved Indications for JAK Inhibitors

3.1. Tofacitinib in Ulcerative Colitis

Originally used in rheumatology, tofacitinib has emerged as a promising therapy for moderate to severe ulcerative colitis (UC) [3]. The OCTAVE trials investigated its efficacy and safety profile in this context. Notably, tofacitinib was associated with significant clinical remission rates compared to placebo [4]. In the OCTAVE trials, which included induction arms (OCTAVE 1 and OCTAVE 2) and a maintenance arm (OCTAVE Sustain), tofacitinib demonstrated efficacy in achieving clinical remission in patients with moderate to severe UC. For instance, in OCTAVE 1, remission was achieved in 18.5% of patients receiving tofacitinib compared to 8.2% in the placebo group ($p = 0.007$), while in OCTAVE 2, remission occurred in 16.6% versus 3.6% ($p < 0.001$). Moreover, the OCTAVE Sustain trial reported significant rates of clinical remission at week 52, with 34.3% and 40.6% of patients in the 5 mg and 10 mg tofacitinib groups, respectively, achieving remission compared to 11.1% in the placebo group ($p < 0.001$ for both comparisons).

Given its efficacy demonstrated in UC, tofacitinib received FDA approval in 2019 for adult patients with moderate to severe ulcerative colitis [5].

However, its clinical development for Crohn's disease (CD) was halted due to its failure to meet endpoints in respective phase II induction and maintenance trials. Furthermore, an open-label extension study investigating the long-term safety of tofacitinib in CD patients reported the worsening of CD as the most common adverse effect [6].

3.2. Upadacitinib for Ulcerative Colitis

Upadacitinib, a selective Janus kinase 1 (JAK1) inhibitor, has demonstrated considerable efficacy in the treatment of moderate to severe ulcerative colitis (UC) [7]. Phase 3 trials (UC1 and UC2) investigated its efficacy compared to placebo, revealing significant rates of clinical remission.

In the UC1 and UC2 trials, which included induction arms, 26–33% of patients with UC achieved clinical remission at week 8 with upadacitinib compared to only 4–5% with placebo [8]. Furthermore, long-term follow-up in UC3 demonstrated sustained clinical remission rates of 42% and 52% at daily doses of 15 mg and 30 mg, respectively [8], compared to 34.3% and 40% for tofacitinib in OCTAVE Sustain at 5 mg and 10 mg doses twice daily.

Recent evaluations of upadacitinib's efficacy include a post hoc analysis that explored early symptomatic improvement for UC. Pooled data from two replicate phase 3 multicenter induction trials, UACHIEVE Induction and UACCOMPLISH, demonstrated rapid relief of UC symptoms with 45 mg of upadacitinib once daily, starting as early as day 1 and continuing up to day 14 [9]. Significant reductions in inflammatory markers and improvements in quality of life were also observed in these trials, reinforcing upadacitinib's potential as a robust treatment option for UC [9].

3.3. Upadacitinib in Crohn's Disease

In 2023, the FDA approved upadacitinib for adults with moderately to severely active Crohn's disease (CD) who have had an inadequate response or intolerance to one or multiple anti-tumor necrosis factor (TNF) blockers. This approval followed clinical trials demonstrating the benefit of upadacitinib for both induction and maintenance treatment in CD [10]. In two phase 3 induction trials, U-EXCEL and U-EXCEED, involving 1021 patients, upadacitinib at a dose of 45 mg significantly increased rates of clinical remission compared to placebo at week 12 (U-EXCEL: 49.5% vs. 29.1%, $p < 0.001$; U-EXCEED: 38.9% vs. 21.1%, $p < 0.001$) (Loftus et al., 2023). The U-ENDURE trial also reported higher rates of

clinical remission at week 52 with upadacitinib compared to placebo (15.1%), with 37.3% of patients on 15 mg and 47.6% of patients on 30 mg of upadacitinib achieving remission [10].

Additionally, another study highlighted the rapidity and significance of upadacitinib's effect on clinical parameters in a refractory patient population with active CD. This effect was concurrent with a swift and sustained decrease in markers of inflammation, such as C-reactive protein (CRP) and fecal calprotectin [11].

3.4. Filgotinib for Ulcerative Colitis

Filgotinib, a Janus kinase (JAK) inhibitor, has garnered attention as a potential therapy for ulcerative colitis (UC), having obtained approval in the European Union (EU), Great Britain, and Japan for treating adult patients with moderately to severely active UC. Initially investigated in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, filgotinib's selective inhibition of the JAK1 subtype has shown promise in preliminary trials.

In a phase 2b/3 SELECTION study involving 1348 patients randomized to receive either 200 mg or 100 mg of filgotinib or placebo daily across two induction studies, notable differences in induction and clinical remission rates were observed. By week 10, the 200 mg filgotinib group exhibited a higher proportion of patients achieving clinical remission compared to placebo (26.1% vs. 15.3% in induction study A, $p = 0.0157$; 11.5% vs. 4.2% in induction study B, $p = 0.0103$) [12]. Also, at week 58, a higher percentage of patients on 200 mg of filgotinib demonstrated clinical remission compared to placebo (37.2% vs. 11.2%, $p < 0.0001$). These favorable outcomes were observed in both biologic-naive and biologic-experienced patients [12]. Filgotinib was also well tolerated, with no significant difference in the incidence of serious adverse events between filgotinib and placebo groups.

While filgotinib has shown promise in UC, its efficacy in Crohn's disease (CD) is yet to be confirmed. Although initial efficacy signals were observed in the phase II FITZROY study [13], the multicenter phase III results in moderate to severe CD are required before definitive conclusions can be drawn. Hence, further research is warranted to establish the efficacy and safety profile of filgotinib in CD patients [1].

4. Unlicensed but Potential Uses for JAK Inhibitors

4.1. JAK Inhibitors in Acute Severe Ulcerative Colitis

Standard-of-care therapies for acute severe ulcerative colitis (ASUC) include intravenous corticosteroids. For those with steroid refractory disease, salvage therapy with infliximab or cyclosporin is then administered. For those who fail to respond to salvage therapy, colectomy remains the standard of care [14]. Tofacitinib's effectiveness for refractory ASUC has been reported, while data on upadacitinib are still lacking.

4.1.1. Tofacitinib in ASUC

Recent evidence suggests that tofacitinib, a rapidly acting Janus kinase inhibitor, may offer a promising strategy for preventing colectomy in patients with ASUC. A retrospective case–control study evaluated the efficacy of tofacitinib induction in biologic-experienced patients admitted with ASUC requiring intravenous corticosteroids (Danese et al., 2022). In this study, tofacitinib demonstrated a significant protective effect against colectomy at 90 days compared with matched controls (hazard ratio [HR], 0.28, 95% confidence interval [CI], 0.10–0.81; $p = 0.018$). Stratification by treatment dose revealed that the 10 mg three times daily regimen was particularly effective (HR, 0.11; 95% CI, 0.02–0.56; $p = 0.008$), while the 10 mg twice daily regimen did not show significant protection (HR, 0.66; 95% CI, 0.21–2.09; $p = 0.5$). Rates of complications and steroid dependence were comparable between tofacitinib and controls [15].

These findings suggest that tofacitinib, when used in conjunction with intravenous corticosteroids, may serve as an effective induction strategy in biologic-experienced patients hospitalized with ASUC [15].

Response: The sentence was revised, as requested, to provide clarity on the premise of Gilmore's review and the claims made.

Revised sentence: In a further review by Gilmore, patients were identified from a prospectively maintained database at a tertiary IBD center. Five patients received tofacitinib at a high dose of 10 mg TDS, immediately following non-response to infliximab salvage therapy. The results showed that four out of the five patients demonstrated a clinical response, with only one proceeding to colectomy. All four patients remained colectomy-free at the 90-day follow-up. Only two of the five patients achieved combined steroid-free clinical and endoscopic remission at 90 days. While both studies appear to achieve rapid onset of response and potential reductions in colectomy rates, understanding if sustained and durable remission is achieved will be essential [16]. Only two of the five patients achieved combined steroid-free clinical and endoscopic remission at 90 days. While both studies appear to demonstrate potential reductions in colectomy rates, understanding if sustained and durable remission is achieved will be essential.

In another retrospective study spanning from January 2021 to July 2023, eight patients diagnosed with ASUC who was unresponsive to intravenous hydrocortisone were analyzed for their responses to tofacitinib [17]. With a mean age of 39 $\pm$ 15 years and a predominantly female composition (87.5%), these patients displayed 87.5% positive responses to oral tofacitinib at a dosage of 10 mg twice a day within the initial five days of treatment. The median follow-up period was extended to six months (IQR: 1–12 months). However, the study reported that one patient required colectomy, and another experienced varicella zoster reactivation, leading to treatment discontinuation [17]. Despite the promising initial response, this investigation underscores the need for further exploration of the long-term efficacy and associated risks of tofacitinib in the context of steroid-refractory ASUC.

4.1.2. Upadacitinib in ASUC

Another JAK inhibitor with potential treatment use for ASUC in adults is upadacitinib. In a case report involving an 18-year-old woman with refractory UC unresponsive to conventional treatments that included infliximab, adalimumab, and tofacitinib, 45 mg of oral upadacitinib was given once a day, resulting in full clinical, biochemical, and steroid-free remission within 60 days, sustaining endoscopic remission at 180 days [18]. In another study, six patients with steroid-refractory ASUC and prior infliximab therapy with no response responded positively to upadacitinib induction. Four achieved corticosteroid-free clinical remission by week 8, demonstrating the complete resolution of symptoms and transmural healing, as assessed via intestinal ultrasound [19].

Despite these encouraging results, larger trials to validate the safety and efficacy of upadacitinib in a broader ASUC population are needed. This would also be important to helps us to understand the role of upadacitinib in ASUC.

4.2. JAK Inhibitors as Steroid Avoiding Agents

JAK inhibitors have demonstrated a rapid onset of action, showing 2.40 (95% CI 2.00, 2.88) and 1.97 (95% CI 1.52, 2.55) times higher likelihoods of achieving clinical response at week 2 with upadacitinib and tofacitinib, respectively, compared to placebo [20]. This suggests their potential as potent induction agents, possibly rivaling steroids during disease flares. However, current trials investigating the use of JAK inhibitors for this purpose are lacking.

4.3. JAK Inhibitors in Fistulating Crohn's Disease

Preliminary data on JAK inhibitors, particularly upadacitinib and filgotinib, in the treatment of fistulating Crohn's disease show promise [21]. In the U-EXCEED and U-EXCEL phase 3 induction trials, upadacitinib treatment demonstrated a substantial proportion of patients achieving complete resolution of draining fistulas, with a reported proportion of 47.7% compared to 9.1% in the placebo group [22]. Furthermore, similarly, filgotinib, in studies focused on perianal Crohn's disease, exhibited encouraging results, with a significant increase in the proportion of patients achieving a combined fistula response at week 24 in the 200 mg group compared to the placebo group [23]. This substantial

improvement in fistula closure rates underscores the potential therapeutic benefit of JAK inhibitors for managing fistulating Crohn's disease.

4.4. JAK Inhibitors as Part of Combination Therapies

The exploration of combination therapies involving JAK inhibitors is in its early stages. Previous studies in rheumatology have shown that JAK inhibitors, in combination with methotrexate, were more efficacious than monotherapy [24]. In a small series combining tofacitinib with biologic therapy for refractory inflammatory bowel disease, 50% of patients achieved clinical response at 8 weeks after the initiation of combination therapy, with 35.7% achieving corticosteroid-free clinical response and 10.7% achieving corticosteroid-free clinical remission [25]. Notably, safety concerns included one case of *Clostridium difficile* infection with infliximab and tofacitinib combined and one case of rash with vedolizumab and tofacitinib combined. Further research is warranted to assess the long-term safety and efficacy of combining advanced therapies, including JAK inhibitors, in the management of IBD.

4.5. JAK Inhibitors for Extraintestinal Manifestations in IBD

As JAK inhibitors have been utilized in rheumatology for some time, there is existing experience in treating joint-related issues. Studies have demonstrated the efficacy of tofacitinib at doses of 5 mg and 10 mg twice daily (bid) compared to placebo in patients with ankylosing spondylitis, showing improvements in signs, symptoms, and objective endpoints [26]. Additionally, randomized controlled studies have shown its effectiveness in peripheral arthritis [27].

Although there are some indications that tofacitinib may be beneficial in uveitis, the evidence supporting this remains limited to case reports [28]. Similarly, upadacitinib has shown promise in managing extraintestinal manifestations (EIMs) such as peripheral and axial arthropathy, anemia, and uveitis. Notably, in a study comparing 30 mg of upadacitinib to placebo over 52 weeks, 65.9% of patients reported the resolution of at least one EIM, a statistically significant difference ($p < 0.01$) [29].

5. Safety Profile of JAK Inhibitors in Immune-Mediated Diseases

The clinical efficacy of JAK inhibitors is well recognized; however, a comprehensive understanding of their safety profiles is crucial for informed medical practice. Hoisnard et al. (2022) conducted a safety assessment of the first three approved JAK inhibitors—ruxolitinib, tofacitinib, and baricitinib—utilizing pharmacovigilance data from the WHO database. Their analysis revealed an increased risk of infectious adverse events, including viral, fungal, and mycobacterial infections, associated with the use of these drugs [30]. These findings are corroborated by the outcomes of the OCTAVE induction trials by Sandborn et al., (2018), which specifically focused on tofacitinib. Additionally, Olivera et al., (2020) conducted a systematic review and meta-analysis, indicating an elevated risk of infection, particularly herpes zoster, with the use of JAK inhibitors, including tofacitinib, upadacitinib, filgotinib, and baricitinib, in patients with IBD and other immune-mediated diseases [31].

Tofacitinib was also found to be associated with gastrointestinal perforation events [30,32]. A dose-dependent correlation between tofacitinib and gastrointestinal perforation risk was observed, with higher doses showing an increased association. However, it is noteworthy that this observation may be confounded by the presence of active IBD in the patient population [30].

Cardiovascular events, particularly in patients aged 50 years or older with cardiovascular risk factors, have emerged as significant adverse events associated with JAK inhibitors [33]. Tofacitinib, in particular, has been associated with an increased risk of major adverse cardiovascular events (MACE), including specific events such as aortic dissection. Long-term studies suggest that while the overall risk of MACE with tofacitinib does not show a progressive increase over time, caution is warranted [34].

In contrast, other JAK inhibitors such as upadacitinib and filgotinib do not appear to have a higher rate of MACE [35,36]. These findings underscore the importance of conducting a comprehensive risk–benefit assessment when considering the use of these drugs.

These findings underscore the importance of conducting a comprehensive risk–benefit assessment when considering the use of these drugs [37]. A recent post-marketing study comparing tofacitinib with an anti-TNF agent found significant differences in the occurrence of pulmonary embolism (PE) and mortality [37,38]. Incidence rates of PE and mortality were notably higher among patients receiving tofacitinib, particularly those with background risk factors for VTE such as IBD. Consequently, both the FDA and the EMA have issued warnings, restricting tofacitinib use to ulcerative colitis patients refractory or intolerant to anti-TNF agents [33,37]. The mechanism underlying the potential risk of VTE with tofacitinib remains unclear and warrants further investigation.

However, a meta-analysis on VTE and tofacitinib use suggests that the risk of VTE is unlikely to be significantly increased compared to placebo [39]. Due to the low event rates and less precise data, a small increase in risk or small-to-large protective effects cannot be ruled out. These complex findings highlight the need for additional research and the careful consideration of individual patient factors when assessing the risk of VTE associated with JAK inhibitors, particularly tofacitinib, in patients with immune-mediated diseases such as IBD.

Another critical consideration in the individualized risk assessment for the use of JAK inhibitors is pregnancy and breastfeeding. JAK inhibitors can cross the placenta during the first trimester, raising concerns about potential fetal effects. Recommendations generally discourage the use of JAK inhibitors, including tofacitinib, during pregnancy and lactation, with a washout period advised before attempting conception [40].

Long-term extension studies of tofacitinib in conditions such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC), and psoriasis have provided insights into all-cause mortality. These studies have indicated that the risk of all-cause mortality remains similar across cohorts, providing reassurance regarding the long-term safety of tofacitinib [41]. This is supported by systematic reviews and meta-analyses encompassing a spectrum of immune-mediated diseases, including IBD, which have reported no increased mortality risk compared to placebo [31].

In conclusion, the use of JAK inhibitors presents both challenges and opportunities in immune-mediated diseases, including IBD. While these therapies demonstrate promising clinical efficacy, their safety profiles demand thoughtful consideration. Vigilance and individualized patient care are essential in balancing these two factors. By adapting a comprehensive approach, we can optimize the therapeutic potential of these therapies while minimizing potential harm, ensuring the utmost benefit for the patients.

6. Conclusions

JAK inhibitors represent a promising avenue for challenging current treatment paradigms in inflammatory bowel disease. However, further studies are required to comprehensively understand their efficacy and safety for these novel indications. It is also likely that we will see further JAK inhibitors in the IBD armamentarium, which may provide us with opportunities to use these in a variety of clinical scenarios. While current evidence suggests their potential as a novel therapeutic approach, further research is necessary to fully understand their efficacy and safety in these new indications. Moreover, the emergence of additional JAK inhibitors in the IBD armamentarium holds promise for expanding treatment options across various clinical scenarios. Ongoing studies exploring combination therapies involving JAK inhibitors may provide valuable insights into optimizing treatment strategies for patients with IBD. Therefore, continued investigation is crucial to elucidate the long-term efficacy, safety profiles, and optimal utilization of JAK inhibitors in clinical practice.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biologics4020012/s1, Table S1: Clinical Application of JAK inhibitors in Inflammatory Bowel Diseases and related conditions.

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