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A review on Janus Kinase (JAK) inhibitors in ulcerative colitis: A new frontier in GI pharmacotherapy

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease significantly impairing patient quality of life and usually requiring a long-term immunosuppressive regime. As far as treatment is concerned, the classical methods-aminosalicylates, corticosteroids, and biologics-have indeed helped to achieve better control; however, a number of patients are not responding adequately or are losing their response during the course of their treatment. JAK inhibitors have emerged as a very interesting class of oral small molecules which target the intracellular JAK-STAT signaling pathway that plays a central role in the pathogenesis of UC. Tofacitinib, as the first JAK inhibitor licensed for the treatment of moderate to severe UC, has been shown in clinical trials to exhibit a swift onset of action with maintenance of remission over the long term. With JAK1-selective agents such as upadacitinib and filgotinib currently being developed further into the therapeutic arena, some safety concerns about infections, thromboembolic events, and long-term safety emerge. This review covers the mechanism behind, clinical efficacy, and safety profile of JAK inhibitors and their place in the management of UC, portraying them as the newest frontier in personalized gastrointestinal pharmacotherapy.

Keywords: Ulcerative colitis, Janus kinase inhibitors, JAK-STAT pathway, Tofacitinib, Upadacitinib, Filgotinib, Inflammatory bowel disease, Targeted therapy, Immunomodulators, Gastrointestinal pharmacotherapy

Introduction

Ulcerative colitis (UC) is a chronic form of idiopathic IBD characterized by continuous mucosal inflammation of the colon, beginning distally with involvement of the rectum and extending proximally to varying extents. In contrast to Crohn's disease that may involve any portion of the gastrointestinal tract, UC is limited to the colon, affecting predominantly the superficial layers of the intestinal mucosa. The condition mostly presents with symptoms such as bloody diarrhea, abdominal pain, urgency, and tenesmus and runs on a relapsing-remitting course that severely affects the quality of life of patients.[1]

The precise etiology of UC is still unknown; however, the general hypothesis favors a dysfunctional immune response against intestinal microbiota in genetically predisposed individuals. A number of triggering factors have been considered, such as environmental exposures, infectious agents, food, and stress. With the passage of time, long-standing inflammation in UC would predispose to certain complications, including colorectal carcinoma; hence, there was a great need to look for long-term treatment modalities that can induce remission and keep the patient in the state of remission.[2]

Pathogenesis of ulcerative colitis

1. Genetic Predisposition

Genetic factors play an important role in the causation of ulcerative colitis. A positive family history is among the strongest risk factors, and multiple susceptibility loci have been identified in UC by genome-wide association studies. The major susceptibility loci of interest are related to immune regulation, epithelial integrity, and cytokine signaling, with HLA-DRB1, IL23R, and JAK2 being among them. While Crohn's is more associated with HLA class II genes, UC is more inclined to HLA class II genes, especially those affecting the mucosal immune system. Nonetheless, genetics alone cannot explain all UC cases, indicating a more significant role for environmental and immune factors.

2. Epithelial Barrier Dysfunction

In the healthy gut, the colonic epithelium and mucus layer provide a physical and chemical barrier against luminal microbes and antigens. The colonic epithelium barrier is compromised in UC, with a thinner mucus layer, reduced expression of MUC2 (major mucin), and disruption of tight junction proteins. Such changes allow increased intestinal permeability to bacterial products and antigens penetrating the mucosa, activating immune responses, and inflammation. Failing of the barrier acts as one of the fundamental events in initiate and maintain the mucosal injury in UC.[3,4]

3. Dysregulated Innate and Adaptive Immunity

In UC, abnormal autoimmune activation toward commensal gut flora occurs. Compromised innate immune reactions are characterized by dysfunctional activities in neutrophils and macrophages causing release of cytokines in excessive amounts. Adaptive immunity is considered to have a defective Th2-type response-IL-5 and IL-13 are produced abundantly, leading to eosinophilic inflammation and epithelial cell apoptosis. Regulatory T cells (Tregs), which are supposed to suppress excessive immune reactions, are also deficient in UC. This loss of immune tolerance contributes to chronic, relapsing inflammation.

4. Microbiota Dysbiosis

Significant dysbiosis takes place in the patient's microbiota with an increase in pathogenic bacteria, which includes an elevation of Escherichia coli and a decrease in beneficial commensals such as Faecalibacterium prausnitzii. Mucosal immunity and the generation of anti-inflammatory microbial metabolites, mainly butyrate, are compromised by these changes. Disruption of microbiota systems dysfunctions the mucosal barrier and disturbs immunity, which consecutively exaggerates inflammation and drives the course of chronicity.[5,6]

5. Cytokine and Chemokine Cascade

UC is marked by an abnormal and increased release of pro-inflammatory cytokines and chemokines. The key cytokines are tumor necrosis factor-alpha (TNF-α), interleukins such as IL-1β, IL-6, IL-13, and interferon-gamma (IFN-γ). The cytokines induce leukocyte recruitment to sites of infection, damage epithelial cells, and eventually cause tissue injury. They mostly act through the JAK-signal transducer and activator of transcription (STAT) pathway, which is gaining momentum as a therapeutic target in UC. The chronic production of the mediators sustains the inflammation, thereby impeding mucosal healing.

6. Oxidative Stress and Tissue Injury

Activated immune cells, especially neutrophils, generated enormous ROS and NO during inflammation. These molecules injure epithelial cells, mitochondrial function, and DNA of their constituent cells, leading to an increase in cell death and mucosal compromise. The oxidative stress, on the other hand, augments the release of pro-inflammatory mediators causing a continuous inflammatory cycle resulting in mucosal ulceration and bleeding as classical entities of UC.

7. Environmental Triggers

Several environmental factors have been considered possible causes and triggers of UC. These include diet (particularly low fiber, high fat), antibiotics, infections, stress, and smoking cessation. Unlike Crohn's disease, smoking cessation increases the risk of UC. These triggers may either alter gut microbiota composition, worsen barrier dysfunction, or alter immune responses in genetically predisposed people.

8. Neuroimmune and Vascular Factors

Recent research proposes that UC could be an outcome of the neuroimmune interactions and changes in vasculature in the gut. Altered neural signaling can affect gut motility, barrier function, and local immune responses. Furthermore, increased vascular permeability and angiogenesis in the inflamed mucosa allow inflammatory cells to infiltrate. Though they are not as well studied compared to immune or microbial mechanisms, they stand to contribute to the complicated mesh which sustains chronic inflammation.[7,8]

Limitations of Current Therapeutic Strategies

Despite advances in the management of ulcerative colitis (UC), there remain several limitations to conventional therapeutic approaches. Ameinosalicylates, corticosteroids, immunomodulators (e.g., azathioprine, 6-mercaptopurine), and biologics (anti-TNF agents, anti-integrins, and anti-IL-12/23 agents) have been administered in attempts to induce and maintain remission with varying degrees of success. However, a significant proportion of patients pose in front either of lack of response to therapy (primary non-response) or of secondary loss of response (secondary non-response). According to immunogenicity considerations, particularly with monoclonal antibodies, anti-drug antibodies are developed which, in turn, decrease drug efficacy while increasing the possibility of an adverse event. Furthermore, the parenteral mode of administration of biologics entails intravenous infusion or subcutaneous injection, which may be considered somewhat inconvenient from the perspective of patient compliance. While corticosteroids have an undeniable place in the control of acute flares, their systemic side effects are substantial, and it is well established that they should not be used for long-term maintenance because of toxicity. Besides, these therapies have a broad effect on the immune system. The impairment of the immune system predisposes the patients to opportunistic infections, malignancies, and metabolic disorders. Thus, the constraints being enumerated necessitate the presentation of safer, effective, and more patient-friendly options.[9]

Emergence of targeted therapies and the rationale for JAK inhibition

Novel targeted therapies are now being designed to target specific implicated molecular pathways in the pathogenesis of UC. One such promising class is the JAK inhibitors, thereby opening a new frontier in GI pharmacotherapy. The JAK-STAT pathway is important for pro-inflammatory cytokines signaling implicated in immune dysregulation in UC, including interleukins (IL-2, IL-6, IL-12, IL-23), interferon-γ, and others. These small molecules, when blocking enzymes just termed JAK, therefore, block cytokine signaling: simultaneously in the cell, so working in a more general fashion-than the monoclonals, which are designed to target a specific cytokine. Furthermore, JAK inhibitors are orally administered and thus enhance convenience and adherence of patients. Their rapid onset of action, non-immunogenic nature, and ability to curb inflammation through multiple pathways make them attractive contenders for consideration in

refractory or intolerant subjects to conventional or biologic therapies. Thus, inhibiting JAK falls in line with the present traction toward precision medicine in UC, where treatment is tailored according to the severity of disease, patient attributes, and the goals of therapy.[10,11]

Janus Kinase (JAK) Pathway: A therapeutic target

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway constitutes a very important intracellular signaling mechanism that controls immune function, inflammation, cell growth, differentiation, and survival. It is implicated in many different autoimmune and inflammatory disorders, including ulcerative colitis (UC). Hence, targeting this pathway is considered an attractive method of fighting immune-mediated inflammation present in UC.

The Janus kinase family consists of four cytoplasmic tyrosine kinases, namely JAK1, JAK2, JAK3, and TYK2 (Tyrosine Kinase 2). They represent the crucial molecules of the JAK-STAT signaling pathway responsible for activating and mediating the biggest array of cytokines and growth factors. Structurally similar but functionally distinguishable, each member influences different facets ranging from immune regulation, hematopoiesis, and inflammatory response.[12]

1. Structural Features of JAKs

All JAKs share a conserved multi-domain architecture with the following key components:

Domain	Function
FERM Domain (N-terminal)	Cytokine receptor subunits bind here, which act to anchor JAK to the receptor.
SH2-like Domain	Helps to stabilize the receptor interaction and to determine signal specificity.
Pseudokinase Domain (JH2)	Regulates the kinase activity of the adjacent domain (auto-inhibitory control)
Tyrosine Kinase Domain (JH1)	Catalytic domain responsible for phosphorylation of tyrosine residues on target proteins, including STATs.[13]

"Janus," in actuality, is named after the two-faced Roman god, symbolizing the presence of both kinase and pseudokinase domains in JAK proteins.

2. Classification of JAK Family Members

JAK	Gene	Expression	Cytokine Receptors Associated	Primary Functions
JAK1	*JAK1*	Ubiquitous	IL-2, IL-4, IL-6, IL-10, IL-15, IFN-α, IFN-γ, IL-22	Central role in inflammatory signaling; pairs with other JAKs to mediate pro-inflammatory cytokines.
JAK2	*JAK2*	Widely expressed	IL-6, IL-12, EPO, GM-CSF, TPO, GH	Critical for hematopoiesis (e.g., erythropoiesis); mutations associated with myeloproliferative disorders.
JAK3	*JAK3*	Hematopoietic cells	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 (γ-chain cytokines)	Immune cell development, especially T and NK cells; JAK3 defects cause SCID (Severe Combined Immunodeficiency).
TYK2	*TYK2*	Ubiquitous	IL-12, IL-23, IFN-α, IL-10, IL-6	Bridges type I interferon and IL-12/23 signaling; plays a role in autoimmunity and antiviral defense.[14,15]

Mechanism of the JAK-STAT pathway

The JAK-STAT pathway is said to be a direct and quick transmission of a signal from the cytomembrane to the nucleus that is initiated by cytokines, growth factors, or interferons, ultimately leading to the direct regulation of gene expression, bypassing second messengers. The sequence of mechanism can be briefly enumerated as follows

Step 1: Cytokine Binding and Receptor Dimerization

The signaling occurs when a cytokine (IL-6, IFN-γ, IL-12) binds to its specific transmembrane cytokine receptor residing in an inactive state on the cell surface. Most cytokine receptors consist of two or more subunits that associate with a specific Janus Kinase (JAK) individually. Cytokine binding induces conformational change and dimerization (or rearrangement) of receptor subunits,thus bringing the JAKs associated with each other into very close proximity.[16]

Step 2: JAK Activation via Trans-Phosphorylation

In close proximity, the JAK kinases (JAK1, JAK2, JAK3, or TYK2) trans-phosphorylate each other by one of the JAK kinases phosphorylating tyrosine residues on the other JAK kinase, which mutually activates them and allows them to further phosphorylate specific tyrosine residues on the cytoplasmic tails of the cytokine receptor itself.

Step 3: Recruitment of STAT Proteins

These newly phosphorylated tyrosine residues on the receptor act as docking sites for the Signal Transducers and Activators of Transcription (STATs). SH2 domains of particular STATs can recognize and attach to these phosphotyrosines. Recruitment of different STAT isoforms (STAT1 to STAT6) depends on the cytokine involved.[17]

Step 4: Phosphorylation and Dimerization of STATs

Upon attachment, the JAKs phosphorylate the receptor-bound STATs on essential tyrosine residues. This phosphorylation aids in the dimerization of the STATs—commonly as homodimers (e.g., STAT3–STAT3) or heterodimers (e.g., STAT1–STAT2). The STAT dimers then undergo conformational changes, which are required for their entry into the nucleus.

Step 5: Nuclear Translocation of STATs

Once phosphorylated, STAT dimers enter the nucleus through nuclear pores. Inside the nucleus, STAT dimers bind to specific DNA response elements located at the promoters of target genes to commence or repress transcription. The genes involved bring forth cellular functionalities covering a wide range, such as inflammation, cell proliferation, survival, differentiation, and immune regulation.[18]

Step 6: Negative Feedback Regulation

To avoid uncontrolled signaling, the pathway is so far prevented by several inhibitory feedbacks such as:

- **Suppressor of Cytokine Signaling (SOCS):-** It binds to JAKs or receptors to impede further signaling.
- **Protein Inhibitor of Activated STATs (PIAS):-** It inhibits STAT activity in the nucleus.
- **Protein Tyrosine Phosphatases (PTPs):-** They dephosphorylate JAKs and STATs.

This negative control makes sure that the response lasts for only a brief period and is tightly controlled so that no autoimmunity or excessive inflammation can occur.[19]

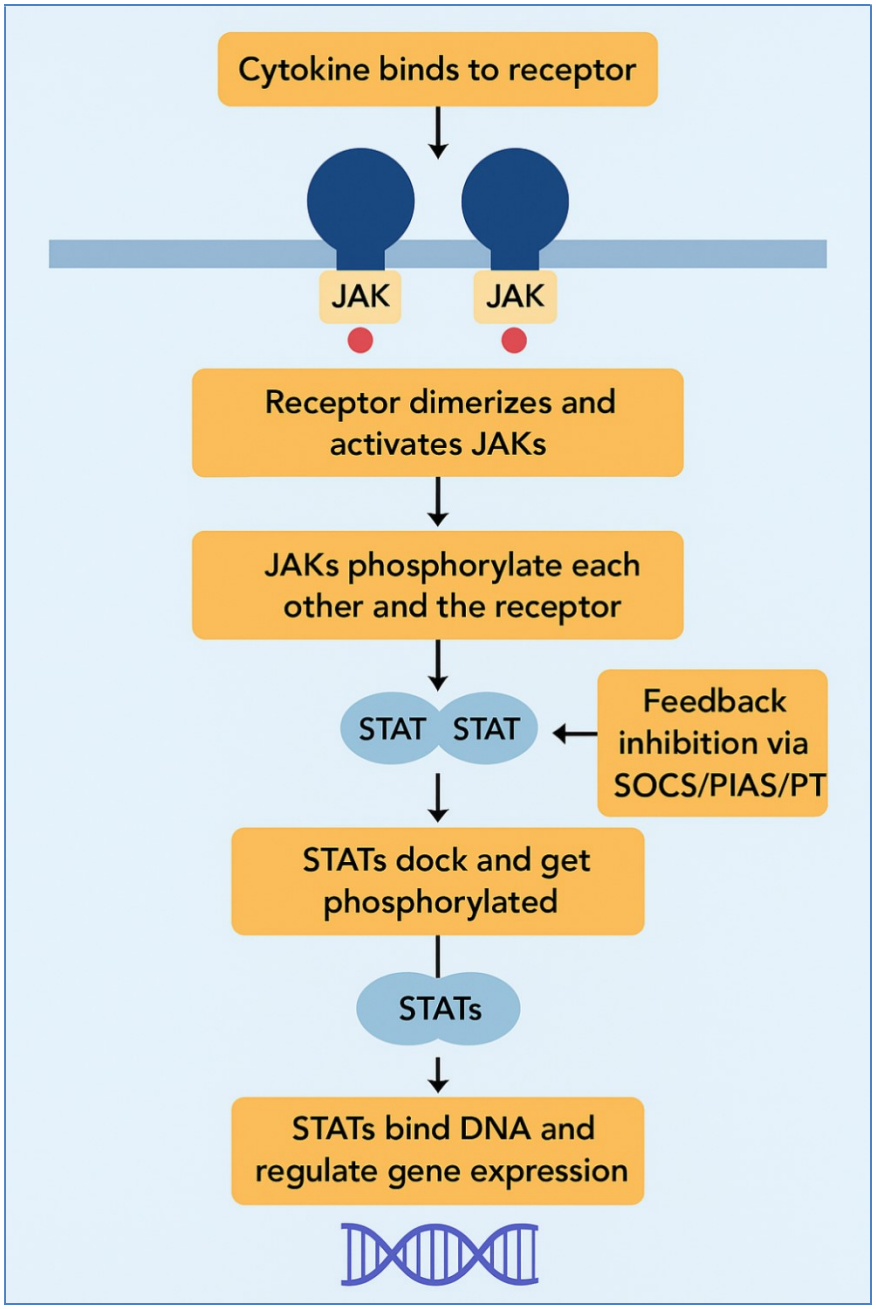

Figure 1 : Mechanism of JAK-STAT Pathway

Pathogenic contribution of the JAK-STAT pathway in ulcerative colitis

The JAK-STAT pathway is known to play an important role in effectuating inflammatory and immune responses in ulcerative colitis (UC). Chronic mucosal inflammation in UC is driven by dysregulated cytokine signaling that perpetuates immune cell activation and epithelial barrier dysfunction. JAKs mediate phosphorylation of receptor-associated kinases for many pro-inflammatory cytokines, such as interleukins IL-6, IL-2, IL-7, IL-12, IL-21, IL-23, and IFN-γ. Following cytokine binding, trans-phosphorylation leads to the activation of JAKs associated with the receptor (including JAK1, JAK2, JAK3, and TYK2), which then phosphorylate STAT transcription factors. Phosphorylated STAT molecules dimerize and move into the nucleus, where they bind to DNA to regulate genes that promote cell proliferation, survival, differentiation, and pro-inflammatory mediator production.[20]

In UC, JAK-STAT overactivation leads to excessive T-helper cell responses (particularly Th1 and Th17 lineages), increased secretion of inflammatory mediators, and recruitment of neutrophils and monocytes into the colonic mucosa. Therefore, this causes apoptosis of epithelial cells, disruption of the intestinal barrier, and persistence of inflammation in UC. Increased phosphorylation of STAT3 has been detected in UC patients' intestinal biopsies and correlated with the disease severity. Also, the IL-23/Th17 axis, which depends mostly on JAK2 and TYK2 signaling, is massively toggled in active UC and plays a role in sustaining chronic inflammation. Thus, the JAK-STAT pathway forms a central node integrating a myriad of inflammatory signals, putting it in a position to be specifically targeted for therapeutic intervention so as to restore the immune balance and mucosal healing in UC.[21]

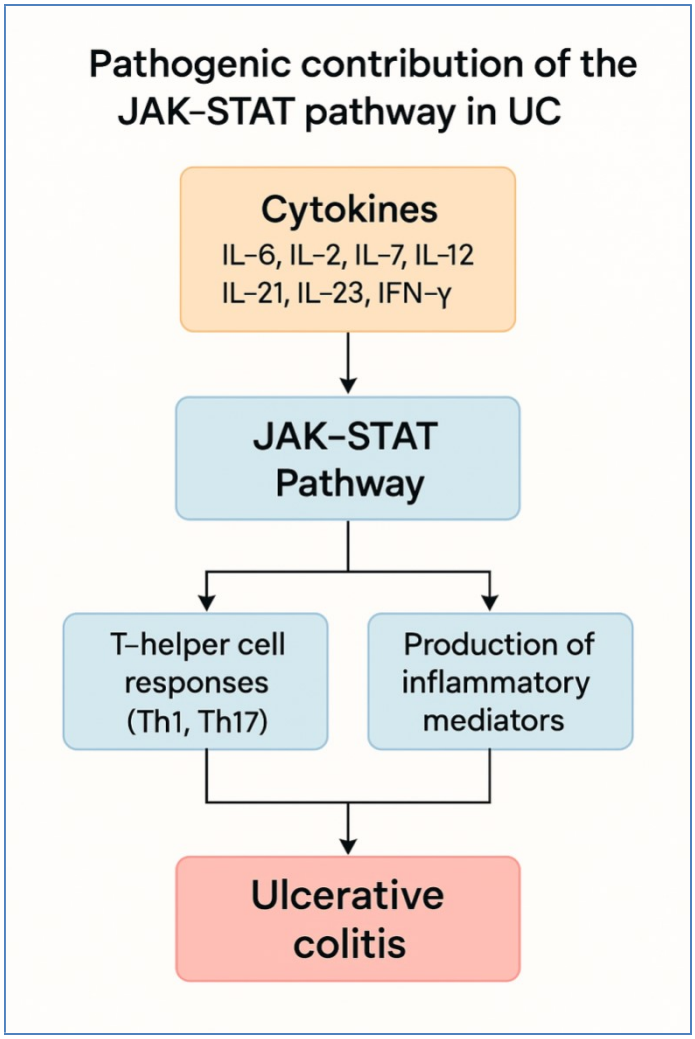

Figure 2 : Pathogenic Contribution Of The Jak-Stat Pathway In Ulcerative Colitis

Overview of JAK Inhibitors

Being small molecules, small-molecule inhibitors specifically block the kinase activity of one or more JAKs (JAK1, JAK2, JAK3, TYK2), thus inhibiting the JAK-STAT signal transduction. This targeted interference modulates immune and inflammatory responses, with a large emphasis being placed on their role in the therapy of various autoimmune diseases, such as ulcerative colitis (UC).[22]

Unlike biologic agents that target extracellular cytokines or receptors, JAK inhibitors act within cells to prevent STAT protein phosphorylation and thereby block the transcription of pro-

inflammatory genes. This allows them to exert a broad suppressive action on cytokine signals simultaneously, especially those propagated by γ-chain cytokines (e.g., IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) and inflammatory mediators like IL-6, IL-12, and IL-23 implicated in UC pathogenesis.

Several JAK inhibitors have been developed and validated for various autoimmune diseases. Tofacitinib (pan-JAK inhibitor with preference toward JAK1 and JAK3), in the context of UC, was the first JAK inhibitor to receive approval for moderate to severe UC. Other drugs like Upadacitinib (selective JAK1 inhibitor) and Filgotinib (selective for JAK1 as well) are in late clinical development or have already been approved for particular inflammatory conditions while being tested for UC.

One prime advantage of JAK inhibitors is that they are administered orally, have a rapid onset of action, and can modulate more than one inflammatory pathway. However, due to safety concerns such as infections (including herpes zoster), thromboembolic events, and changes in lipid profile, monitoring of patients should be intensified, and patient selection should be performed judiciously. All in all, JAK inhibitors present an exciting novel dimension in UC management as a means for effective and convenient inflammation control via targeted immune modulation.[23,24]

Mechanism of Action of JAK Inhibitors

1. Interruption of Cytokine Signaling at the Receptor Level

Cytokines bind with their respective transmembrane receptors, and this is the initial point of the activation of the JAK-STAT signaling pathway. Cytokine receptors do not have intrinsic kinase activities; instead, JAKs (JAK1, JAK2, JAK3, TYK2), with which they are closely associated, carry out signal transduction. Dimerization of the receptors occurs after cytokine binding, thus bringing the associated JAKs in close proximity with each other to be phosphorylated and activated. JAK inhibitors interfere at this initial step, hence prevent phosphorylation of the JAKs and block the propagation of the signal from the receptor.[25]

2. Prevention of STAT Phosphorylation and Dimerization

Activated JAKs generally phosphorylate certain tyrosine residues on the receptor, which serve as docking sites for STAT (Signal Transducer and Activator of Transcription) proteins. STATs bind to these phospho-tyrosines and are then phosphorylated by JAKs, which enables dimerization of the STAT proteins. The dimers then migrate to the nucleus to promote transcription of certain genes involved in inflammation, immune cell proliferation, and survival. This gene transcription is halted by JAK inhibitors, which prevent the activation of STATs that would otherwise promote inflammation in diseases like ulcerative colitis.[26]

3. Inhibition of Multiple Pro-inflammatory Cytokines Simultaneously

One important advantage of JAK inhibitors is their ability to block multiple cytokine pathways simultaneously. JAK1 and JAK3 are involved in signaling through the common gamma-chain cytokines such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, all of which are implicated in lymphocyte function. JAK2 mediates signals for other cytokines, for instance, IL-6, GM-CSF, and erythropoietin. JAK-inhibitors by means of selective or broad selective mechanism can suppress a variety of inflammatory mediators leading to the control of UC-related inflammation.[27]

4. Modulation of Innate and Adaptive Immune Responses

JAK inhibitors keep adaptive immune mechanisms suppressed, such as those acting through T and B cell functions, and they also control innate immune responses. Inhibition of IL-6 and interferon signaling decreases macrophage and dendritic cell activation, which are important for initiating and sustaining inflammation in the colon. Hence, its JAK inhibition being a double immunosuppressant

effect serves as a great treatment choice for autoimmune conditions with multifactorial immune dysregulation, such as ulcerative colitis.[28]

5. Rapid Onset of Action and Reversibility

With monoclonal antibodies, longer half-lives mean any adverse effect can take a great time, probably weeks, to clear. On the other hand, JAK inhibitors are small molecules given orally with rather short half-lives. This pharmacokinetic property allows for a quicker onset of clinical effect and better reversibility in the case of adverse effects or infections. For example, if someone feels they are having an adverse event, in the case of JAK inhibitors, they can just stop the drug, whereas with biologics, the effects tend to linger. These properties make their dosing more safety conscious and hence more flexible to tailor to patients for treatment of UC.[29]

Classification: PAN-JAK inhibitors vs. selective JAK inhibitors

JAK inhibitors are generally classified on the basis of their selectivity for one, some, or all of the four known JAK isoforms: JAK1, JAK2, JAK3, and TYK2.

- **Pan-JAK inhibitors**: Inhibiting multiple JAK isoforms with pan-JAK inhibitors such as tofacitinib (mainly JAK1 and JAK3 with some JAK2 activity) results in broader cytokine signaling suppression. While this confers potent anti-inflammatory effects, it can give rise to adverse effects, including infections and hematological abnormalities..
- **Selective JAK inhibitors:** Selective JAK inhibitors such as upadacitinib and filgotinib are exactly that: they select an isoform, usually one identified as JAK1, for target, since it is more directly implicated in mediating inflammation in UC. Selectivity is thus thought to preserve the efficacy and decrease the off-target effects, rendering selectivity safer for patients.[30]

Pharmacokinetics and Pharmacodynamics of JAK inhibitors

Property	Tofacitinib	Upadacitinib	Filgotinib
Absorption	Rapid; Tmax ~1 hr	Tmax ~2–4 hrs	Tmax ~2–3 hrs
Bioavailability	~74%	High	Moderate
Half-life	~3 hours (short)	~9–14 hours	~6 hours (active metabolite longer)
Metabolism	Hepatic (CYP3A4)	CYP3A4 and CYP2D6	CYP3A4
Excretion	Feces and urine	Feces > urine	Renal and fecal
Pharmacodynamics	Dose-dependent inhibition of JAK pathways; rapid onset	More selective for JAK1 → fewer off-target effects	JAK1 inhibition maintains IL-6, IL-2 blockade with fewer hematologic effects [31]

Comparison with Other Biologics and Small Molecules

Feature	JAK Inhibitors	Biologics (e.g., Anti-TNF, Anti-IL-12/23)	Other Small Molecules (e.g., S1P modulators)
Mode of Administration	Oral	Intravenous / Subcutaneous	Oral
Target	Intracellular (JAK enzymes)	Extracellular cytokines/receptors	Sphingosine-1-phosphate (S1P) receptors
Onset of Action	Rapid (days to weeks)	Moderate (weeks)	Moderate
Immunogenicity Risk	Low (non-protein drug)	High (protein-based, risk of ADA)	Low
Monitoring Requirements	Lipids, CBC, liver enzymes	Anti-drug antibodies, infusion reactions	Heart rate, liver enzymes
Cost	Moderate to High	High	Moderate
Efficacy in Biologic Failures	Good (including post-anti-TNF failure)	Variable (depends on drug)	Under evaluation
Adverse Effects	Thrombosis, infections, lipid changes	Infusion reactions, infections	Bradycardia, macular edema
Examples	Tofacitinib, Upadacitinib, Filgotinib	Infliximab, Ustekinumab, Vedolizumab	Ozanimod[32]

Safety profile

Due to their immunosuppressive effects, JAK inhibitors' safety profile while in the treatment of UC needs to be kept under view. An unfortunate adverse effect is infection, with herpes zoster being the most common one. This disease becomes more frequent with aging, in addition to certain ethnicities like Asians. Opportunistic infections such as tuberculosis and fungal infections are bothersome considerations; hence, screening for TB and hepatitis B/C takes precedence before starting treatment with these drugs, with vaccinations administered accordingly. Another major safety concern would be the increased risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) following usage of these agents at high dosages, for example, tofacitinib. Hence, the FDA highlighted a warning about a possible raise in the signal of major adverse cardiovascular events and malignancies in patients receiving prolonged treatment with JAK inhibitors.

Since these lipid alterations are so frequent, any further changes in the level are usually expected to stabilize, with no clearculpability placed upon greater cardiovascular events, although testing lipid levels from time to time is still advised. Blood side effects-such as neutropenia, lymphopenia, or anemia-can also be observed, which in turn means that full blood counts should be arranged from time to time. In very rare cases, gastrointestinal perforations have been reported-with the highest risk being when JAK inhibitors were used with NSAIDs or corticosteroids. Because of these potential risks, selecting patients for treatment carefully and monitoring them throughout the course of therapy is, therefore, imperative, particularly in patients with pre-existing cardiovascular risk, past history of malignancy, or immunosuppression.[33,34]

Patient selection and practical considerations for JAK inhibitors in ulcerative colitis

The prescription of Janus kinase (JAK) inhibitors for ulcerative colitis must be based on patient selection criteria concerning factors such as

disease severity, treatment history, comorbidities, and risk stratification. JAK inhibitors like tofacitinib have so far been mostly given to adult patients with moderate to severe ulcerative colitis who have demonstrated an inadequate response to or loss of response to, or intolerance of conventionally used therapies such as corticosteroids or thiopurines; or biologics such as anti-TNF agents or integrin antagonists. Besides, JAK inhibitors can be a viable choice for patients who prefer oral therapies and those who suffer from needle phobia as they are administered orally.

However, careful assessment is required in patients with risk factors for venous thromboembolism, cardiovascular disease, history of malignancy, or chronic/recurrent infections. The elderly, those over 65, need to be watched more closely because of their increased likelihood of adverse events such as infections or cardiovascular accidents. Baseline tests should include complete blood count, lipid profile, liver function tests, and screening tests for tuberculosis, hepatitis B, and hepatitis C. Follow-up assessments should be done on a periodic basis after starting the treatment.[35,36]

In practical ways, shared decision-making is paramount. Patients must be informed about the threats and benefits, including possible adverse events and the need for adherence to follow-up. Contraceptive counseling is recommended for any woman of childbearing age because safety data in pregnancy are sparse. All in all, when advised prudently in well-chosen patients, JAK inhibitors stand as an efficacious therapeutic armament. This recommendation is made in conjunction with the principles of individualized care and close monitoring.

Position of JAK inhibitors in treatment guidelines for ulcerative colitis

JAK inhibitors are evolving up the ranks into major clinically relevant treatment guidelines for ulcerative colitis (UC) because of efficacious results, oral applicability, and rapid onset of action. Based on the guidelines laid down by the ACG and ECCO, JAK inhibitors, particularly tofacitinib, are recommended toward moderate to severe UC cases that develop inadequate response, loss of response, or intolerance to anti-TNF therapy, or with other biologics.

They are not usually given first-line treatments because of concern about safety, particularly infections, thrombosis, and cardiovascular events. However, they have been placed as second- or third-line agents, once conventional immunosuppressants and biologics have failed. JAK inhibitors may also be an early consideration in those with fast-moving disease or when the patient prefers oral medication.

According to the AGA 2023 Update, JAK inhibitors are recognized as worthy alternatives to biologics, with an emphasis on their short time to response, which may facilitate symptom control during an acute flare. However, an individualized risk assessment is stressed, especially for older adults, smokers, and those with cardiovascular or malignancy risks.

In brief, the treatment guidelines acknowledge JAK inhibitors as a valid option in the treatment algorithm of ulcerative colitis, especially after failure of conventional agents but also emphasizing careful patient selection and ongoing risk-benefit evaluation.[37,38]

Challenges and limitations of JAK inhibitors in ulcerative colitis

Despite the considerable promise shown by Janus kinase (JAK) inhibitors for the management of ulcerative colitis (UC), certain issues and challenges preclude their widespread use and longer application of use:

1. **Safety Concerns**: Perhaps the most important limitation lies in the safety profile of JAK inhibitors. Clinical trials and post-marketing data have demonstrated an increased risk of serious infections (e.g., herpes zoster), venous thromboembolism (VTE), major adverse cardiovascular events (MACE), and malignancies. The greatest risks are posed to older adults and patients already at risk for such conditions. Such risks require a careful

selection of patients prior to therapy, thus limiting drug use in certain populations.

2. **Regulatory Warnings and Restrictions**: Various regulatory agencies have issued warnings on the use of JAK inhibitors, particularly tofacitinib, and about its use in patients at risk. The caution has made physicians more cautious about prescribing the drugs and reluctant to start treatment.
3. **Lack of Long-Term Safety Data**: Short- and medium-term efficacy data have been fairly solid, but uncertainty over whether a response is maintained over time, or safety, remains a real concern. More real-world evidence and longitudinal studies are perhaps required to evaluate whether certain risks arise cumulatively over time.
4. **Cost and Access**: AK inhibitors are expensive, and in many healthcare systems, insurance coverage or national guidelines govern access. This limits the availability of these medicines to wider patient populations, especially in low- and middle-income countries
5. **Patient-Specific Factors**: Age, comorbidities, prior biologic exposure, and genetic predispositions could reduce biological effect and increase susceptibility to adverse effects of JAK inhibitors-an important need for personalized medicine, yet, this poses a real challenge to treatment algorithms.
6. **Risk of Treatment Failure and Relapse**: Not all patients respond adequately to initial therapies (primary non-response). Others lose responses over time to the treatment (secondary loss of response) and must be shifted to alternative therapies.
7. **Therapeutic Positioning**: There is a wide array of available therapies: anti-TNFs, anti-integrins, and anti-IL agents. The exact positioning of JAK inhibitors in the treatment sequence is still up for debate, considering their perceived safety trade-offs.[39,40]

Future directions and ongoing research in JAK inhibitors for ulcerative colitis

Highly promising avenues of research and development are currently, and rapidly, paving improvements in efficacy, safety, and precision in treatment via the JAK-inhibitor field for UC. These include novel agents, more cutting-edge targeting of patients, and new mechanisms:

1. **Development of Next-Generation Selective JAK Inhibitors:** A central focus is to create highly selective JAK inhibitors (e.g., JAK1- or TYK2-selective agents) to balance therapeutic efficacy with minimal off-target effects and adverse events such as thromboembolism and infections. Upadacitinib (JAK1 selective) and deucravacitinib (TYK2 selective) are agents undergoing clinical trials for IBD with promising signals for safety and efficacy.
2. **Biomarker-Guided Precision Therapy**: Studies are underway for biomarkers (e.g., profiles of JAK pathway activation, genetic polymorphisms) to identify patients who may benefit the most from JAK inhibitors and those at an increased risk of side effects. This paves the way for personalized treatment strategies with improved outcomes and reduction of harm.
3. **Combination Therapies:** Studies are focusing on combo regimens involving JAK inhibitors among other biologics or immunomodulators to boost treatment responses or address refractory UC. In this respect, staggered or synergistic therapies may focus on maximizing remission and mucosal healing without dramatising immunosuppression.[41,42]
4. **Novel Routes of Administration:** Topical or locally acting JAK inhibitors (a.k.a. gut-selective agents) are being looked at with the idea that concentrating in the gastrointestinal tract may provide therapeutic benefits with lesser systemic exposure and toxicity. These oral formulations are currently in early-phase investigation.
5. **Real-World Data and Long-Term Safety Monitoring:** Several post-marketing surveillance programs and registry studies are under way to assess the long-term safety, comparative effectiveness, and quality-of-life changes in real-world patient cohorts. Such data are very crucial to update guidelines and treatment algorithms.

6. **Expansion of Indications**: Besides its use in UC, JAK inhibitors are being considered for Crohn's disease, pouchitis, and extraintestinal manifestations of IBD such as arthritis or dermatologic complaints. Favorable results in these disease states could broaden their use for the management of IBD.
7. **Head-to-Head Comparative Trials:** There are ongoing and planned studies comparing JAK inhibitors with other biologics like anti-TNFs, anti-integrins, and IL-23 inhibitors. The goal of these trials is to establish relative efficacy, duration of response, and safety to more appropriately position JAK inhibitors in treatment algorithms.[43,44,45]

Conclusion

JAK inhibitors are a novel and effective remedy for UC, allowing patients with moderate to severe disease to be treated orally. These small molecules target the intracellular JAK-STAT signaling pathway that is central to pro-inflammatory cytokine activity in UC. Clinical trials have evidenced induction and maintenance of remission, particularly in patients resistant to conventional therapies or biologics. Thus, agents such as tofacitinib, upadacitinib, and filgotinib have enriched the portfolio of therapeutic options with rapid action onset, non-injectable routes of administration, and opportunities for personalized therapy. Yet, concerns about safety-have begun to arise-and these include infections, thromboembolic events, and long-term immunosuppression-along with the need for vigilant patient selection and monitoring. Augmented by ongoing research into newer selective inhibitors and head-to-head comparisons with other biologics, their role will become surer. In sum, JAK inhibitors are set to become the next big thing in gastrointestinal pharmacotherapy with potentially epoch-making implications for treatment strategies in UC.

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