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Optimal use and cycling strategies of Janus kinase inhibitors in ulcerative colitis: current evidence and clinical implications from the KASID Guidelines Task Force Team

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Janus kinase (JAK) inhibitors are an important treatment option for ulcerative colitis, providing rapid onset of action, oral administration, and efficacy even after biologic failure. The 3 approved agents—tofacitinib, filgotinib, and upadacitinib—differ in JAK isoform selectivity, leading to clinically meaningful differences in efficacy and safety. Evidence from network meta-analyses, clinical trials, and real-world studies consistently shows that upadacitinib provides the highest efficacy for induction and maintenance of remission, whereas filgotinib demonstrates the most favorable safety profile. The strong efficacy of upadacitinib and tofacitinib is particularly relevant in patients with severe disease, including acute severe ulcerative colitis, and upadacitinib maintains high efficacy regardless of prior advanced therapy exposure. JAK inhibitors also benefit extraintestinal manifestations. Although risks such as herpes zoster, serious infection, thromboembolism, and major cardiovascular events differ among agents, long-term data suggest generally acceptable safety when used appropriately. Intraclass JAK-to-JAK cycling is feasible, with about half of patients achieving steroid-free clinical remission in retrospective cohorts. Based on mechanistic, clinical, and real-world evidence, filgotinib may be a first-line option for patients with lower disease activity or when safety is a priority, whereas upadacitinib or tofacitinib may be preferred in higher disease activity. Strategically selecting agents may improve durability and outcomes. (**Intest Res 2026;24:27-37**)

Key Words: Ulcerative colitis; Janus kinase inhibitors; Tofacitinib; Filgotinib; Upadacitinib

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon and rectum, associated with relapsing mucosal inflammation, persistent symptoms, and reduced quality of life.[1,2] Contemporary therapeutic strategies follow a treat-to-target approach, aiming for symptom relief as well as normalization of inflammatory biomarkers and achievement of endoscopic healing.[3] Despite advances in biologics and small-molecule drugs, many patients continue to experience inadequate response, drug intolerance, or disease progression, underscoring the need for treatments that are more effective, faster acting, and adaptable to clinical context.

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway integrates diverse cytokine signals and plays a central role in amplifying mucosal inflammation in UC.[4] Therefore, pharmacologic inhibition of this pathway has become an important therapeutic approach. Three oral JAK inhibitors—tofacitinib, filgotinib, and upadacitinib—are currently approved for UC. These agents differ in their selectivity for individual JAK isoforms, resulting in distinct pharmacologic and therapeutic profiles.[5]

These mechanistic differences translate into clinically relevant variations in efficacy and safety.[5] Understanding them is essential for individualizing therapy based on the clinical phenotype, treatment history, extraintestinal manifestations (EIMs), comorbidities, and anticipated safety risks of patients.

Given the highly heterogeneous disease course of UC, treatment adjustments during JAK inhibitor therapy are common. When primary or secondary loss of response, adverse events, or intolerance occurs, cycling between agents should be considered. Emerging comparative studies and growing real-world evidence now support the clinical relevance of JAK-to-JAK cycling based on the mechanistic distinctions among these JAK inhibitors.

This review, conducted by the Guidelines Taskforce Team of the Korean Association for the Study of Intestinal Diseases (KASID), aims to synthesize mechanistic, clinical, and real-world evidence to outline the optimal positioning of each JAK inhibitor in UC and to offer an evidence-based framework for cycling approaches in clinical practice.

JAK ISOFORM SELECTIVITY

The 3 JAK inhibitors approved for treating UC—tofacitinib, filgotinib, and upadacitinib—differ primarily by their selectivity for individual JAK isoforms, and these pharmacologic distinctions largely explain their variable efficacy and safety.[5] Tofacitinib is a nonselective (pan-JAK) inhibitor that primarily targets JAK1 and JAK3 and partially inhibits JAK2.[6,7] Its broad inhibitory profile produces potent suppression of diverse inflammatory pathways, but dose-dependent cytopenias and elevated lipid levels—effects associated with pan-JAK inhibition—may occur.[8] Upadacitinib is a highly selective JAK1 inhibitor with minimal activity against JAK2 and JAK3. Filgotinib is also JAK1-selective and demonstrates an even higher JAK1 selectivity ratio than that of upadacitinib.[9] These features may reduce JAK-related off-target effects and improve tolerability.

CONSIDERATIONS FOR AGENT SELECTION

1. Comparative Efficacy of JAK Inhibitors

Comparing the efficacy of the 3 approved JAK inhibitors—tofacitinib, filgotinib, and upadacitinib—is vital for defining their therapeutic roles in UC. While no head-to-head trials have directly compared these agents, network meta-analyses and real-world studies provide consistent insights into their relative effectiveness.

In a network meta-analysis by Burr et al.,[10] upadacitinib ranks first for clinical remission in anti-tumor necrosis factor (TNF)-naive and anti-TNF-experienced patients, outperforming nearly all other advanced therapies. It also ranks second to infliximab for endoscopic remission. Among the JAK inhibitors, the induction rankings for clinical and endoscopic remission are upadacitinib, followed by tofacitinib and then filgotinib. Lasa et al.[11] conducted a network meta-analysis, showing that upadacitinib demonstrates the highest efficacy for inducing clinical remission, although it has the least favorable adverse-event profile. Zhang et al.[12] conducted another network meta-analysis of multiple advanced therapies (excluding filgotinib), showing that upadacitinib ranks first for inducing efficacy—including clinical response, clinical remission, and endoscopic improvement—and also ranks first for maintenance efficacy in clinical remission and endoscopic improvement. Based on the surface under the cumulative ranking curve values, upadacitinib ranks higher than tofacitinib across all evaluated domains. More recent network meta-analyses report similar findings.[13]

Real-world studies on the efficacy of JAK inhibitors for UC continue to grow. In a multicenter retrospective study by Nogami et al.,[14] which included outcomes from 98 patients treated with filgotinib and 70 treated with upadacitinib, upa-

dacitinib demonstrates higher week-8 clinical response (71.4% vs. 55.1%; adjusted risk ratio [RR], 1.40; 95% confidence interval [CI], 1.09–1.80) and higher clinical remission (65.7% vs. 46.9%; adjusted RR, 1.54; 95% CI, 1.16–2.05). Subgroup analysis reveals that among bio-exposed patients with prior biologic therapy, upadacitinib produces higher rates of clinical response and clinical remission than those of filgotinib. In another recent propensity score–matched analysis, among patients with prior anti-TNF exposure, upadacitinib achieves higher rates of steroid-free clinical remission than those of tofacitinib or filgotinib.[15] A single-center real-world study comparing tofacitinib and filgotinib reports a higher week-8 clinical response with tofacitinib (72.2%) than with filgotinib (48.5%). Furthermore, among patients without a week-4 clinical response, the week-8 clinical remission rate is 38.5% with tofacitinib but 0% with filgotinib ($P=0.011$).[16]

Recently, a large multicenter real-world study compared the effectiveness of all 3 JAK inhibitors in active UC.[17] This retrospective cohort comprised 228, 215, and 159 patients treated with upadacitinib, filgotinib, and tofacitinib, respectively. The primary endpoints were clinical remission at weeks 10, 26, and 58, and at the most recent follow-up. Propensity score matching was employed to generate 3 pairwise matched cohorts, in which upadacitinib generally shows superior efficacy over filgotinib and tofacitinib. Upadacitinib maintains response rates above 70%, even in patients previously exposed to other JAK inhibitors. Analyses of treatment-outcome risk factors reveal that a higher number of prior advanced therapies is associated with reduced efficacy of filgotinib and tofacitinib.[17] A prospective study reports similar findings: among patients previously treated with anti-TNF agents, upadacitinib achieves clinical remission rates in 69.2% and 81.5% of patients at weeks 4 and 8, respectively. Among 9 patients previously exposed to tofacitinib, 7 (77.8%) achieved clinical remission at week 8.[18]

Additionally, a meta-analysis reveals that tofacitinib is more effective in biologic-naive patients than in biologic-exposed patients.[19] Filgotinib similarly demonstrates diminished treatment effectiveness in patients with prior biologic or JAK inhibitor exposure. In a Japanese multicenter retrospective study, filgotinib discontinuation is more frequent in patients with previous biologic or JAK inhibitor use than in those without such a history.[20] In a *post hoc* analysis of the SELECTION trial, the efficacy of filgotinib declines with an increasing number of previously failed biologics.[21]

While head-to-head trials are needed to determine absolute superiority, and network meta-analysis rankings should be interpreted with caution, multiple analyses consistently indicate high efficacy of upadacitinib. Among JAK inhibitors, upadacitinib is the most effective, and unlike tofacitinib and filgotinib, its efficacy is less affected by prior biologic or JAK inhibitor exposure.

2. Special Clinical Situations

1) Acute Severe Ulcerative Colitis

For patients with acute severe ulcerative colitis (ASUC) who are unresponsive to intravenous (IV) corticosteroids, current guidelines recommend infliximab or cyclosporine as second-line rescue therapy.[22] Recently, JAK inhibitors—owing to their rapid onset of action—have gained attention as potential rescue options for ASUC,[23] with tofacitinib and upadacitinib considered the most plausible therapeutic candidates.

Tofacitinib reaches peak plasma levels within 1 hour after dosing and can induce clinical improvement by day 3 of oral therapy, making it suitable for ASUC, where rapid therapeutic effects are essential.[24,25] A systematic review of case reports and cohort studies of tofacitinib use in ASUC shows 30-, 90-, and 180-day colectomy-free survival rates of 85%, 86%, and 69%, respectively.[26] In a pooled cohort of 42 patients from case reports, 69% achieve clinical remission at the end of follow-up, and 55% of these reach endoscopic remission.[26] In the GETAID cohort (n=55) evaluating tofacitinib for refractory severe UC, 49 patients exhibit a history of infliximab failure, and 19 have prior cyclosporine exposure. At week 6, 60% of patients achieve a clinical response, and 45.5% achieve clinical remission. At week 14, 23 of 55 patients (41.8%) achieve a clinical response, and 34.5% achieve clinical remission.[27] The same GETAID study reports colectomy-free survival rates of 78.9% at 3 months and 73.6% at 6 months, suggesting favorable longer-term outcomes.[27] The 3-month colectomy-free survival rate is comparable to that reported with infliximab and cyclosporine.[28] In the TACOS trial, a randomized controlled study comparing tofacitinib 10 mg three times daily with placebo in patients with ASUC, tofacitinib shows significantly greater efficacy than that of the placebo at day 7 (odds ratio, 3.42; 95% CI, 1.37–8.48; $P=0.007$).[29] However, the tofacitinib dose used in this trial was higher than that typically used in clinical practice. While most treatment-related adverse events in the study are mild, this dosing regimen requires further evaluation to clarify its efficacy–safety balance.[29] Additionally, the TOCASU trial comparing tofacitinib with cyclosporine in steroid-refractory ASUC is currently ongoing (NCT05112263).

Upadacitinib, a selective JAK1 inhibitor, induces rapid clinical improvement, with a study reporting symptom reduction within a single day of treatment.[30] Its evidence base in ASUC remains smaller than that for tofacitinib; however, several case reports, case series, and small retrospective studies have been published. In a retrospective cohort of 25 patients, 24% underwent colectomy within 90 days, with no difference based on prior anti-TNF exposure.[31] Dalal et al.[32] examined upadacitinib as rescue therapy in 9 patients with ASUC and prior biologic exposure who failed IV corticosteroids. Among them, 1 patient required colectomy, while the others achieved clinical response and steroid-free clinical remission over 8–16 weeks of follow-up. Gilmore et al.[33] show that 6 patients—all previously exposed to infliximab—were administered upadacitinib after failing 3 days of IV corticosteroids, and only 1 patient required colectomy. A systematic review analyzing 11 studies involving 55 patients treated with upadacitinib for ASUC reports that most patients experience rapid and sustained improvement, with a 90-day colectomy rate of 16.3%.[34]

Comparative studies of JAK inhibitors in ASUC have also been conducted. For instance, Honap et al.[35] performed a multicenter retrospective analysis of 111 patients with ASUC, showing that upadacitinib demonstrates a higher response rate than that of tofacitinib between days 3 and 7 (84% vs. 54%; $P=0.02$), although response and remission rates are similar at days 98 and 182. Another multicenter retrospective study of 124 patients similarly reports no significant differences in outcomes between upadacitinib and tofacitinib.[36]

As evidence accumulates, attention shifts from demonstrating efficacy to determining the optimal placement of JAK within the ASUC treatment pathway. JAK inhibitors may be used earlier in the treatment algorithm for ASUC, potentially preceding infliximab or cyclosporine as rescue therapy, because they undergo rapid washout.[37] JAK inhibitors are fully cleared within 1–2 days of discontinuation, allowing immediate transition to infliximab or cyclosporine if therapy fails. Conversely, when infliximab is used first, a washout period may be required before starting an alternative rescue therapy.[37] Recent ASUC guidelines also suggest that JAK inhibitors may be considered for rescue therapy.[38,39] However, evidence supporting their use before anti-TNF agents or cyclosporine in ASUC remains limited. Therefore, such an approach should be used cautiously, and further dedicated studies are warranted.

2) Extraintestinal Manifestation

Anti-TNF agents effectively treat most EIMs and have long served as standard therapy. Although developed later, vedolizumab and ustekinumab show potential benefits for some EIM subtypes, but they are not yet supported as formal therapeutic options.[40] In contrast, evidence of the efficacy of JAK inhibitors against EIM emerged early in their use for inflammatory bowel disease (IBD) treatment.

In the OCTAVE trials evaluating tofacitinib for UC induction and maintenance, some patients with peripheral arthritis exhibited improved joint symptoms.[41] Similarly, in a retrospective cohort study of 112 patients with UC, 35 had baseline peripheral arthralgia, and by week 24, 26 patients (74.2%) showed symptomatic improvement and 14 (40%) achieved complete resolution.[42] A case report also reports improved axial and peripheral spondyloarthritis with combined tofacitinib and vedolizumab therapy.[43]

Case series and case reports show that tofacitinib is effective for erythema nodosum (EN) and pyoderma gangrenosum (PG).[44-46] Vavricka et al.[47] report STAT3 overexpression in EN and PG skin lesions on immunohistochemistry, supporting a mechanistic rationale for JAK inhibitor efficacy in these conditions.

Although limited, studies report tofacitinib use in patients with IBD-associated primary sclerosing cholangitis (PSC). Schregel et al.[48] conducted the first multinational, multicenter, retrospective study to evaluate tofacitinib in PSC-IBD. Of 43 patients with PSC-IBD treated with tofacitinib, 42 were analyzed as one was not administered tofacitinib for PSC-IBD treatment. Ninety-eight percent had prior biologic exposure, and of 21 patients with previous biliary interventions, only 2 required new endoscopic procedures during tofacitinib therapy. Liver stiffness remained stable, and only 1 of 38 patients (3%) developed cirrhosis during follow-up. Longer treatment duration was associated with reduced alkaline phosphatase levels. No serious adverse events were reported, and only 2 patients discontinued treatment for reasons unrelated to colitis, indicating a favorable safety profile.[48]

Upadacitinib is expected to be effective for EIMs. In a *post hoc* analysis of the induction and maintenance trials, upadacitinib improved EIMs, with week 52 resolution occurring in 66% of patients treated with 30 mg, 42% on 15 mg, and 24% in the placebo group.[49] Among patients with baseline peripheral or axial arthropathy, week 52 resolution was significantly higher with 30 mg versus placebo ($P=0.010$), while 15 mg showed numerically higher rates.[49] Case reports also report successful treatment of skin manifestations, including PG, with upadacitinib.[50,51]

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Filgotinib has no direct evidence supporting its use for EIMs in IBD. However, because it is approved for rheumatoid arthritis and effective in ankylosing spondylitis and noninfectious uveitis,[52-54] EIM benefit may be anticipated.

Although the overall evidence remains limited, data supporting JAK inhibitor use for EIMs continue to accumulate; JAK inhibitors can be considered a reasonable therapeutic option given their intrinsic efficacy.

3. Safety

Major adverse events associated with JAK inhibitors include infection, thromboembolism, cardiovascular adverse events, and malignancy.[8] In addition, JAK inhibitors are contraindicated during pregnancy.[55] Safety has been a major concern in their introduction into UC. In the ORAL Surveillance trial involving patients with rheumatoid arthritis, tofacitinib was linked to increased risks of thromboembolism, major adverse cardiovascular events (MACEs), opportunistic infections—including herpes zoster and tuberculosis— and cancers, including non-melanoma skin cancer, compared with anti-TNF therapy.[56] Owing to these safety signals observed in other diseases, safety has been prioritized in UC JAK inhibitor use. However, contrary evidence also exists. In a systematic review and meta-analysis of 42 studies with 813,881 patients with immune-mediated inflammatory diseases treated with either JAK inhibitors or anti-TNF agents, Solitano et al.[57] report that venous thromboembolism risk was slightly higher with JAK inhibitors, but serious infection, malignancy, or MACE did not differ significantly. A meta-analysis of 50 studies evaluating the efficacy and safety of JAK inhibitors for atopic dermatitis similarly reports no significant increase in serious adverse events, except for cutaneous lymphoma and anal cancer in a few reports; only 2 venous thromboembolism events were linked to upadacitinib.[58] *Post hoc* analysis of ORAL Surveillance shows no difference between tofacitinib and anti-TNF therapy in composite cardiovascular endpoints, including all ischemic cardiovascular events and heart failure. However, the overall cardiovascular risk was higher with tofacitinib 10 mg twice daily than with anti-TNF therapy, likely due to increased venous thromboembolism.[59]

Real-world evidence in IBD shows that JAK inhibitors have relatively favorable safety profiles. A Japanese real-world study of 46 patients with UC over 156 weeks reports no serious adverse events with tofacitinib treatment.[60] Sandborn et al.[61] report that over 4.4 years of data from phase 2, phase 3, and open-label long-term extension studies of tofacitinib (OCTAVE program), adverse event rates were similar to placebo, and serious infections and malignancies were infrequent. Except for a higher incidence of herpes zoster, the overall safety profile of tofacitinib was similar to that of anti-TNF agents. Across 9.2 years of follow-up in a pooled analysis of the OCTAVE induction and maintenance trials, the long-term extension study, and a randomized phase 3b/4 trial, tofacitinib showed incidence rates (IRs) of adverse events of special interest (AESIs) below 1 per 100 patient-years, except for herpes zoster (IR, 1.80; 95% CI, 1.37–2.32) and serious infection (IR, 3.24; 95% CI, 2.63–3.94).[62] In a multicenter retrospective study in Korea, tofacitinib shows an acceptable safety profile, while a post-marketing surveillance study reports only 2 AESIs among 106 patients, both of which were serious infections, comprising 1 case of an anal abscess and 1 case of cytomegalovirus colitis.[63,64]

Recent safety data for upadacitinib in UC come from the phase 3 U-ACTIVATE long-term extension study.[65] Patients (n = 467; 1,027.9 patient-years) who were administered consistent dosing were evaluated. Treatment-emergent adverse event rates were 238.5 and 233.4 per 100 patient-years for upadacitinib 15 mg and 30 mg, respectively. Serious adverse event rates were 11.7 and 12.5 per 100 patient-years. These findings suggest that upadacitinib has a favorable risk–benefit profile for treating moderately to severely active UC.[65]

Among JAK inhibitors, filgotinib generally has the most favorable safety profile. In an integrated analysis of the SELECTION trial and its long-term extension study (SELECTION LTE), filgotinib 200 mg showed a slightly higher incidence of herpes zoster than placebo, while rates of serious infection, thromboembolic events, and MACE remained low, supporting an overall acceptable safety profile.[66]

A recent Japanese real-world study compared the safety of the 3 JAK inhibitors. Except for a significantly higher incidence of acne with upadacitinib, no major safety differences were observed among the agents.[17] An analysis comparing safety in patients aged ≥65 years versus <65 years reveals that older patients treated with upadacitinib or tofacitinib had a 3-fold higher risk of herpes zoster than younger patients. In contrast, filgotinib had the lowest herpes zoster incidence (<3%) in both age groups. In younger patients, upadacitinib was associated with a 3-fold higher risk of acne.[67] Other real-world studies similarly report higher adverse event rates—including herpes zoster and acne—with upadacitinib than with other JAK inhibitors.[14,68]

OPTIMAL USE AND CYCLING OF JAK INHIBITORS IN UC

As advanced therapies for UC expand, treatment options have increased, but therapy cycling due to loss of response remains a clinical challenge. Optimizing advanced therapies is essential to provide patients with sustained therapeutic benefit, and cycling strategies must be applied carefully.

A JAK-to-JAK cycling strategy involves transitioning from 1 JAK inhibitor to another instead of changing to a different therapeutic class when treatment loses effectiveness. This may be an efficient approach in advanced therapy sequencing. Although JAK inhibitors belong to the same class, their mechanisms differ, and evidence indicates that JAK-to-JAK cycling can be effective. Moreover, rheumatoid arthritis studies show higher drug persistence when switching to a second JAK inhibitor after first-line failure than when switching to an anti-TNF agent, suggesting potential benefits for treatment continuity.[69]

Innocenti et al.[70] report outcomes of JAK inhibitor sequencing in a relatively large multicenter retrospective cohort. Patients with UC (n=243) who initiated a second JAK inhibitor after prior JAK inhibitor exposure were included. The primary endpoint was steroid-free clinical remission, with rates of 48%, 49%, and 28% at weeks 12, 26, and 52, respectively. Because of the retrospective design and varying UC approval timelines for JAK inhibitors, sequencing patterns available for comparison were limited to tofacitinib-to-upadacitinib, tofacitinib-to-filgotinib, filgotinib-to-upadacitinib, and other less common sequences. A significant finding is that the tofacitinib-to-filgotinib sequence shows lower drug persistence than tofacitinib-to-upadacitinib and filgotinib-to-upadacitinib.[70] Another multicenter retrospective study similarly reported outcomes of intraclass JAK-to-JAK cycling.[71] In this study, 47.9% of patients achieved steroid-free clinical remission after induction, and upadacitinib use was associated with higher remission rates.[71]

Under the Korean National Health Insurance reimbursement policy, several restrictions are imposed on the use of JAK inhibitors in patients with UC. First, despite the overall acceptable safety profile of JAK inhibitors, their use as first-line advanced therapy is not permitted in patients aged ≥65 years, those with high cardiovascular risk, or those at increased risk of malignancy. In addition, despite increasing evidence supporting the benefits of JAK-to-JAK cycling in patients with UC, this approach is not permitted, in contrast to the reimbursement policy for rheumatoid arthritis, in which JAK-to-JAK cycling is allowed. As a result, failure of 1 JAK inhibitor in patients with UC requires switching to another therapeutic class rather than to a second JAK inhibitor. This restriction carries important downstream consequences. Clinicians may be reluctant to start therapy with filgotinib, despite its favorable safety profile, because choosing a safety-first agent at baseline prevents later escalation to more potent options such as upadacitinib or tofacitinib, which are often needed in patients with severe disease activity, including ASUC or those presenting with EIMs. Consequently, the current policy structure paradoxically limits individualized treatment sequencing and may compromise long-term disease control. Furthermore, tofacitinib recently lost patent protection, allowing multiple generic versions to enter the Korean market at significantly lower prices. If JAK-to-JAK cycling were allowed, clinicians could adopt a stepwise approach: starting with a lower-cost generic tofacitinib and escalating to a second JAK inhibitor when clinically indicated. In addition to supporting real-world evidence for intraclass cycling, this strategy could reduce national insurance drug costs without compromising therapeutic efficacy. Therefore, revising reimbursement criteria to allow JAK-to-JAK cycling may provide clinical benefits for patients and reduce national health-insurance costs.

PROPOSED ALGORITHM FOR THE USE OF JAK INHIBITORS

Table 1 summarizes the key characteristics of the 3 JAK inhibitors. Fig. 1 illustrates a proposed algorithm for their clinical use, based on the available evidence reviewed and the expert

Table 1. Characteristics of the 3 JAK Inhibitors

	Selectivity and affinity	Relative efficacy	Relative safety	ASUC evidence	EIM evidence
Upadacitinib	JAK1	High	Moderate	Supported	Supported
Tofacitinib	Pan-JAK (JAK1/JAK3 > JAK2/TYK2)	Moderate	Moderate	Supported	Supported
Filgotinib	JAK1	Low to moderate	High	Limited	Suggestive

JAK, Janus kinase; ASUC, acute severe ulcerative colitis; EIM, extraintestinal manifestation; TYK, tyrosine kinase.

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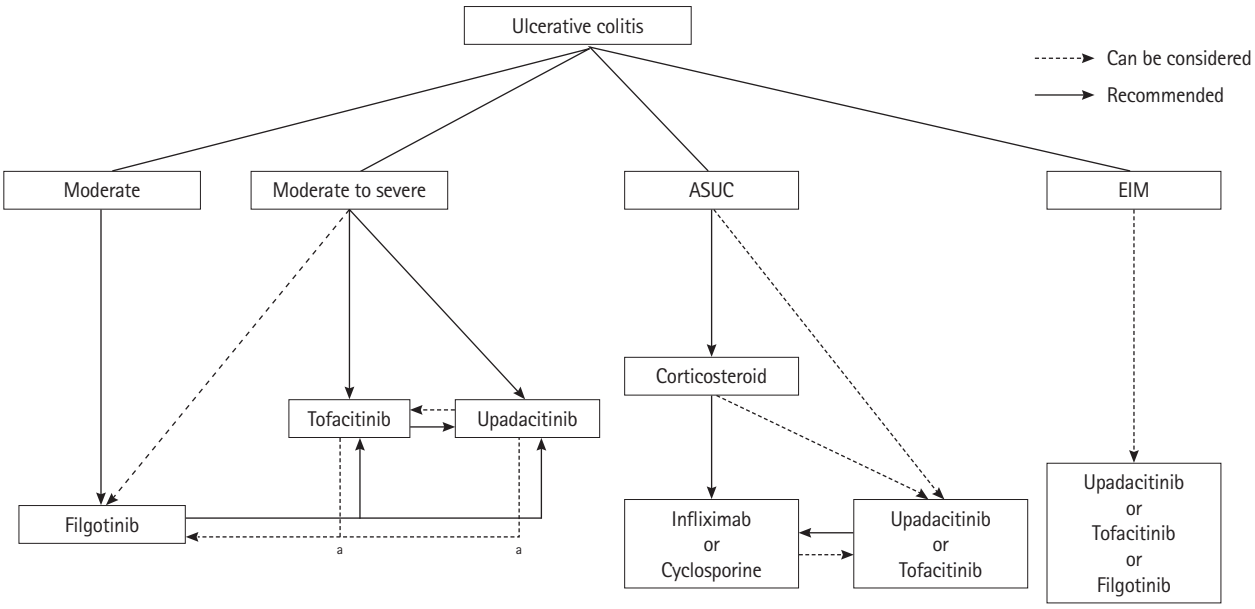


Fig. 1. Proposed algorithm for the optimal use of JAK inhibitors. This algorithm focuses exclusively on the optimal use and cycling strategies of JAK inhibitors and does not address other advanced therapies. This figure is based on the reviewed evidence and the expert opinions of the authors in the field of IBD. [a]When discontinued due to adverse events. JAK, Janus kinase; ASUC, acute severe ulcerative colitis; EIM, extraintestinal manifestation.

opinions of the authors, who are specialists in IBD. Although the overall safety profile of upadacitinib is comparable to that of tofacitinib and may be relatively less favorable than that of filgotinib, upadacitinib demonstrates the strongest efficacy among JAK inhibitors regardless of treatment sequence. In contrast, filgotinib has a favorable safety profile but is less effective than upadacitinib and slightly less or similarly effective than tofacitinib. Filgotinib also seems to have lower efficacy and durability when used as a second JAK inhibitor. Therefore, for patients with moderate disease activity or greater susceptibility to adverse events, filgotinib may be used initially, with a switch to tofacitinib or upadacitinib if disease activity worsens. In contrast, for patients with ASUC requiring rapid and robust efficacy, upadacitinib or tofacitinib is more appropriate. All 3 agents can be considered in the presence of EIMs.

Other factors should be considered: if a patient develops a severe adverse event on a JAK inhibitor that prevents continued therapy, transitioning to a different drug class may be safer than intraclass cycling. However, if adverse events require discontinuing upadacitinib or tofacitinib, switching to filgotinib—a more favorable safety profile—can be considered. Acne, a common adverse event of upadacitinib, can be a major cosmetic concern—particularly younger patients with UC—and should be discussed thoroughly before starting therapy.

Meanwhile, in a multicenter retrospective analysis, Akiyama et al.[17] report that higher platelet counts predicted lower clinical remission and filgotinib persistence, whereas longer disease duration predicted higher remission and tofacitinib persistence. These factors may guide therapeutic selection and support optimal JAK inhibitor use.

While more high-quality evidence is needed to refine and validate JAK inhibitor optimization strategies, applying the proposed algorithm with individual patient factors may guide effective treatment decisions.

CONCLUSIONS

Tofacitinib, filgotinib, and upadacitinib differ in JAK isoform selectivity and pharmacokinetic/pharmacodynamic characteristics, requiring individualized therapy. Evidence indicates that upadacitinib is the most effective, whereas filgotinib has the most favorable safety profile. Upadacitinib or tofacitinib may be preferred in patients with ASUC for their rapid onset and strong efficacy. All 3 agents can be considered in the presence of EIMs. Future head-to-head trials and high-quality real-world evidence are needed to refine sequencing strategies and optimize the clinical use of JAK inhibitors in UC.

ADDITIONAL INFORMATION

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