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REVIEW

Positioning and sequencing of advanced therapies in inflammatory bowel disease: A guide for clinical practice

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Abstract

Over the past decade, the therapeutic armamentarium for inflammatory bowel disease (IBD) has substantially expanded with the incorporation of multiple classes of advanced therapies. Currently, in addition to tumor necrosis factor-α inhibitors, the therapeutic arsenal for IBD includes anti-integrin agents, interleukin (IL)-12/23p40 and IL-23p19 antibodies, Janus kinase inhibitors, and sphingosine 1-phosphate receptor modulators. Although advances in IBD pharmacotherapy have enabled disease remission and improved control of intestinal inflammation in many individuals previously considered clinically 'intractable', they have also increased the complexity of decision-making related to the initial positioning and sequencing of therapies in the heterogeneous clinical presentations of IBD. Until molecular and genetic markers capable of predicting thera-

peutic responses become available in practice, the choice of initial and subsequent therapy in individuals with IBD is based on factors including disease severity, phenotype, risk of complications, comorbidities, extraintestinal manifestations, and the balance between efficacy, safety, convenience, and access. This review explores the factors that influence treatment decisions regarding initial therapy selection and sequencing across IBD scenarios, offering practical tips for personalizing therapy based on the safety and efficacy of advanced treatments and the individual's risk of disease- or therapy-related adverse outcomes.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Advanced therapy; Biologics; Sequencing; Treatment strategy; Janus kinase inhibitors; Biologic agents

Core Tip: One of the key challenges clinicians face in managing individuals with inflammatory bowel disease (IBD) is determining which advanced therapy to initiate and how to sequence treatments when needed. In the absence of readily available molecular markers, these decisions, although often complex, are guided by patient- and disease-specific factors, including disease severity, phenotype, complication risk, comorbidities, extraintestinal manifestations, the balance between drug efficacy and safety, convenience, and treatment access. In this review, we examine the various considerations influencing therapeutic decision-making in different IBD clinical contexts and offer practical tips to support more personalized approaches based on the individual's clinical profile.

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INTRODUCTION

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), comprises immune-mediated inflammatory disorders that remain incurable and often necessitate the continuous use of advanced targeted therapies to achieve sustained control of intestinal inflammation and disease remission[1]. Remarkable advances in basic, translational, and clinical research over the past decade have facilitated the development of numerous novel agents targeting IBD. Currently, alongside tumor necrosis factor (TNF)-α inhibitors, the therapeutic arsenal for IBD includes anti-integrin agents, interleukin (IL)-12/23 and IL-23p19 inhibitors, Janus kinase (JAK) inhibitors, and sphingosine 1-phosphate (S1P) receptor modulators[2]. While these pharmacological advances have enabled both remission and inflammatory control in patients previously considered clinically "intractable", they have also introduced greater complexity into decisions surrounding initial treatment selection and therapeutic sequencing across the diverse clinical contexts seen in IBD. "Positioning" refers to the selection of the optimal advanced therapy for first-line treatment, tailored to individual patient profiles, disease activity, and drug attributes. "Sequencing" involves the strategic selection and ordering of subsequent therapeutic agents following the failure of the initial treatment, whether due to primary non-response, secondary loss of response (LOR), or adverse events. This review aims to provide a practical overview of key factors influencing the positioning and sequencing of advanced therapies in patients with IBD.

Comparative effectiveness research, including head-to-head trials, network meta-analyses (NMA), and real-world studies (*e.g.*, observational cohort studies, case-control and cross-sectional studies, and case series), particularly those employing propensity score matching to simulate randomization, offers the potential to detect meaningful differences in efficacy and safety among various advanced therapeutic strategies[3]. Although some sources, such as randomized controlled trials (RCTs) and systematic reviews of RCTs with or without meta-analyses, offer a high level of evidence, observational studies contribute valuable insights, especially for evaluating long-term safety or therapeutic performance in patient populations frequently underrepresented in RCTs. Ideally, both RCTs and real-world evidence (RWE) should be integrated to leverage their complementary strengths and mitigate their respective limitations. This combined approach supports the rational incorporation of biologics and small molecules into clinical practice[4].

Indeed, these studies provide a valuable framework for selecting the most appropriate initial or subsequent therapy based on clinical context and disease characteristics. The decision regarding an initial therapeutic strategy and subsequent treatment sequencing for an individual with IBD is typically guided by available evidence, integrated with clinical expertise, access to advanced therapies, and shared decision-making with the patient. Additional factors influencing treatment selection include the route of administration [oral, subcutaneous (SC), or intravenous (IV)], dosing schedule, speed of response, long-term efficacy, and safety (Figure 1). This individualized approach will remain central until further genetic and molecular advances allow prediction of response to specific advanced therapies, similar to precision strategies employed in oncology[4,5].

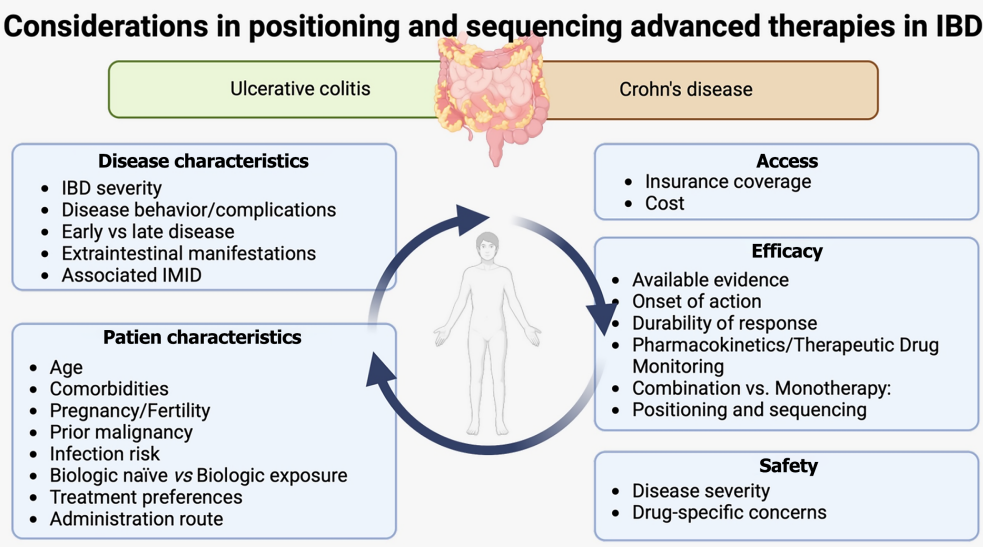

Figure 1 Considerations in positioning and sequencing advanced therapies in inflammatory bowel disease. IBD: Inflammatory bowel disease. Image created with BioRender.

Therapy selection in IBD is shaped not only by efficacy and effectiveness data but also by multiple non-clinical and patient-specific variables that significantly influence outcomes (Figure 2). Social determinants, such as medication availability, healthcare infrastructure, and financial limitations, often play a decisive role in therapeutic planning, particularly in settings with constrained access to advanced therapies[6]. Geographic variables, including the prevalence of endemic infections like tuberculosis, hepatitis B, and strongyloidiasis, may further influence the choice of immunosuppressive or biologic agents to minimize infection-related risks[7].

Moreover, nutritional status is a key determinant of treatment response, as both malnutrition and elevated visceral adiposity have been associated with altered pharmacokinetics and variable therapeutic effects, impacting drug metabolism and immunogenicity[8]. Other relevant considerations, such as serum biomarkers, metabolic capacity, and genetic polymorphisms, also affect drug exposure, clearance, and sustained response to biologics, reinforcing the need for precision-based approaches[9]. In light of these complexities, strategies incorporating pharmacogenomics, therapeutic drug monitoring (TDM), and predictive biomarkers are gaining prominence as tools to optimize individualized treatment decisions[10].

It should be emphasized that regardless of the advanced therapy selected for individuals with moderate-to-severe IBD particularly in CD it is crucial to initiate treatment as early as possible, ideally within the first 12 months after disease onset. Several studies have demonstrated improved clinical and endoscopic outcomes in CD among patients treated with biologics within the first two years of disease progression[11,12].

Moreover, transmural healing has gained importance in CD management, as it appears to be associated with more favorable outcomes than mucosal healing[13,14]. A recent multicenter retrospective study further demonstrated that early initiation of biologic therapy within 12 months of CD diagnosis significantly enhances transmural healing rates (*e.g.*, complete normalization of all magnetic resonance enterography parameters), which correlates with better long-term outcomes, including reduced risk of bowel damage progression, CD-related surgery, and therapy escalation[15].

It is also essential to define, following the initial choice of IBD-directed therapy and during subsequent sequencing, the appropriate therapeutic regimen for remission induction in moderate-to-severe IBD, as well as the maximum duration for evaluating a therapy's effectiveness. This approach aims to avoid prematurely discontinuing potentially effective therapy while also preventing delays in switching when a therapy proves clearly ineffective[2,16,17].

Table 1 outlines the maximum recommended time frames for assessing the effectiveness of IBD-targeted therapies, along with their respective therapeutic regimens. It is important to note that the most effective advanced therapies for IBD typically demonstrate clinical response within 2-4 weeks, although delayed responses have been well described in both clinical trials and routine practice. Individuals who exhibit a delayed clinical response often show favorable progression during the maintenance phase of therapy, closely resembling the trajectory observed in early responders[18]. Table 2 presents several fundamental principles that serve as an initial guide for the positioning and sequencing of advanced IBD therapies[19-22].

In this narrative review, we comprehensively searched of the PubMed, Embase, and Scopus databases up until 30 December 2024, aiming to identify main studies published in the English language regarding positioning and sequencing of therapies for IBD. We define positioning as the selection of a first-line therapeutic agent for a specific clinical scenario and sequencing as the therapeutic strategy agent(s) following treatment failure. To this end, we employed specific search including 'sequencing treatment', 'network meta-analysis', 'systematic review', 'randomized controlled trials', 'head-to-head trials', 'real-world evidence', 'guidelines' and 'position paper', in conjunction with 'Crohn's disease', 'ulcerative colitis', 'CD', 'UC', 'inflammatory bowel disease', and 'IBD'. The screening process included two independent reviewers (Chebli JMF and Sassaki LY) who initially evaluated titles and abstracts to identify potentially relevant papers. Thereafter, we assessed the full texts of these selected articles to determine their eligibility for inclusion. Further, we manually

Table 1 Timeframe for assessing therapeutic effectiveness in inflammatory bowel disease and associated dosing regimens

Classe of drugs	Therapeutic regimens and timeframes
Aminosalicylates (mesalazine and sulfasalazine only for mild to moderate UC)	Maximum dosing orally (4.8 g/day) combined with topical therapy for 2-4 weeks
Steroids (budesonide, prednisone, hydrocortisone)	(1) Budesonide 9 mg/day for 2 weeks; (2) Prednisone 40 mg/day PO for 2 weeks; and (3) Hydrocortisone (300-400 mg/day) or methylprednisolone (60 mg/day) IV during 3-5 days in acute severe UC
Immunosuppressant (methotrexate and thiopurines)	(1) Methotrexate 25 mg/week IM or SC for 4-6 weeks (only for CD); and (2) Thiopurines 2.0-2.5 mg/kg daily PO for 12-16 weeks (only for maintenance of remission)
Anti-TNF (infliximab, adalimumab, certolizumab pegol and golimumab)	After 2 (adalimumab, golimumab) or 3 (infliximab, certolizumab pegol) loading doses and first maintenance dose, may include proactive TDM
Anti-integrin (vedolizumab)	After 3 Loading doses and 1-3 maintenance doses
Anti-IL-12/23 (ustekinumab); Anti-IL-23p19 (risankizumab, guselkumab and mirikizumab)	After 3 Loading doses and 1-3 maintenance doses
S1P receptor modulators (ozanimod and etrasimod)	(1) Ozanimod 0.92 mg/day for 10 weeks; and (2) Etrasimod 2 mg orally once a day for 12 weeks
Janus kinase inhibitors (tofacitinib and upadacitinib)	(1) Tofacitinib 10 mg orally twice daily for 8-16 weeks; and (2) Upadacitinib 45 mg orally once a day for 8-16 weeks (UC) or upadacitinib 45 mg orally once a day for 12 weeks (CD)

UC: Ulcerative colitis; TNF: Tumoral necrosis factor; S1P: Sphingosine 1-phosphate; IL: Interleukin; PO: Per oral; IV: Intravenous; IM: Intramuscularly; SC: Subcutaneous; CD: Crohn's disease; TDM: Therapeutic drug monitoring.

Table 2 Basic principles in positioning and sequencing advanced therapies in inflammatory bowel disease

Basic principles
Start any effective drug as early as possible
Be aware: The first drug chosen will likely be the most effective for controlling IBD, particularly in Crohn's disease
Avoid repeated courses of steroids before initiating advanced therapies. The need for steroids should alert clinicians to the likely necessity of starting steroid-sparing therapeutic strategies
Assess factors that may influence the pharmacokinetics of biologics, such as hypoalbuminemia, high inflammatory load, extensive gastrointestinal involvement, and others
Consider factors that may impact on the safety of different therapies
Use the best available evidence to guide the selection of initial therapy and, when appropriate, the subsequent sequencing of treatments
Consider the potential need for treatment escalation strategies in the context of more severe disease
Always think ahead: Which agent could also be effective as a second-line treatment?
Consider the patient as a whole: Take into account factors such as age, frailty, underlying comorbidities, extraintestinal manifestations, and others
The selection of advanced targeted therapy must take into account costs, access to treatment, and any barriers to receiving therapy

IBD: Inflammatory bowel disease.

reviewed the reference lists of these papers to ensure that no relevant studies were overlooked during the electronic search. The final inclusion of articles was based on their importance to our current review.

POSITIONING AND SEQUENCING OF THERAPY IN UC

Therapy sequencing is increasingly recognized as a key determinant of long-term outcomes in UC. The initial therapeutic choice influences not only short-term response but may also impact the effectiveness of future treatments. The therapeutic landscape for UC has expanded significantly, with biologics and small molecules now forming the foundation of management. Both biologic agents and small molecules have shown strong efficacy during induction and maintenance phases. However, achieving steroid-free remission and sustained mucosal healing remains difficult, especially among individuals who have failed previous therapies[23]. In the absence of head-to-head trials comparing advanced treatments, sequencing decisions in clinical settings largely rely on indirect comparisons, NMA, and RWE. While NMAs are valuable in this context, variations in study populations, endpoints, and treatment duration can significantly influence the results, warranting cautious interpretation of comparisons.

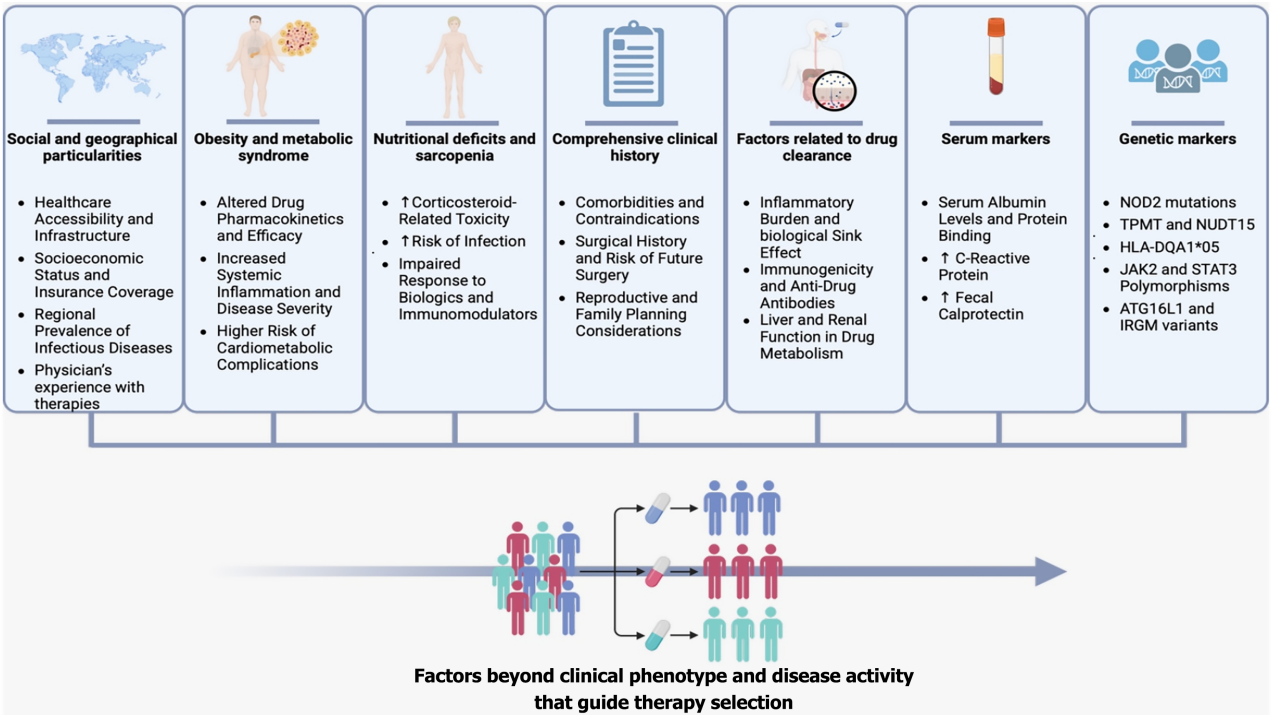

Figure 2 Factors beyond clinical phenotype and disease activity that guide therapy selection. JAK: Janus kinase. Image created with BioRender.

This section reviews sequencing strategies across different UC patient populations, including biologic-naive, biologic-experienced and multirefractory individuals, with a focus on current evidence from clinical trials, real-world studies and practice guidelines.

First-line therapy in UC patients

There remains a lack of direct head-to-head clinical trials comparing advanced therapies in individuals with moderate-to-severe UC. The VARSITY study was the first major trial to directly compare two biologic agents with distinct mechanisms of action in individuals with UC. This phase 3b trial was designed as a randomized, double-dummy, double-blind, multicenter, active-controlled study evaluating the efficacy and safety of vedolizumab (VDZ) *vs* adalimumab (ADA) over 52 weeks in individuals with moderate-to-severe active UC[24]. At week 52, VDZ demonstrated significantly higher rates of clinical remission (primary endpoint), with 31.3% (n = 120/383) for VDZ compared to 22.5% (n = 87/386) for ADA (P = 0.0061). Mucosal healing at week 52 was achieved in 39.7% (n = 152/383) of individuals treated with VDZ and 27.7% (n = 107/386) of those treated with ADA (P = 0.0005)[24].

A recent systematic review and NMA conducted to support the 2024 American Gastroenterological Association Clinical Guidelines for managing moderate-to-severe UC evaluated direct and indirect evidence from 35 trials to guide treatment positioning for inducing and maintaining clinical remission in both biologic-naive individuals and those previously exposed to biologics[25]. The findings suggest that upadacitinib is the most effective therapy for moderately-to-severely active UC in both biologic-naive and biologic-experienced populations. Notably, the disparity in relative efficacy between these groups was more pronounced for certain therapies, especially VDZ and ozanimod[25].

When JAK inhibitors are excluded as a first-line treatment option in accordance with United States Food and Drug Administration guidelines, low-certainty evidence suggests that infliximab (IFX), ozanimod, risankizumab, and guselkumab offer greater clinical benefit in achieving induction remission compared to ADA and mirikizumab in biologic-naïve individuals with moderate-to-severe UC. Among these agents, risankizumab and ozanimod demonstrate the highest efficacy for inducing clinical remission. When JAK inhibitors are included as a first-line option, upadacitinib demonstrates superior efficacy over all other treatments except ozanimod and risankizumab, based on low- to moderate-certainty evidence[25].

In another recently published systematic review and NMA involving 36 studies and 14270 individuals, the comparative efficacy of biologics and small molecules in UC was evaluated. Upadacitinib appears to be superior to other therapies in achieving clinical remission, endoscopic improvement and remission, and histological remission. Additionally, selective IL-23p19 inhibitors, including risankizumab and guselkumab, also showed high efficacy in achieving these therapeutic outcomes[26].

However, efficacy data alone is insufficient to guide first-line treatment selection. The choice of initial therapy in UC depends on disease severity and patient-specific factors. This decision is also shaped by individual characteristics, including preference for administration route (oral, IV, or SC), speed of onset, disease severity, safety profile, and unique risk factors. Balancing these aspects enables a tailored therapeutic approach that optimizes both clinical efficacy and patient adherence.

In a nationwide study evaluating the acceptability of maintenance regimens in IBD, 1850 individuals rated oral therapy as the most preferred option [acceptability numerical scales (ANS) = 8.68 ± 2.52], followed by SC injections (ANS = 7.67 ± 2.94) and IV infusions (ANS = 6.79 ± 3.31; $P < 0.001$). Among biologic-naïve individuals, once-daily oral intake and SC injections every 8-12 weeks were the most accepted regimens. In those previously treated with SC biologics, ≥ 2-week SC intervals were preferred, while individuals previously treated with IV biologics favored SC injections every 8-12 weeks or once-daily oral intake. Treatment escalation or de-escalation had a minimal impact on acceptability. Overall, while oral therapy remains the preferred option, SC therapies with extended dosing intervals (≥ 8 weeks) and once-daily oral intake appear to be the most acceptable regimens[27].

The rapid onset of action of advanced therapies is a critical factor in UC treatment selection, particularly for individuals requiring urgent symptom control. Clinical trial data have shown that biologics such as IFX and VDZ provide notable symptom improvement within the first two to six weeks of therapy. In a post-hoc analysis of phase 3 trials including 374 individuals with UC, VDZ demonstrated superior early response *vs* placebo, particularly among TNF-naive individuals, with 22.3% achieving rectal bleeding scores of 0 and stool frequency ≤ 1 by week 2, compared to 6.6% in the placebo group[28]. Similarly, IFX demonstrated early reductions in stool frequency and rectal bleeding, supporting its use in individuals with high inflammatory burden requiring prompt symptom relief[29].

Small molecules, including JAK inhibitors and S1P receptor modulators, have also shown early efficacy. In two phase 3 trials (U-ACHIEVE induction and U-ACCOMPLISH) involving 988 individuals with moderate-to-severe UC, upadacitinib 45 mg quaque die provided significant symptom relief as early as day 1, with 75.7% achieving > 50% reduction in high-sensitivity C-reactive protein and 48.2% achieving similar reduction in fecal calprotectin by week 2 ($P < 0.001$ *vs* placebo)[30].

Tofacitinib, a JAK inhibitor, demonstrated rapid improvements in stool frequency and rectal bleeding in two phase 3 induction trials (OCTAVE induction 1 and 2) including 1139 individuals, with significant symptom reduction by day 3. Specifically, 28.8% of tofacitinib-treated individuals achieved at least a 1-point reduction in stool frequency subscore compared to 17.9% in the placebo group ($P < 0.01$), while 32.0% achieved ≥ 1-point reduction in rectal bleeding subscore *vs* 20.1% with placebo ($P < 0.01$)[31].

The rapid onset of action observed with JAK inhibitors and IFX makes them particularly appealing for individuals with severe disease or those at risk of hospitalization.

Management of UC in patients with prior biologic failure

The treatment of UC in individuals who have failed prior biologic therapy remains a significant clinical challenge. Although multiple advanced therapies are available, no direct head-to-head trials have compared treatment options specifically in anti-TNF refractory patients. As a result, RWE, retrospective analyses, and NMA are instrumental in guiding sequencing strategies and optimizing outcomes.

A multicenter real-world retrospective study compared tofacitinib ($n = 124$) and ustekinumab ($n = 165$) in patients with UC refractory to anti-TNF therapy. The findings showed comparable corticosteroid-free remission rates at week 16 (37.8% for tofacitinib *vs* 35.6% for ustekinumab). Additionally, no significant differences were seen in early response (17% *vs* 11.7%, $P = 0.47$) or mucosal healing (4.4% *vs* 7.8%, $P = 0.32$). Notably, prior exposure to multiple biologics was associated with a reduced likelihood of response, especially among those receiving ustekinumab[32].

Similarly, a Dutch nationwide registry study assessed the comparative effectiveness of tofacitinib ($n = 63$) and VDZ ($n = 85$) in anti-TNF experienced individuals. Tofacitinib demonstrated significantly higher corticosteroid-free clinical remission rates at week 12 [67.6% *vs* 29.4%, hazard ratio (HR) = 5.87, $P < 0.01$], week 24 (65.7% *vs* 41.2%, HR = 3.20, $P < 0.01$), and week 52 (47.1% *vs* 23.5%, HR = 3.09, $P < 0.01$). Biochemical remission rates, defined as C-reactive protein ≤ 5 mg/L and/or fecal calprotectin ≤ 250 μg/g, were also superior with tofacitinib, particularly at week 24 (HR = 2.32, $P = 0.02$)[33].

The EFFICACI trial, a French double-blind multicenter randomized controlled study, compared VDZ and IFX in individuals with moderate-to-severe UC who had failed a first SC anti-TNF (ADA or golimumab). A total of 151 individuals were randomized (VDZ: $n = 78$; IFX: $n = 73$). At week 14, steroid-free clinical remission was achieved in 34.6% of patients receiving VDZ *vs* 19.2% in the IFX group ($P = 0.033$). Endoscopic improvement (Mayo endoscopic subscore 0 or 1) was also significantly higher with VDZ (46.8% *vs* 29.2%, $P = 0.027$). Adverse event rates were comparable between groups (VDZ: 70.5%; IFX: 63.9%), with eight individuals requiring hospitalization for severe disease flares (five in the IFX group, three in the VDZ group)[27].

There is considerable heterogeneity in the efficacy of advanced therapies for inducing remission in individuals with UC, particularly those previously exposed to TNF antagonists. A systematic review and meta-analysis of 17 RCTs evaluated the efficacy of advanced therapies *vs* placebo for induction of clinical remission, stratified by prior biologic exposure[34]. Lymphocyte trafficking inhibitors (anti-integrins and S1P receptor modulators) demonstrated greater efficacy in TNF antagonist-naive compared to TNF antagonist-exposed individuals [five trials; ratio of odds ratio (OR) = 1.88, 95% confidence interval (CI): 1.02-3.49]. In contrast, JAK inhibitors were less effective in TNF antagonist-naive than in exposed individuals (six trials; ratio of OR = 0.47, 95%CI: 0.22-1.01). No significant difference was seen for selective IL-23p19 antagonists *vs* placebo between TNF antagonist-naive and exposed individuals (six trials; ratio of OR = 1.07, 95%CI: 0.64-1.80). Notably, JAK inhibitors may offer enhanced efficacy, whereas lymphocyte trafficking inhibitors may show attenuated effectiveness in TNF antagonist-exposed patients[34].

Management of UC in multirefractory patients

Individuals with UC who fail multiple lines of advanced therapies, including anti-TNF agents, integrin inhibitors, JAK inhibitors, and anti-ILs, represent a particularly challenging population. As trials evaluating these newer therapeutic agents were conducted more recently, they include a higher proportion of multirefractory individuals, offering valuable

insight into how these drugs perform in this difficult-to-treat subgroup.

In the LUCENT trials, mirikizumab, an IL-23p19 inhibitor, was evaluated in the phase 3 LUCENT-1 and LUCENT-2 studies for moderate-to-severe UC. LUCENT-1 (induction) enrolled 1281 individuals randomized to receive either mirikizumab (n = 958) or placebo (n = 321) intravenously every four weeks for 12 weeks. Clinical remission at week 12 was achieved in 24.2% of mirikizumab-treated individuals compared to 13.3% with placebo (P < 0.001). In LUCENT-2 (maintenance), responders to induction therapy (n = 544) were randomized to receive SC mirikizumab (200 mg every four weeks) or placebo for 40 weeks. At week 40, 49.9% of mirikizumab-treated individuals maintained clinical remission *vs* 25.1% with placebo (P < 0.001). Notably, 40% of enrolled patients had failed prior biologic therapy, and mirikizumab demonstrated efficacy in this subgroup[35].

The phase 3 trials assessing risankizumab, another IL-23p19 inhibitor, included a significant proportion of individuals previously exposed to biologics or JAK inhibitors. Approximately 50% had failed prior advanced therapies, including 62% with exposure to one anti-TNF agent and 20% to two biologics. Risankizumab demonstrated clinically meaningful remission rates in this heavily pretreated population, supporting its potential role in multirefractory UC[36].

Guselkumab has been studied in the phase 3 QUASAR program evaluating its efficacy and safety in moderate-to-severe UC. The induction study included patients with prior biologic or JAK inhibitor failure, with 49.1% classified as advanced therapy experienced. Among these, 87.5% had failed anti-TNF therapy, 54.4% had prior VDZ exposure, and 19.2% had received tofacitinib. At week 12, clinical remission rates were significantly higher in the guselkumab group than in the placebo group (22.6% *vs* 7.9%, P < 0,001), with sustained benefits observed at week 52 in the maintenance phase. Subgroup analysis confirmed efficacy across different lines of prior therapy, including those with multiple biologic failures[37].

Etrasimod, an S1P receptor modulator, has been evaluated in the ELEVATE UC 12 and ELEVATE UC 52 trials, which investigated its efficacy in both biologic-naive and biologic-experienced patients with moderate-to-severe UC. In biologic/JAK inhibitor-naive individuals, clinical remission at week 12 was significantly higher with etrasimod 2 mg (28.9%) compared to placebo (15.6%), yielding an absolute difference of 13.8% (P < 0.05). In the biologic-experienced population, remission rates were lower but remained favorable, with 22.6% of etrasimod-treated individuals achieving remission at week 52 compared to 6.7% in the placebo group (Δ = 13.9%, P < 0.05). Notably, patients with only one prior biologic or JAK inhibitor exposure showed higher remission rates (33.3% at week 12 and 29.5% at week 52) compared to those who had failed multiple advanced therapies (15.8% and 15.0%, respectively). These findings highlight the potential role of etrasimod as an effective oral option for patients with prior treatment failure, particularly those with only one prior biologic or JAK inhibitor exposure[38].

Acute severe UC

Rescue therapy for steroid-refractory acute severe UC (ASUC) is typically managed with IFX or cyclosporine. Given their rapid onset of action, lower susceptibility to drug clearance related to hypoalbuminemia, and demonstrated efficacy in individuals with more severe disease, JAK inhibitors represent promising therapeutic options for ASUC, particularly in those with prior IFX failure.

In a systematic review of cohort studies, a case-control study, case reports, and case series including 148 individuals with corticosteroid-refractory ASUC and prior IFX failure, tofacitinib treatment was associated with high short-term colectomy-free survival, with a 90-day colectomy-free survival rate of 86% in refractory patients who would otherwise be considered candidates for colectomy[39].

The TACOS study[40] was a RCT designed to assess the efficacy of tofacitinib in combination with corticosteroids in enhancing treatment response in ASUC. This single-center, double-blind, placebo-controlled study randomized patients to receive either hydrocortisone 100 mg IV every six hours plus tofacitinib 10 mg three times daily or hydrocortisone with placebo for seven days. A total of 104 individuals were included, and the response rate was significantly higher in the combination group (83.01%) compared to placebo (58.82%) (P = 0.007). Regarding safety, one patient in the tofacitinib group developed dural venous sinus thrombosis. The authors concluded that combining hydrocortisone with tofacitinib in ASUC enhances the likelihood of treatment response and reduces the need for salvage interventions such as colectomy.

In a retrospective propensity score-matched cohort study, upadacitinib showed efficacy and safety comparable to IFX in real-world individuals with ASUC, with no significant differences in colectomy rates[41]. Additionally, a recent systematic review and meta-analysis of six studies, including a total of 66 individuals, suggested that upadacitinib may be an effective and safe option for ASUC. The study demonstrated low rates of colectomy and serious adverse events, along with high rates of early clinical response and corticosteroid-free remission. However, the study was limited by a follow-up period of less than 6 months in 85% of the population[42].

Taken together, the above-mentioned studies support the use of tofacitinib or upadacitinib as viable alternatives to IFX for hospitalized individuals with UC, including those with prior anti-TNF failure, emphasizing the importance of individualized risk assessment in therapeutic decision-making[41]. However, large high-quality studies remain necessary.

Table 3 depicts practical pearls in sequencing advanced therapies in UC and the available evidence base.

POSITIONING AND SEQUENCING OF THERAPY IN CD

Despite the wide range of treatment options available for CD, many individuals still fail to achieve clinical remission. Emerging therapeutic classes, comparative drug studies, combination therapy trials, and deeper insights into CD pathophysiology offer promising avenues for optimizing treatment strategies for moderate-to-severe disease. However,

Table 3 Practical pearls in positioning and sequencing advanced therapies in ulcerative colitis and the available evidence base

Practical pearls in positioning and sequencing advanced therapies in ulcerative colitis and the available evidence base
For first line use in moderate-to-severe UC, vedolizumab demonstrated significantly higher rates of clinical remission and mucosal healing at week 52 when compared to adalimumab (RCT)
Upadacitinib is the most effective therapy for moderately-to-severely active UC, in both biologic-naive and biologic-exposed populations (NMA)
In the clinical setting in which upadacitinib cannot be used as first-line therapy (due to label restrictions or contraindications), infliximab and vedolizumab are probably the most adequate therapies to be used in the induction of remission in biologic-naive patients with moderate to severe UC (NMA, RWE)
Infliximab, ozanimod, risankizumab, and guselkumab provide a greater clinical benefit in achieving induction remission compared to adalimumab and mirikizumab in biologic-naive patients with moderate-to-severe UC, when JAK inhibitors are excluded as a first-line treatment option (NMA)
Upadacitinib appears to be superior to other therapies in achieving clinical remission, endoscopic improvement and remission, and histological remission. Selective IL-23 inhibitors, such as risankizumab and guselkumab, also exhibited high efficacy in achieving these outcomes (NMA)
In the clinical setting of moderate to severe steroid-responsive or corticosteroid-dependent UC, where the patient is not at imminent risk of hospitalization, and considering the balance of effectiveness and safety, vedolizumab can be considered as first-line therapy, although ustekinumab and interleukin-23p19 inhibitors are also good options (RWE)
In patient's refractory to first-line therapy with vedolizumab, the use of infliximab, ustekinumab, IL-23p19 inhibitors or JAK inhibitors are effective in inducing remission (RWE)
Tofacitinib and ustekinumab showed comparable corticosteroid-free remission, early response rates, and mucosal healing in UC patients refractory to anti-TNF therapy (RWE)
Tofacitinib demonstrated significantly higher corticosteroid-free clinical remission, biochemical remission and fecal calprotectin ≤ 250 μg/g when compared to vedolizumab in anti-TNF experienced patients (RWE)
Vedolizumab was superior to infliximab in patients with moderate-to-severe UC who had failed a first subcutaneous anti-TNF (adalimumab or golimumab), in clinical and endoscopic outcomes (RCT)
Lymphocyte trafficking inhibitors (anti-integrins and S1P receptor modulators) demonstrated greater efficacy in TNF antagonist-naive compared to TNF antagonist-exposed patients (NMA)
S1P receptor modulators, such as ozanimod and etrasimod, are oral agents that may be considered as first-line therapy in patients with mild to moderate UC refractory to aminosalicylates (RCT, RWE)
Ustekinumab, mirikizumab, risankizumab guselkumab and etrasimod demonstrated efficacy in moderate-to-severe UC failed prior biologic therapy (RCT)
JAK inhibitors represent promising therapeutic options for ASUC, particularly in those with prior infliximab failure (systematic review)
Combining hydrocortisone with tofacitinib in ASUC increases the likelihood of treatment response and reduces the need for salvage therapies such as colectomy (RCT)
Upadacitinib demonstrated efficacy and safety comparable to infliximab in patients with ASUC, with no significant differences in colectomy rates (RWE)
In patients with moderate to severe UC without imminent risk of hospitalization, who are elderly, frail, have severe comorbidities, or are at high risk of major cardiovascular events or thromboembolic events, vedolizumab, ustekinumab, or IL-23p19 inhibitors are the preferred therapies, and JAK inhibitors should be avoided in these clinical contexts (NMA, RWE)
In the scenario where pharmacoeconomic issues are a priority, initial therapy with biosimilars makes the first-line choice more cost-effective

Janus kinase inhibitors (including upadacitinib) are not considered in biologic-naive patients in some countries, given United States Food and Drug Administration labeling restricting the use of this class of drugs to biologic/tumoral necrosis factor antagonist exposed individuals. ASUC: Acute severe ulcerative colitis; RCT: Randomized controlled trial; UC: Ulcerative colitis; NMA: Network meta-analysis; RWE: Real-world evidence; JAK: Janus kinase; IL: Interleukin; TNF: Tumoral necrosis factor; S1P: Sphingosine 1-phosphate.

the ideal sequencing approach, whether for biologic-naïve individuals or those previously exposed to advanced therapies, remains uncertain[16]. This section explores current sequencing strategies in CD, including evidence for first-line biologics, comparative trial data, and approaches to postoperative recurrence.

Key management goals in CD include rapid remission induction, accurate disease severity stratification, and maintenance of steroid-free remission, all of which have contributed to a treat-to-target approach emphasizing selection of the "right therapy for the right patient at the right time"[5]. Early and appropriate intervention is linked with better short- and long-term outcomes, including fewer hospitalizations, reduced complications, and lower surgery rates, and may help reduce overall healthcare costs[43]. Recent strategies have shifted the therapeutic focus from solely achieving clinical remission to targeting deeper outcomes, such as endoscopic healing and even histological and transmural improvements, which may influence long-term disease progression[44-46]. For example, the PROFILE study compared a top-down approach (early combined immunosuppression with IFX and immunomodulator) to an accelerated step-up strategy in newly diagnosed individuals with CD. Although no significant biomarker-treatment interaction was observed ($P = 0.944$), the top-down group achieved significantly higher sustained steroid- and surgery-free remission rates (79% *vs* 15%, $P < 0.0001$), supporting its consideration as a potential standard of care for active, newly diagnosed CD[47].

CD demonstrates increasing efforts to tailor treatments to individual disease profiles, especially given the limited number of studies focused on specific phenotypes. For example, factors such as proximal disease location, younger age, perianal involvement, stricturing or penetrating behavior, higher baseline disease activity, and smoking have been associated with lower long-term remission rates[44,48].

Optimal treatment selection and sequencing in CD require a multifaceted approach that balances efficacy with individual-specific characteristics[49]. From an efficacy perspective, key considerations include speed of action, durability of response, pharmacokinetics, and TDM. The decision between combination therapy and monotherapy can significantly influence both short- and long-term outcomes. Early initiation of the most appropriate advanced therapy helps prevent disease progression and complications, while steroid-sparing strategies reduce dependency and adverse effects. A proactive, forward-thinking strategy that preserves second-line options for timely escalation is essential, along with addressing cost and access barriers. Integrating these principles enables a personalized treatment model that maximizes both efficacy and safety in CD management[44,48,49].

Advanced therapy continues to serve as the foundation for managing moderate -to -severe CD, and dual biologic therapy has shown promise in select subgroups particularly individuals with refractory disease, immune-mediated inflammatory diseases, or extraintestinal manifestations (EIMs). However, these strategies may carry a higher risk of adverse events, including increased rates of infections and malignancies. To advance individualized care strategies for refractory CD, further research is necessary to enhance the predictive utility of advanced therapies, clarify the safety and appropriate indications for dual therapy, and determine criteria for discontinuing one of the agents[50]. Additionally, evaluating emerging biomarkers and exploring the integration of artificial intelligence in disease management may further optimize care for individuals with CD[51].

Recent real-world comparative effectiveness data of advanced therapies for CD patients

Real-world comparisons of first-line biologics in CD remain limited. Recently, Supovec *et al*[52] evaluated drug persistence and patient-reported outcome-2 remission rates among first-line treatments—including anti-TNF agents, VDZ, and ustekinumab in a real-world cohort of 588 adults with CD, using individual-level data from the United Registries for Clinical Assessment and Research IBD platform. No significant differences in drug survival were identified among these agents. The estimated drug survival rates (with 95%CIs) were 0.81 (0.77-0.84) for anti-TNFs, 0.89 (0.82-0.96) for VDZ, and 0.88 (0.79-0.97) for ustekinumab at year 1, and 0.52 (0.46-0.58), 0.58 (0.37-0.78), and 0.58 (0.39-0.77) at year 4, respectively. The authors concluded that first-line anti-TNFs, VDZ, and ustekinumab demonstrate comparable drug persistence and effectiveness in CD[52].

A recent large-scale study from the United Kingdom IBD BioResource analyzed 13222 individuals and assessed the long-term continuity of various first-line therapies. In this study, IFX, ADA, and VDZ exhibited differences in treatment persistence, with IFX demonstrating superior survival free of treatment failure. While these agents showed similar effectiveness in luminal CD, IFX clearly outperformed ADA in perianal CD. Further analysis showed that VDZ was more effective when used as a first-line agent, and in the second line setting, ustekinumab and VDZ provided comparable outcomes following anti-TNF failure potentially surpassing a second anti-TNF in cases of secondary non-response. These findings highlight the importance of strategic biologic positioning in treatment sequencing and reinforce the need for individualized therapy selection in CD management[53].

A semi-Markov model was employed to determine the optimal positioning of VDZ within various treatment sequences including corticosteroids, IFX, ADA, ustekinumab, and best supportive care. The analysis revealed that initiating VDZ as the first biologic led to superior outcomes, such as higher quality-adjusted life-years, improved individual-reported disease activity, and reduced surgery rates[54]. Compared to its use in later treatment lines, early VDZ therapy demonstrated more favorable clinical effectiveness across all outcome measures[54]. These findings emphasize the value of real-world data in refining therapeutic sequencing strategies, ultimately supporting long-term disease control and quality of life.

The ROTARY study evaluated real-world persistence of successive biologic therapies in individuals with CD and UC using data from the Optum Clinical Database (2012-2020). Biologic sequencing patterns varied between conditions, with ADA followed by IFX (21.2%) being most common in CD, and ADA followed by VDZ (24.5%) predominant in UC. In both diseases, first-line treatment with IFX or VDZ was associated with significantly lower switching or discontinuation rates compared to ADA. Specifically, in CD, IFX (HR = 0.654; 95%CI: 0.602-0.710) and VDZ (HR = 0.606; 95%CI: 0.537-0.685) showed better persistence, while in UC, IFX (HR = 0.657; 95%CI: 0.588-0.734) and VDZ (HR = 0.692; 95%CI: 0.591-0.810) outperformed ADA. Moreover, the study showed that most individuals began therapy with a TNF-α antagonist, often followed by another TNF-α or VDZ. Notably, both VDZ and IFX demonstrated superior persistence when used as first- or second-line options, and ustekinumab showed better durability than ADA when administered second-line. These findings highlight the critical role of initial biologic selection and treatment sequencing, as early decisions can significantly affect long-term therapy durability and overall outcomes in IBD management[20].

Comparative studies and meta-analyses in CD patients

Although the SEVUE trial[55] was the first head-to-head study comparing two different biological therapies in CD, the SONIC study was the first controlled comparative trial between two treatment strategies. The SONIC study was a pivotal RCT that significantly impacted CD management by comparing the efficacy of IFX, azathioprine, and their combination in individuals naive to both biologic and immunomodulator therapies[56,57]. Its findings demonstrated that combination therapy with IFX and azathioprine was superior to either agent alone in achieving clinical remission, mucosal healing, and composite remission outcomes that included clinical remission, mucosal healing, and normalization of C-reactive protein levels[56,58]. Overall, the robust evidence provided by the SONIC study has influenced clinical guidelines and treatment strategies, firmly establishing combination therapy as the preferred approach in biologic- and immunomod-

ulator-naïve individuals with CD[19,57,59].

The SEAVUE trial evaluated the efficacy and safety of ustekinumab *vs* ADA as monotherapy in biologic-naive individuals with moderate-to-severe CD. In this randomized, double-blind, parallel-group, active-comparator phase 3b trial conducted across 18 countries, clinical remission rates at week 52 were similar between ustekinumab (64.9%) and ADA (61.0%) (Δ = 4.0%; 95%CI: -5.5% to 13.5%; P = 0.417). Endoscopic response rates were also comparable, with ustekinumab achieving 41.9% and ADA 36.9% (Δ = 4.9%; 95%CI: -5.1% to 14.8%; P = 0.349). Furthermore, corticosteroid-free clinical remission at week 52 was nearly identical (ustekinumab: 60.7% *vs* ADA: 57.4%; P = 0.485). These findings indicate that ustekinumab is an effective alternative to ADA in this population, demonstrating similar efficacy in achieving clinical remission, endoscopic response, and corticosteroid-free remission, while the safety profiles for both agents were consistent with prior reports[55].

Recently, the SEQUENCE study compared risankizumab and ustekinumab in individuals with moderate-to-severe CD who were intolerant to or had failed anti-TNF therapy. This phase 3b, multicenter, open label, randomized, controlled, head-to-head trial included blinded assessments for two primary endpoints: Clinical remission at week 24 and endoscopic remission at week 48. The results demonstrated that risankizumab was non-inferior to ustekinumab for clinical remission at week 24 (58.6% *vs* 39.5%) and superior for endoscopic remission at week 48 (31.8% *vs* 16.2%). Additionally, secondary endpoints at week 48 significantly favored risankizumab, with higher rates of clinical remission (60.8% *vs* 40.8%), corticosteroid-free remission (48.6% *vs* 31.4%), and endoscopic response (45.1% *vs* 21.9%) (P < 0.001 for all comparisons). The incidence of adverse events was comparable between the two groups. These findings establish risankizumab as an effective alternative in this population, demonstrating superior endoscopic outcomes compared to ustekinumab and reinforcing the importance of personalized treatment selection in CD[60].

Two newly studied therapies for CD, guselkumab and mirikizumab, have recently released phase 3 trial data, both of which included a direct comparison to ustekinumab. The GALAXI program, particularly the GALAXI 2 and 3 phase 3 clinical trials, evaluated the efficacy of guselkumab *vs* ustekinumab and placebo in individuals with moderate-to-severe CD. Results demonstrated that guselkumab was statistically superior to ustekinumab, particularly in achieving endoscopic response and remission. Both agents exhibited acceptable safety profiles, with guselkumab's tolerability remaining consistent with previously reported data in other indications[61]. However, as the full results of these phase 3 trials have yet to be fully published, further analysis is needed to comprehensively assess their long-term efficacy, safety, and potential implications for clinical practice.

In contrast, the VIVID-1 phase 3 trial assessed the efficacy and safety of mirikizumab as an induction and maintenance therapy in CD. While mirikizumab showed a favorable safety profile and clinically meaningful efficacy over placebo, it did not achieve statistical superiority over ustekinumab in clinical or endoscopic outcomes[62]. These findings highlight the differential efficacy of IL-23p19 inhibitors, with risankizumab and guselkumab emerging as promising options with greater endoscopic benefit.

In the absence of direct comparative studies evaluating different advanced therapies for CD, NMAs have emerged as valuable tools to guide clinicians in optimizing treatment sequencing. However, NMAs also have inherent limitations, including variations in study design, participant populations, and outcome endpoints, which can restrict their applicability to individual decision-making in clinical practice.

A NMA conducted by Singh *et al*[63] assessed the efficacy and safety of various biologics in moderate-to-severe CD, including both biologic-naïve and biologic-exposed individuals. In biologic-naïve individuals, IFX [surface under the cumulative ranking (SUCRA) = 0.93] and ADA (SUCRA = 0.75) ranked highest for induction of clinical remission, while among biologic-exposed individuals, ADA (SUCRA = 0.91) and ustekinumab (SUCRA = 0.71) demonstrated the highest efficacy. IFX and ADA were also the most effective agents for maintaining remission, whereas ustekinumab had the lowest risk of serious adverse events and infections. These findings positioned IFX and ADA as preferred first-line agents, with ustekinumab emerging as a strong second-line option for moderate-to-severe CD[63].

A separate systematic review and meta-analysis comparing IFX and VDZ in moderate-to-severe CD and UC found that IFX was superior for induction therapy in both diseases, while the two agents demonstrated comparable efficacy in maintenance therapy, with similar safety profiles[64].

In fistulizing CD, an NMA of 10 RCTs highlighted the effectiveness of anti-TNF agents particularly IFX and ADA for inducing response and remission. IFX was superior to ADA for fistula response but not for remission, while ustekinumab showed efficacy for response but not for remission. Based on these findings, IFX remains the preferred first-line therapy for fistulizing CD, giving its superior efficacy in inducing response[65].

With the advent of selective IL-23p19 inhibitors, a systematic review and meta-analysis compared IL-12/23 and IL-23p19 inhibitors for CD. This study, which included 18 trials and 5561 individuals, found that although IL-23p19 inhibitors numerically outperformed ustekinumab in remission and endoscopic outcomes, the difference was not statistically significant. These findings suggest that targeting IL-23 alone may enhance endoscopic outcomes, reinforcing its potential as a promising alternative[66].

The efficacy and safety of small-molecule therapies in UC and CD were evaluated in a 2023 systematic review and meta-analysis, including 35 RCTs. This analysis confirmed that JAK inhibitors and S1P receptor modulators effectively induced clinical, endoscopic, and, in some cases, histological remission in IBD. However, indirect comparisons of these therapies in CD should be interpreted with caution due to limited direct evidence[67].

In 2023, Barberio *et al*[68] conducted an NMA comparing biologics and small molecules for luminal CD, evaluating induction, maintenance, and safety outcomes in biologic-naïve and biologic-exposed individuals. IFX ranked first for induction of remission in luminal CD, whereas risankizumab was the most effective agent across both biologic-naive and biologic-exposed groups. For maintenance therapy, upadacitinib 30 mg quaque die ranked highest. Notably, none of the studied therapies demonstrated a higher likelihood of adverse events, serious adverse events, or infections compared to placebo[68].

A more recent NMA by Vuyyuru *et al*[69] compared advanced therapies for achieving endoscopic outcomes in moderate-to-severe CD. During induction, JAK1 inhibitors ranked highest (P = 0.97) for endoscopic response, followed by IL-23p19 inhibitors (P = 0.77). Among biologic-exposed individuals, JAK1 inhibitors were more effective than both IL-12/23 and IL-23p19 inhibitors. In maintenance therapy, there were no significant differences among drug classes for endoscopic remission, although anti-TNF ranked highest (P = 0.88), followed by anti-IL-12/23 (P = 0.83) and JAK1 inhibitors (P = 0.72). These results suggest that JAK1 inhibitors and IL-23 agents may be among the most effective non-TNF-targeting options for inducing endoscopic response[69].

Additionally, an NMA evaluating early efficacy of biologics and small molecules in moderate-to-severe luminal CD included 25 RCTs with 7414 individuals, comparing clinical remission rates within six weeks of treatment initiation. IFX ranked highest for early clinical remission. Among biologic-exposed individuals, upadacitinib and risankizumab demonstrated the highest probability of achieving a CD activity index-100 response, though no trials evaluated IFX in this subgroup. Adjusting for steroid use and ileal disease did not significantly alter treatment rankings, reinforcing the importance of early therapeutic decisions in CD across biologic-naïve and biologic-exposed populations[70].

Systematic reviews and NMAs provide valuable comparative insights into the efficacy and safety of advanced therapies for CD, particularly in the absence of direct head-to-head trials. While IFX and ADA remain well-established first-line options, emerging data suggest that anti-IL and JAK1 inhibitors may serve as promising alternatives, particularly in biologic-exposed individuals.

Comparisons based on NMAs must be interpreted with caution, as differences in study populations, endpoints, and treatment duration can significantly influence the results. As newer therapies continue to emerge, ongoing real-world studies and future head-to-head trials will be essential in refining treatment sequencing and positioning, ultimately optimizing long-term outcomes for individuals with CD.

Postoperative recurrence in CD

Selecting the optimal advanced therapy in CD requires considering both individual risk factors and post-surgical recurrence risk. In high-risk individuals undergoing ileocecal or ileocolonic resection, first-line prophylactic therapy is guided by biologic-naïve status and prior biologic exposure[71,72]. Typically, individuals at high-risk for postoperative CD recurrence include those with two or more of the following factors: Prior bowel resection, penetrating disease, perianal fistulizing disease, current smoking, age under 30 years, ileal resection length greater than 50 cm, residual macroscopic disease, or granuloma in the surgical specimen[72].

The REPREVIO trial, a double-blind, randomized, placebo-controlled study across 13 European centers, evaluated VDZ for preventing postoperative recurrence in CD. At week 26, VDZ significantly reduced severe endoscopic recurrence [23.3% in the VDZ group *vs* 62.2% in the placebo group; difference: -38.9% (95%CI: -56.0 to -17.3); P = 0.0004] and improved the modified Rutgeerts scores (77.8% probability of a lower score; P < 0.0001). Serious adverse events occurred in 7.0% of VDZ-treated individuals and 5.4% of those treated with placebo, with no new safety concerns. These findings suggest that VDZ may reduce severe postoperative recurrence in CD, although long-term studies are needed to confirm its durability and clinical impact[73].

Despite prophylactic strategies, many individuals with CD experience postoperative recurrence, necessitating prompt and effective treatment interventions. Endoscopic recurrence, defined as a Rutgeerts score of i2 or higher within 6 to 12 months after surgery, is a strong predictor of future clinical relapse and should guide therapeutic intensification[74,75]. Studies have shown that severe endoscopic recurrence correlates with a higher risk of clinical recurrence. Therefore, early detection through endoscopic monitoring is essential to optimize postoperative management and improve long-term outcomes[75,76].

For individuals with endoscopic recurrence despite prophylaxis, optimizing existing therapy is the first step. This may include dose escalation of anti-TNF agents, switching from thiopurines to biologics, or using combination therapy in those who initially received monotherapy[59,77].

For individuals experiencing postoperative recurrence of CD without prior prophylaxis, advanced therapy should be considered to prevent disease progression and complications[77]. Anti-TNF agents have been widely used as first-line therapy in both prevention and treatment of postoperative CD recurrence[78]. VDZ has shown effectiveness in reducing recurrence, particularly in individuals with low systemic inflammation and predominantly colonic disease. Ustekinumab is another effective option, especially in those who have not responded adequately to prior biologic therapies, due to its favorable safety profile[79].

There is limited data regarding the use of anti-IL-23p19 agents, JAK inhibitors, and S1P modulators in the treatment of postoperative CD recurrence, and further research is required to clarify their role in this setting. For individuals with severe endoscopic recurrence (Rutgeerts i4) or symptomatic recurrence, early initiation of advanced therapy is critical, as treatment delays increase the risk of progression to complicated disease.

Table 4 presents practical pearls in sequencing advanced therapies in CD and the available evidence base.

MANAGING SECONDARY LOR IN PATIENTS WITH IBD

Managing secondary LOR in IBD requires a personalized approach, particularly in cases of anti-TNF failure and paradoxical inflammation. This section reviews evidence-based strategies for managing secondary LOR in IBD, with an emphasis on TDM-guided interventions and optimal sequencing after therapeutic failure. The choice of the next therapeutic step depends on the availability of TDM and the underlying mechanism of treatment failure[4,22].

Table 4 Practical pearls in positioning and sequencing advanced therapies in Crohn's disease and the available evidence base

Practical pearls in positioning and sequencing advanced therapies in Crohn's disease and the available evidence base
For first line use in active mild-to-moderate CD refractory to conventional therapy, anti-TNF therapy, vedolizumab, anti-IL 12/23, anti-IL-23p19 may be similarly effective (RWE, NMA)
Vedolizumab is more effective when used in the first line (RCT, RWE)
In the scenario where pharmacoeconomic issues are a priority, initial therapy with biosimilars of infliximab, adalimumab or ustekinumab makes the first-line choice more cost-effective
Anti-TNF therapy (infliximab or adalimumab) preferably combined with thiopurines (for infliximab) may be the first line of treatment in severe CD (stricturing or penetrating phenotype, extensive small bowel disease, complex perianal disease, high inflammatory load or severe extraintestinal manifestation) (RCT, RWE, NMA)
Anti-TNF and anti-IL12/23 therapy are similarly effective in bio-naive patients with uncomplicated, early-onset moderate to severe CD (RCT, RWE)
Vedolizumab, anti-IL12/23, and Anti-IL-23p19 may be considered as first-line choice when safety issues become outstanding (RWE, NMA)
After failure of the first anti-TNF, advanced second-line therapies are less effective, including a second anti-TNF (RCT, RWE)
Anti-IL 12/23, anti-IL-23p19 and upadacitinib agents are still effective after failure of one or more anti-TNF (RCT, RWE)
Anti-TNF, upadacitinib, and IL-12/23 or IL-23p19 inhibitors are also effective after vedolizumab failure (RWE)
Anti-TNF, upadacitinib, and IL-23p19 inhibitors are effective after anti-interleukin 12/23 failure (RWE)
Anti-IL-23p19 are more effective than IL-12/23 inhibitors after failure of one or more anti-TNFs (RCT), with unclear data regarding upadacitinib positioning in this setting; A second anti-TNF associated with an immunosuppressor could be considered as a second choice, after pharmacokinetic failure due to immunogenicity of the first anti-TNF (RWE). The use of upadacitinib may be particularly favored for patients with high clearance of biologics, hypoalbuminemia, colonic CD, concomitant axial spondyloarthritis, or perianal fistulizing disease refractory to anti-TNF therapy

Janus kinase inhibitors (including upadacitinib) are not considered in biologic-naive patients in some countries, given United States Food and Drug Administration labeling restricting the use of this class of drugs to biologic/tumoral necrosis factor antagonist exposed individuals. CD: Crohn's disease; IL: Interleukin; TNF: Tumoral necrosis factor; NMA: Network meta-analysis; RWE: Real-world evidence; RCT: Randomized controlled trial.

In the absence of TDM, an initial approach involves dose optimization through either dose escalation or interval reduction of the current anti-TNF agent. However, when TDM is available, treatment decisions should be guided by serum drug levels and the presence of anti-drug antibodies. Individuals with subtherapeutic drug levels may benefit from dose escalation and the addition of an immunomodulator to enhance drug efficacy. In cases where high levels of anti-drug antibodies are detected, switching to another anti-TNF agent with an immunomodulator may be an option, although transitioning to a different therapeutic class can also be considered. It is important to emphasize that anti-TNF therapy should not be discontinued before reaching appropriate trough levels of IFX or ADA (for example, greater than 10 to 15 μg/mL), ensuring adequate drug exposure before a treatment switch[4,22,80].

Secondary LOR to non-anti-TNF therapies, such as VDZ and anti-IL agents, presents a clinical challenge in IBD management. The role of TDM in these cases is not as well-established as it is for anti-TNF agents, and the mechanisms underlying secondary LOR remain incompletely understood[81,82].

Emerging data suggest that TDM can be beneficial in managing secondary LOR to VDZ and ustekinumab. For instance, a study indicated that dose escalation or reinduction of ustekinumab in individuals with CD experiencing LOR resulted in remission or response in 69 percent of cases. However, standardized therapeutic ranges and antibody assays for these agents are still under investigation, limiting the widespread application of TDM in this context[83].

When secondary LOR occurs due to pharmacodynamic mechanisms often observed in primary non-responders switching to a different therapeutic class may be considered[84,85].

Notably, some studies suggest that following IL-23 inhibitor use, anti-TNF agents may regain effectiveness, indicating that prior IL-23 blockade does not necessarily preclude a future response to TNF inhibitors[86]. Furthermore, the “angry cells” hypothesis proposes that inflammation may be perpetuated by pro-inflammatory stromal cells (including macrophages, fibroblasts, granulocytes, and lymphocytes) that sustain inflammation through TNF-independent pathways[87]. This phenomenon may explain cases of pharmacodynamic resistance where inflammation remains active despite adequate TNF-α inhibition.

Comparative and non-inferiority clinical trials are important to discuss the current status and the future of IBD treatment[88]. Studies have shown that anti-TNF-α therapies appear to be the most 'sustainable' first-line option when considering the balance between benefits, risks, and costs, but vedolizumab, ustekinumab, and risankizumab may also be suitable as initial choices, particularly when safety concerns are prioritized. In cases of pharmacodynamic failure, switching to a different drug class is preferable. In this case, therapy considering anti-IL23p19 agents represents the most effective alternative, although the role of upadacitinib remains uncertain[89].

Ultimately, managing secondary LOR in IBD requires an individualized approach that incorporates pharmacologic insights, clinical judgment, and emerging evidence to optimize outcomes across therapeutic classes.

POSITIONING AND SEQUENCING OF THERAPY IN SPECIAL POPULATIONS

Certain IBD subgroups require individualized treatment strategies to balance efficacy and safety (Figure 3). Older individuals, due to comorbidities and altered drug metabolism, face an increased risk of infections and adverse events, favoring therapies with lower immunogenicity and more favorable safety profiles[90]. This section outlines therapeutic considerations for specific subpopulations with IBD, including pregnant and lactating individuals, patients with a history of cardiovascular disease or malignancy, those with demyelinating conditions and the elderly.

Similarly, IBD management during pregnancy and in individuals with active malignancy requires careful risk-benefit assessment. While most IBD therapies can be safely continued during pregnancy with appropriate monitoring, those with active cancer or significant comorbidities need cautious therapy selection to avoid worsening their condition. These safety-driven strategies ensure personalized, risk-adapted therapy choices, optimizing long-term outcomes in IBD management[91,92].

Therapeutic sequencing in IBD should account for infection risk, malignancy history, and immunogenicity. Anti-TNF agents are associated with higher rates of opportunistic infections, while JAK inhibitors carry increased thromboembolic and cardiovascular risks. The safety pyramid ranks corticosteroids and anti-TNFs (especially with thiopurines) as higher risk, whereas VDZ and anti-IL therapies have more favorable safety profiles. Anti-TNF agents should be avoided in individuals with melanoma, drug-induced lupus, severe paradoxical psoriasis, recurrent infections, or advanced heart failure. Similarly, JAK inhibitors are relatively contraindicated in individuals with a history of thromboembolism, significant cardiovascular risk, or age greater than 65 years[4,93].

A detailed discussion of these considerations is presented below.

Pregnant and lactating patients

The management of IBD in pregnant and lactating individuals requires careful evaluation of both maternal and fetal safety. The primary objective is to maintain disease remission while minimizing the risks associated with medication exposure. In this context, several therapies have demonstrated efficacy in controlling IBD without incurring significant maternal or fetal complications. However, some treatments are supported by limited safety data regarding fetal exposure, while others are known to be teratogenic. During pregnancy, methotrexate (for at least 3 months prior) and JAK inhibitors (for at least 1 month prior) must be discontinued. Overall, 5-aminosalicylates (5-ASA) are widely indicated for mild to moderate UC, whereas immunosuppressive therapies such as thiopurines and anti-TNF agents exhibit robust safety profiles in pregnant and lactating individuals, with remission induction rates comparable to those in the general population[91,94].

5-ASA: 5-ASA compounds, including mesalazine and sulfasalazine, are considered first-line therapies for mild to moderate UC and have been extensively studied in pregnant and lactating populations. Evidence indicates that 5-ASA is generally safe during pregnancy, with no significant increase in the risk of congenital malformations, preterm birth, or low birth weight. High doses of mesalazine (greater than 3 g *per* day) have been associated with a potential risk of fetal nephrotoxicity, although such occurrences are rare. Sulfasalazine, owing to its sulfapyridine component, may interfere with folate metabolism and increase the risk of neural tube defects; therefore, folic acid supplementation (at least 2 mg *per* day) is recommended for pregnant individuals. During lactation, minimal amounts of 5-ASA are excreted in breast milk, and mesalazine is considered compatible with breastfeeding. However, sulfasalazine may pose a slight risk of hemolysis in neonates with glucose-6-phosphate dehydrogenase deficiency[92,95-97].

Corticosteroids: Corticosteroids can be employed during pregnancy to manage active disease flares. Although their use is associated with potential adverse effects such as gestational diabetes and hypertension, the benefits of controlling disease activity generally outweigh these risks[92,95-97].

Thiopurines (azathioprine and 6-mercaptopurine): Despite being classified as Food and Drug Administration category D, thiopurines are considered safe during pregnancy and lactation based on current evidence. These agents cross the placenta but have not been linked to a significant increase in congenital malformations. Some studies suggest a slightly higher risk of preterm birth, low birth weight, and transient neonatal myelosuppression, particularly when used in combination with other immunosuppressants[92,95-97].

Anti-TNF agents: These biologics are generally safe during pregnancy. Certolizumab, in particular, demonstrates the lowest placental transfer, while IFX, ADA, and golimumab are actively transferred across the placenta, especially in the third trimester. Nonetheless, these agents are considered compatible with breastfeeding, as only minimal amounts are excreted in breast milk. Their overall safety profile in nursing infants is well-established, although adjustments to vaccination schedules may be warranted[92,95-97].

Anti-integrin and anti-ILs: Emerging data suggest that anti-integrin and anti-IL agents are safe during pregnancy and lactation, with no significant safety signals reported to date. In IBD management, most data pertain to VDZ and ustekinumab, which have a longer duration of clinical use. Conversely, data regarding newer agents such as guselkumab, risankizumab, and mirikizumab in pregnant individuals remain limited[92,95-97].

Relative contraindications: JAK inhibitors are generally contraindicated in pregnancy due to teratogenic effects observed in animal studies. However, these effects have not been substantiated in human studies involving IBD or other immune-mediated diseases. In life-threatening situations for the pregnant individual, in the context of shared decision-making, their use might be considered given their rapid onset of action and high therapeutic response rate[98,99].

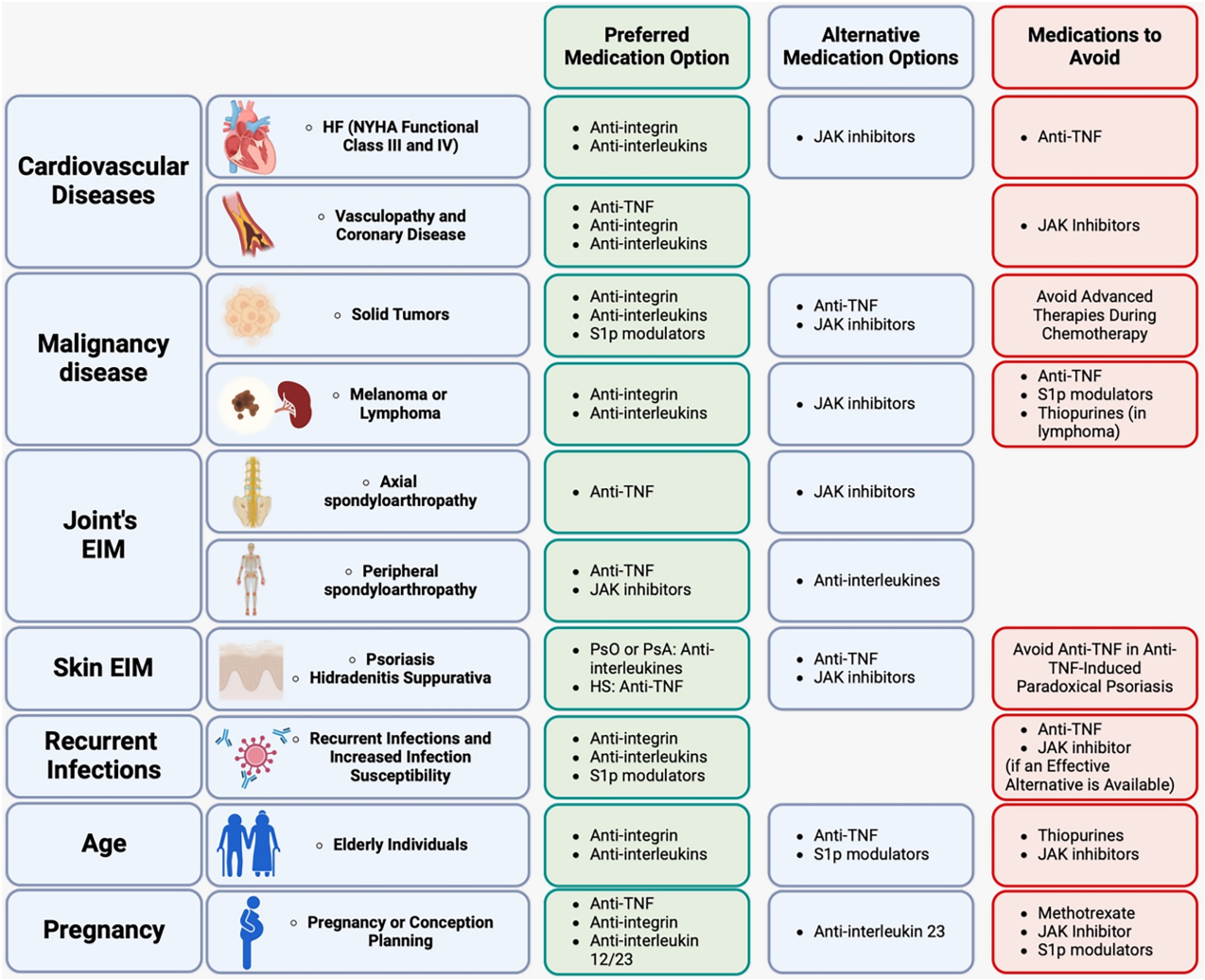

Figure 3 Inflammatory bowel disease treatment guide: Preferred, alternative, and avoidable medications by patient profile. EIM: Extraintestinal manifestation; HF: Heart failure; NYHA: New York Heart Association; TNF: Tumoral necrosis factor; S1P: Sphingosine 1-phosphate; JAK: Janus kinase; PsA: Psoriatic arthritis; PsO: Psoriasis. Image created with BioRender.

Absolute contraindications: Methotrexate is strictly contraindicated during pregnancy because of its well-documented teratogenic effects. In addition, due to its low efficacy as monotherapy and the availability of alternative treatments, methotrexate should not be considered in this patient population[98,99].

History of malignancy or active cancer

In individuals with a history of malignancy, the use of immunosuppressive therapies such as thiopurines and anti-TNF agents has raised concerns due to their potential association with an increased risk of cancer recurrence. However, retrospective studies have not consistently demonstrated a significant increase in cancer recurrence with these agents, although available data remain limited and subject to bias[100-102].

Thiopurines are specifically associated with a higher risk of non-melanoma skin cancer and lymphomas, and their use should be avoided in individuals with a history of Epstein-Barr virus-related lymphoma or human papillomavirus-related carcinomas. Methotrexate is generally considered a safer option, though data on its long-term safety in this population are also limited[103-105].

JAK inhibitors offer effective treatment for moderate-to-severe IBD, but concerns persist regarding long-term safety, particularly malignancy risk. Tofacitinib, filgotinib, and upadacitinib trials have reported non-melanoma skin cancer and other malignancies, primarily in high-risk individuals with predisposing factors such as age, smoking, chronic inflammation, or prior immunosuppressant use, rather than direct drug exposure. As JAK inhibitors are increasingly used in broader populations, ongoing post-marketing surveillance and real-world data remain crucial to refining their long-term safety profile and guiding risk-based patient selection[106].

For individuals with active cancer, the decision to continue IBD therapy remains complex and should be individualized. A multicenter cohort study found no significant difference in cancer progression between individuals treated with TNF-α antagonists and those receiving non-TNF biologics, suggesting that the choice of biologic should be guided primarily by IBD severity in collaboration with an oncologist[107,108].

Among biologics, VDZ and anti-ILs have not been associated with an increased cancer risk in individuals with a history of malignancy, making them potentially safer options in this population[109,110].

Nonetheless, given the heterogeneity of cancer types and the limited prospective data, close oncological monitoring remains essential when selecting an IBD treatment strategy for these individuals. However, it should be recognized that typically during chemotherapy for malignancy, immunosuppressive therapy directed to IBD should be discontinued until completion of treatment with the chemotherapeutic agent[108].

Relevant comorbidities in therapeutic decision-making

Individuals with IBD have an increased risk of cardiovascular disease, including heart failure and ischemic heart disease, due to chronic inflammation and medication-related adverse effects. JAK inhibitors are linked to hypertension and dyslipidemia, which may worsen heart failure, while S1P modulators can cause bradycardia and QT interval prolongation, adding to cardiovascular concerns[111-114].

For individuals with heart failure, selecting therapies with lower cardiotoxicity is critical. TNF inhibitors are relatively contraindicated in New York Heart Association class III-IV heart failure, as studies suggest increased mortality in this population. Given the inherently elevated cardiovascular risk in IBD, TNF inhibitors may further exacerbate cardiovascular disease risks. In contrast, VDZ and anti-IL therapies appear to have safer profiles in individuals with concomitant heart failure[115,116].

Individuals with IBD also have a higher risk of demyelinating diseases, including multiple sclerosis and optic neuritis, which may be exacerbated by anti-TNF therapies. Consequently, anti-TNF agents are contraindicated in individuals with pre-existing demyelinating disorders. In these cases, VDZ and anti-IL therapies are preferred due to their lack of association with demyelination risk[117,118].

Additionally, S1P modulators (*e.g.*, ozanimod) may be viable options for UC individuals with multiple sclerosis, positioning ozanimod as a first-line choice in such cases. While JAK inhibitors have not been directly linked to demyelination, their broad immunomodulatory effects warrant close monitoring in individuals with neurological comorbidities[119].

Older individuals

When selecting therapy for IBD in older individuals, multiple factors must be considered, including the presence of frailty and comorbidities such as cancer, heart failure, and demyelinating diseases[120]. JAK inhibitors have been linked to an increased risk of serious infections, notably herpes zoster, making vaccination against the virus advisable. It is important to note that elderly individuals exhibit the highest incidence of cardiovascular risk factors, which is why JAK inhibitors should be avoided in those ≥ 65 years of age, unless there are no other therapeutic possibilities for controlling IBD[90,101,121].

Given the safety concerns associated with thiopurines, anti-TNF agents, and JAK inhibitors, alternative therapies may be preferred in elderly individuals due to their more favorable safety profiles regarding cancer, cardiovascular disorders, and infections. In this context, VDZ and anti-IL agents are particularly noteworthy and should be considered as first-line options for moderate-to-severe IBD in elderly individuals, provided that their efficacy aligns with the disease phenotype [19,122]. Nevertheless, despite the risks, anti-TNF agents remain considered safe in this population and should be implemented when they represent the most appropriate therapeutic option and no contraindications exist[123].

IBD PATIENTS WITH EIMS

EIMs are common in IBD and can significantly impact quality of life by affecting the skin, joints, eyes, liver, and other organs[124-126]. The management of IBD with EIMs requires a comprehensive approach that addresses both the underlying intestinal inflammation and specific extraintestinal complications.

Anti-TNF agents have well-established efficacy in treating IBD-associated EIMs, effectively managing musculoskeletal, cutaneous, and ocular complications. These agents are particularly beneficial for EIMs that occur independently of intestinal disease activity, such as uveitis and axial spondyloarthritis. While anti-TNF therapies are widely used for several cutaneous EIMs, including pyoderma gangrenosum and psoriasis, they can also induce paradoxical reactions, with paradoxical psoriasis being the most frequently reported adverse effect[126-128].

Emerging therapies, including JAK inhibitors and anti-IL agents, are broadening the therapeutic options for EIMs. JAK inhibitors have demonstrated efficacy in treating rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, and axial spondylarthritis, while anti-IL agents have shown particular effectiveness in managing psoriasis and psoriatic arthritis. Although their precise roles in EIMs management remain under investigation, these agents are increasingly integrated into treatment regimens[124,125,127-129].

VDZ has shown efficacy in treating EIMs associated with luminal disease activity, such as type 1 peripheral arthritis and erythema nodosum; however, it does not appear to affect EIMs that are independent of IBD activity[130].

Table 5 provides an overview of the most common EIMs, their relationship with IBD activity, and the recommended therapeutic options.

Ultimately, the choice of therapy depends on the specific EIMs present and their correlation with intestinal inflammation. EIMs that parallel intestinal disease may improve with effective IBD treatment, whereas those independent of gut activity often require targeted interventions. Collaboration with specialists in rheumatology, dermatology, and ophthalmology is essential for the optimal management of these complex manifestations.

Table 5 Summary of common extraintestinal manifestations, their association with intestinal activity, and recommended therapies

Extraintestinal manifestation	Association with intestinal activity	Therapies
Peripheral arthritis (type 1)	Associated	Anti-TNF agents, vedolizumab, anti-IL agents, JAK inhibitors
Peripheral arthritis (type 2)	Independent	NSAIDs (with caution), methotrexate, anti-TNF agents, JAK inhibitors
Axial spondyloarthritis	Independent	Anti-TNF agents, JAK inhibitors
Uveitis	Independent	Anti-TNF agents, topical or systemic corticosteroids
Episcleritis	Associated	IBD therapy, topical corticosteroids
Pyoderma gangrenosum	Independent or associated	1st line option: Anti-TNF agents, systemic corticosteroids; 2nd line option: Cyclosporine; 3rd line option: JAK inhibitors, anti-IL agents
Erythema nodosum	Associated	IBD therapy, systemic corticosteroids
Psoriasis and psoriatic arthritis	Independent	1st line option: Anti-IL agents; 2nd line option: Anti-TNF agents; 3rd line option: JAK inhibitors
Primary sclerosing cholangitis	Independent	Treatment is independent of IBD treatment; Ursodeoxycholic acid, liver transplantation in severe cases
Osteoporosis	Independent	Treatment is independent of IBD treatment; Calcium, vitamin D, bisphosphonates
Venous thromboembolism	Associated	Treatment is independent of IBD treatment; Anticoagulation therapy
Autoimmune hemolytic anemia	Associated	Systemic corticosteroids, immunosuppressants

IL: Interleukin; TNF: Tumoral necrosis factor; JAK: Janus kinase; IBD: Inflammatory bowel disease; NSAIDs: Non-steroidal anti-inflammatory drugs.

CONCLUSION

IBD is not a single, uniform entity but a complex, multisystemic disorder with highly heterogeneous phenotypic expressions, resulting from a dynamic interplay between genetic, immune, and microbiological factors[131]. The molecular pathways that initiate and sustain intestinal and systemic inflammation are not necessarily the same across individuals. Moreover, in a single person, these pathways often evolve over time, leading to variable disease behavior and therapeutic responses[132]. The expansion of the therapeutic armamentarium, including novel drugs with distinct mechanisms of action, combination strategies, and microbiome-targeting therapies, represents promising avenues to overcome the therapeutic ceiling of current treatments for IBD, where a substantial proportion of individuals with IBD fail to achieve sustained remission or experience secondary LOR. Future research in personalized medicine, especially in characterizing patient-specific molecular signatures, may transform treatment selection. By leveraging multi-omics baseline biomarkers such as genomics, transcriptomics, proteomics, microbiome, and metabolomics, it may be possible to develop predictive models and precision-based tools to guide both initial and subsequent patient-centered therapeutic decisions[10,133]. Ultimately, this approach may enable clinicians to match each individual with the most effective treatment strategy from the outset, minimizing trial-and-error approaches and improving the long-term outcomes. Moreover, the specific pathways selected in IBD treatment can exhibit significant variability across different countries and healthcare settings. This heterogeneity arises from a multiple factor, including disparities in the availability and regulatory approval of novel therapeutic agents, variations in national formularies and reimbursement policies, the influence of regional clinical practice guidelines, and geographic variations in the prevalence of endemic infections (such as tuberculosis or hepatitis B) that may impact the risk-benefit assessment of certain biologics or small molecules. In addition to these factors, other limiting factors such as cost-effectiveness, availability of medicines and health infrastructure in each country or region, can influence the choice and positioning of available therapies. Consequently, a standardized or universal approach to positioning and sequencing is often impractical. In conclusion, the management of IBD is transitioning into a new era marked by unprecedented complexity and therapeutic opportunity. As our understanding of the disease deepens, encompassing its molecular heterogeneity, the evolving landscape of therapeutic options, and the influence of regional and systemic factors it becomes increasingly evident that individualized, context-sensitive strategies are essential. Bridging the gap between scientific advances and real-world implementation will require continued investment in translational research, global collaboration, and equitable healthcare policies. Only through this multifaceted, patient-centered approach can redefine therapeutic success in IBD, achieving durable remission and meaningful improvements in quality of life for all affected individuals.

FOOTNOTES

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to the conception and design of the study, acquisition of data, drafting of the article, and making critical revisions related to the important intellectual content of the manuscript; All the authors approved for the final version of the article to be published.

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